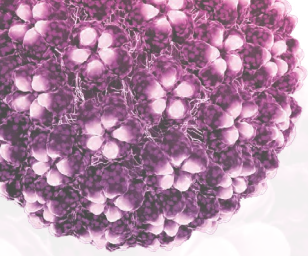

PAPILOCARE®

INTERNATIONAL CLINICAL CASES PROGRAM DR. EDUARDO VILAPLANA

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THIRD EDITION DR. EDUARDO VILAPLANA

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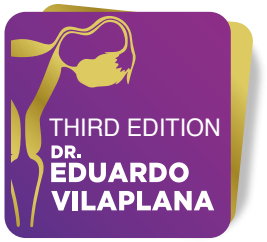

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SUMMARY

CLINICAL CASES

REGRESSION OF HIGH-GRADE CIN AND VaIN AFTER TREATMENT WITH PAPILOCARE® IN PATIENT UNDER 25 YEARS OF AGE

Dr. Pham Ho Thuy Ai

Tu Du Hospital, Vietnam

ABSTRACT

CIN 2+ is prevalent in young, nulliparous women, aiming to postpone excisional treatment and prioritize conservative management for this group due to future obstetric concerns.

KEY WORDS

Cervical cancer. HPV. Papilocare®. Conservative management.

INTRODUCTION

According to the World Health Organization's statistics in 2020, cervical cancer is the fourth most common cancer in women globally and the sixth most common cancer in women in Viet Nam[1]. It has the highest incidence and death rates in low- and middle-income countries[2]. The management strategy for cervical cancer is currently a top priority. The WHO Global strategy sets out a plan to eliminate cervical cancer as a public health problem: 90% of girls vaccinated with the HPV vaccine by age 15, 70% of women screened with a high-quality test by ages 35 and 45, 90% of women with cervical disease receiving treatment[1]. Similar to CIN, VaIN is a pre-malignant lesion and a rare disease, representing less than 1% of all intraepithelial neoplasia of the female genital tract.

CIN and VaIN are a potential consequence of human papillomavirus (HPV) infection. In Europe, more than 80% of CIN 2+ to genotypes 16, 18, 31, 33, 45, 52, 583. The highest incidence of CIN 2, CIN 3 and AIS was observed in the age group 25–29 years. The research observed that CIN 2 was more prevalent in younger ages compared to CIN 3[5]. The research on sexual behavior in Vietnam in 2019 revealed that the average age for first sexual intercourse among women is 18-20 years with 36.8% respondents who reported having premarital sex were 19-24 years of age and 7.5% were aged 15-18 years;

Urban areas have a higher rate than rural regions, It shows a trend towards a younger age compared to previous years. Results from other studies also showed an increased rate of premarital sex and the acceptance of premarital sex in younger Vietnamese[1]. The change in sexual behaviours among young people in Vietnam is leading to increased risk of HPV infection and transmission, consequently raising the likelihood of progression to precancerous cervical lesions.

Excision treatment is a current recommendations for all patients of histologically confirmed CIN 2+ or adenocarcinoma in situ (AIS) to reduce the potential risk of cervical cancer. The choice depending on the adequacy of the colposcopic examination, techniques, cost, patient age and future obstectrics. Although the rates of HPV infection and CIN are high in young women, the progression rates to cervical cancer are low because the lesions often regress[9]. A study reported that the regression rate of CIN 2 occoured in 71.1% of women under 25 years old and there were no cases of progression to invasive cancer[4]. Numerous studies and guidelines advocate conservative management for CIN 2 in individuals age under 25. Adopting a "wait and see" approach may lead to a better obstetric outcome for young patients.

Papilocare® vaginal gel is the initial treatment scientifically proven highly effective in eliminating both HPV and early precancerous cervix lesions. The collected data on Papilocare® vaginal gel indicates normalization of lesions in nine out of ten patients and makes the high-risk HPV test negative in 63% of cases and with only six months of treatment. The results contribute to affirming the benefits of this gel for patients with precancerous conditions and high-risk HPV infection.

CLINICAL HISTORY

A 19-year-old female presenting from a private gynecologist for the positive results both HPV 16 and 12 other types (high-risk). Therefore, it was decided to perform a colposcopy.

She had no family history of interest.

Personal history:

Asthma under treatment. No known allergies. No toxic habits.

Obstetric and Gynecology history:

- Nulligravid. Menarche at age 12.
- First intercourse: 15.
- Menstrual type: regular 5/35.
- Contraceptive method: fertility awareness-based methods.
- Not vaccinated against HPV.

PHYSICAL EXAMINATION

Colposcopy examination: Unsatisfactory with type 3TZ. Using acetic acid an area of coarse mosaic is observed from 6 to 7 o'clock, diameter 0.5 cm without reaching the endocervical canal and an extensive acetowhite area at 2 to 8 o'clock in vaginal wall. When applying lugol's solution it continues to show a negative Lugol zone in acetowhite area. Two biopsies at 6 o'clock cervical and at 4 o'clock vaginal and endocervical curettage were taken.

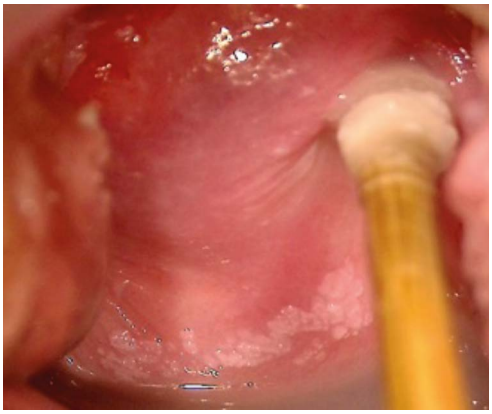

FIGURE 1.

FIGURE 2.

- Biopsy 1: CIN 2 (high-grade).
- Biopsy 2: VaIN 2.
- Endocervical curettage: Negative.

TREATMENT AND EVOLUTION

Based on the patient's age, we have decided to closely observation their progression (cytologic and colposcopic follow-up) and administer all three doses of the HPV vaccination. During the conservative period, the Papilocare® treatment regimen was implemented for six-month. After four months of use, the patient returned to the clinic for check-up:

- Pap's: ASC-H.
- HPV test: negative.
- Colposcopy: Unsatisfactory. Using acetic acid a fine mosaic (minor changes) from 6 to 7 o'clock and negative lugol in this area. No acetowhite or lugol negative in vaginal. Biopsy was taken at 6 o'clock and repeat endocervical curettage.
  – Biopsy: CIN 1 (low-grade).
  – Endocervical curettage: Negative.

Although a cytology still show a high-grade lesion, the acetowhite on the cervical show better transformation observed during colposcopy and the persistence of HPV. There is still hope that upon completing the Papilocare® treatment, the abnormal cytology may regress.

FINAL DIAGNOSIS

CIN 2 and VaIN 2 with high-risk HPV infection in adolescents, hoping to postpone conisation to observe the regression. The reduction of cervical lesions and clearance of HPV infection could be the result of treatment with Papilocare® vaginal gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Factors associated with CIN 2 regression and progression to CIN 3 were correlated with HPV persistence, spe-

cifically HPV 16/18 infections. But the infections are transitory and clear up on its own in almost cases[6]. As with CIN 1, data in adolescents suggest that CIN 2 has a much higher likelihood of regression with showing CIN 1 or less after 3 years[7]. Based on the ASCCP guidelines from 2019, management of CIN 2 in patients whose concerns about the effects of treatment on a future pregnancy outweigh their concerns about cancer. Specifically for patients under 25 years, the priority is to choose observation through cytology and colposcopy for 12 months[6]. So in this case, we opt for observation and wait for the regression of cervical lesions in the hope that the patient can avoid cervical conization.

Some studies show that Papilocare® is a vaginal gel that have positive effects on HPV-dependent cervical lesions and HPV clearance[8]. Its unique formulation based on seven components, among which the extract of *Coriolus versicolor* stands out, a fungus widely used in traditional Chinese medicine, and Bioecolia®, a prebiotic that promotes the growth of cells, beneficial bacteria such as *Lactobacillus crispatus*[10]. Reported that normalization of low-grade lesions of the cervix in 88% of patients infected with high-risk HPV after six months of treatment. So treatment with Papilocare® in these cases may be maximized the probabilities of regression. After implementing conservative management this case with Papilocare® Vaginal Gel leading to the clearance of HPV infection and diminishment of cervical lesions, favorable result.

Although numerous studies indicate the effectiveness in regression precancerous lesions and clearing HPV infection, the choice to use Papilocare® Vaginal Gel still needs to be individualized, depending on lesion characteristics, the risk of lesion progression to malignancy, patient's age and future pregnancy.

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COLPOSCOPIC IMPROVEMENT OF LOW-GRADE CERVICAL HPV LESIONS FOLLOWING TREATMENT WITH PAPILOCARE® FOR SIX MONTHS

Dr. Doris María Castillo Gutiérrez

Hospital Español de Veracruz, Mexico

ABSTRACT

In clinical settings where we have low-grade lesions caused by low- or high-risk virus, it is important to offer non-invasive treatment modalities that can aid viral clearance and regression of the lesions faster than surveillance. There is evidence that this can be achieved with the use of preparations that enhance cervical epithelialisation. In this regard, the following clinical case is presented.

KEY WORDS

Low-grade lesion. cervical intraepithelial neoplasia. HPV. *Coriolus versicolor*. Centella asiatica.

CLINICAL HISTORY

25-year-old patient, nulligravid, menarche at age 13, sexually active since age 18, number of sexual partners: 2. Uses condoms. First cervical cytology at the age of 24, reporting a low-grade lesion. She started Gardasil® at the age of 24.

PHYSICAL EXAMINATION

Patient with low-grade lesion with PCR positive for virus type 35.

Colposcopy was performed on 23 November 2022, where a faint acetowhite image with mosaic appearance was observed over the entire anterior and posterior lip, measuring approximately 7 mm, Schiller's test was positive and there were no atypical vessels. Glandular ectropion was present. A radiographic biopsy was taken at 12 and 10 o'clock, confirming type 1 cervical intraepithelial neoplasia. One of the differential diagnoses in this case is immature squamous metaplasia, which must always be confirmed by cervical biopsy.

TREATMENT AND PROGRESS

Treatment with Papilocare® was started in December 2022, using it daily for one month, then every other day. On 14 June 2023, cytology and colposcopy were repeated, with a notable improvement in the cervical lesion. The last dose

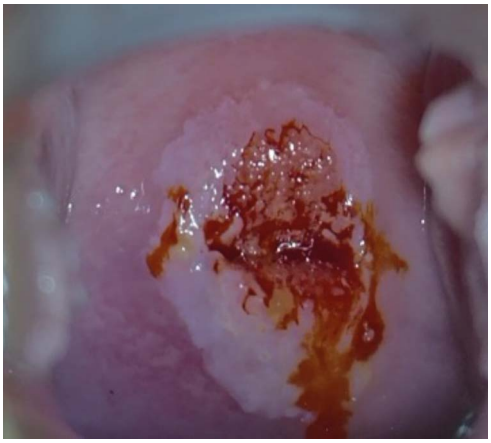

FIGURE 1. Colposcopy prior to treatment with Papilocare®. An acetowhite image is seen around the periphery of the external cervical os, as well as glandular ectropion.

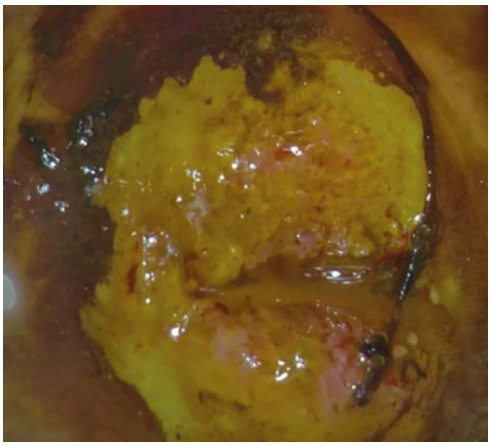

FIGURE 2. Colposcopy prior to treatment with Papilocare®. Schiller's test was positive.

of Gardasil® was administered during the same consultation. The patient will continue to be treated with Papilocare® for the next six months.

FINAL DIAGNOSIS

Cytology currently shows a low-grade lesion; however, colposcopy shows a marked improvement of the lesions. There is a faint acetowhite image in the radius at 12 o'clock, measuring 2 mm, with positive Schiller's test but no presence of atypical vessels. Significant decrease in glandular ectropion.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Different human papillomaviruses (HPV) are the most common cause of viral infection of the reproductive tract. Most sexually active women and men will become infected at some point in

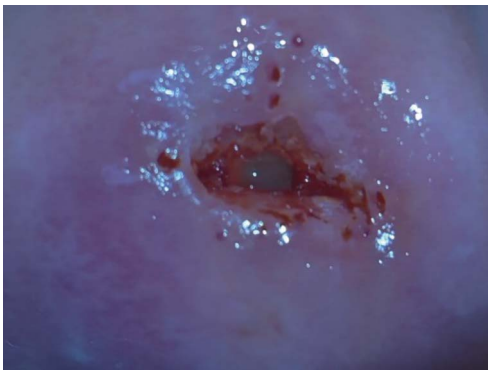

FIGURE 3. Colposcopy six months after starting treatment with Papilocare®.

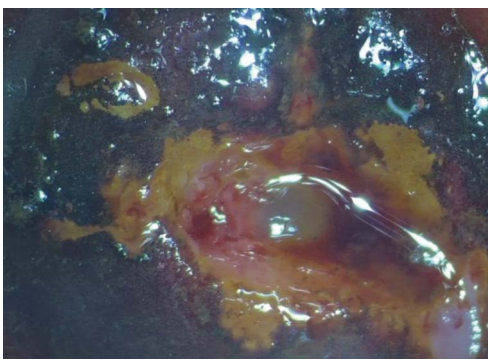

FIGURE 4. Schiller's test six months after starting treatment with Papilocare®. Marked improvement in glandular ectropion and cervical lesion size was observed.

their lives, and some people may have recurrent infections. More than 90% of the affected populations successfully clear the infection[1].

Cervical screening programmes aim to prevent cervical cancer by detecting and treating cervical intraepithelial precursor lesions (CIN)[2]. It is estimated that up to 80% of sexually active women are infected with HPV of some type during their lifetime, and more than 50% are infected with a high-risk oncogenic virus.

Cervical cancer and CIN lesions are caused by persistent HPV infection. High-grade lesions represent a heterogeneous group consisting of a subset of CIN lesions characterised by the production of new viral particles, and a subset of transforming CIN lesions that show dysregulation of E6 and E7[2].

The prevalence of HPV infections differs between countries and may even vary between regions within countries. This difference is somewhat influenced by migration, sexual behaviour, the degree of cervical lesion in the women sampled and diagnostic methods, which all play an important role[3].

In Hurtado-Salgado's prevalence study in Mexico, the prevalence was higher in women aged 35-39 years with 10.4% (95% CI: 10.3 to 10.5) and in women aged 60-64 years with 10.1% (95% CI: 10.0 to 10.3). The prevalence was highest in the southeast, at 10.5% (95% CI: 10.4–10.6). It is striking that women who lived in less marginalised areas had a significantly higher prevalence of 10.3% (95% CI: 10.2-10.4) compared to those living in highly marginalised areas, 8.7% (95% CI: 8.5–8.7). HPV16 infection was detected in 0.92% (2293/23 854) of women and HPV18 infection was detected in 0.39% (978/23 854) of women[4].

High-risk HPVs cause virtually 100% of cases of cervical cancer, and there is epidemiological evidence that they are clearly linked to vulvar, vaginal, penile and anal cancers. Worldwide, HPV16 and HPV18 contribute to more than 70% of all cases of cervical cancer. HPV types 31, 33, 35, 45, 52 and 58 cause approximately 20% of cases of cervical cancer worldwide.

In the study by Alarcón-Romero, the frequency of virus 16 increased with age, peaking in women aged >45 years. One of the reasons that could influence this increase is the woman's immune status, which could affect the acquisition and reactivation of HPV infections. The three most prevalent high-risk HPV genotypes in cervical cancer patients in that study were HPV16, HPV18 and HPV45[3].

It is now accepted that approximately half of even high-grade cervical squamous intraepithelial lesions disappear on their own within two years of diagnosis. Therefore, many women can be managed expectantly, thus avoiding routine loop electrosurgical excision (LEEP) and the related adverse effects. This should be done on a case-by-case basis. Furthermore, in Nourrisson's study, it was reported that at least in women under 40 years of age, 59% of high-grade intraepithelial lesions / CIN 2 regressed spontaneously when managed expectantly[5].

The goal of treatment with Papilocare® is to increase regression and decrease the risk of progression. It also pre-

vents overtreatment, which can increase reproductive and obstetric risks to the patient. However, we may have other benefits such as important changes in the vaginal microbiota.

One of the ingredients of Papilocare® is *Coriolus versicolor,* a fungus with global distribution, which contains polysaccharides with a variety of biological activities, such as promoting the immune response and antiviral, antitumour and antidiabetic properties, among other potential uses that are under investigation[6].

In the EPICERVIX study, with the use of a *Coriolus versicolor*-based vaginal gel, a statistically significant increase in *Lactobacillus* spp. was observed at the end of treatment compared to the baseline documented for *L. iners* and *L. crispatus.* However, other species, such as *Gardnerella vaginalis,* decreased significantly. There is emerging evidence that a higher diversity of vaginal microbiota together with a reduced relative abundance of *Lactobacillus* spp. is involved in HPV acquisition and persistence[7]. Higher microbiota diversity and lower abundance of lactobacilli have been reported to be associated with HPV infection, and *L. iners* has been associated with low- and high-grade lesions[8].

In the study by Criscuolo, negative colposcopy increased from 43.0% to 55.8% after six months in the control group, and from 52.6% to 79.4% in women treated with *Coriolus versicolor*-based vaginal gel over six months. The percentage of women with negative cytology increased from 19.8% at baseline to 47.7% after six months in the control group, and from 33.0% to 77.3% in treated women. The treatment schedule was based on 21 consecutive days of therapy in the first month, and every other day for two months thereafter[9]. In the PALOMA study, the percentage of patients presenting normal Pap smears with concordant colposcopy observations after six months was significantly higher in the treatment group than in the control group (84.9% *vs* 64.5%, p = 0.031), with significant differences in clearance compared to the control group (75.9% vs 41.9%). Papilocare® has demonstrated significant efficacy in the treatment of low-grade HPV-associated cervical lesions and a positive trend in increasing viral clearance after a period of six months[10].

While early diagnosis of cervical intraepithelial lesions is considered appropriate, it can lead to overtreatment; therefore, it is important to offer the option of follow-up in selected patients according to their risk. The current use of Papilocare® increases the speed of regression of the lesions, as well as the chances of viral clearance and avoiding progression or persistence, at least in low-grade lesions. There are also many additional potential uses for Papilocare®, such as for vulvar intraepithelial neoplasia or condylomatosis, including high-grade CIN 2 lesions or following excisional treatment, which would be interesting to explore.

In the case of our young patient, there is a great benefit from the use of Papilocare®, calming the anxiety of the patient, who wanted an ablative treatment, but was advised to use Papilo-

care® and maintain a healthy lifestyle. Complete regression of the lesion is expected within the next six months.

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CONSERVATIVE APPROACH TREATMENT WITH PAPILOCARE® IN NULLIPAROUS PATIENT WITH POSITIVE HSIL SURGICAL MARGINE AFTER SECOND LOOP EXCISION PROCEDURE

Dr. Aljosa Mandic

Oncology Institute of Vojvodina, Serbia

ABSTRACT

The relationship between endocervical and ectocervical margin status and residual or recurrence after cervical intraepithelial neoplasia (CIN) resection has been controversial. Park et al. pointed out that a positive incisional margin will increase the residual or recurrence rate after CIN resection[1]. Alder et al.[2] pointed out that the margin status cannot accurately predict postoperative residual or recurrence.

KEY WORDS

Positive surgical margines. Cervical dysplasia.

CLINICAL HISTORY

Patient was 30 year old who came at the Institute with PAP smear LSIL four months after loop excision because of HSIL in other hospital. Cytology was reported according to the Bethesda system. Histopathological diagnosis was regarded as negative for intraepithelial lesion or malignancy (NILM) when no abnormalities with evidence of HPV were detected. Histopathological low-grade squamous intraepithelial lesion (LSIL) was defined as either HPV atypia/atypia condylomatosa or cervical intraepithelial neoplasia grade 1 (CIN 1).

Family history was negative on malignancy, nulliparous, no clinical symptoms, menstrual cycles regular.

PHYSICAL EXAMINATION

Gynecological exam was without clinical pathological findings. Exam under the speculum: Cervix was epithelialized after procedure no macroscopically suspicious. Colposcopy was normal findings. Detection of HPV was not performed before the initial treatment so in this situation the biopsy and endocervical curettage was performed.

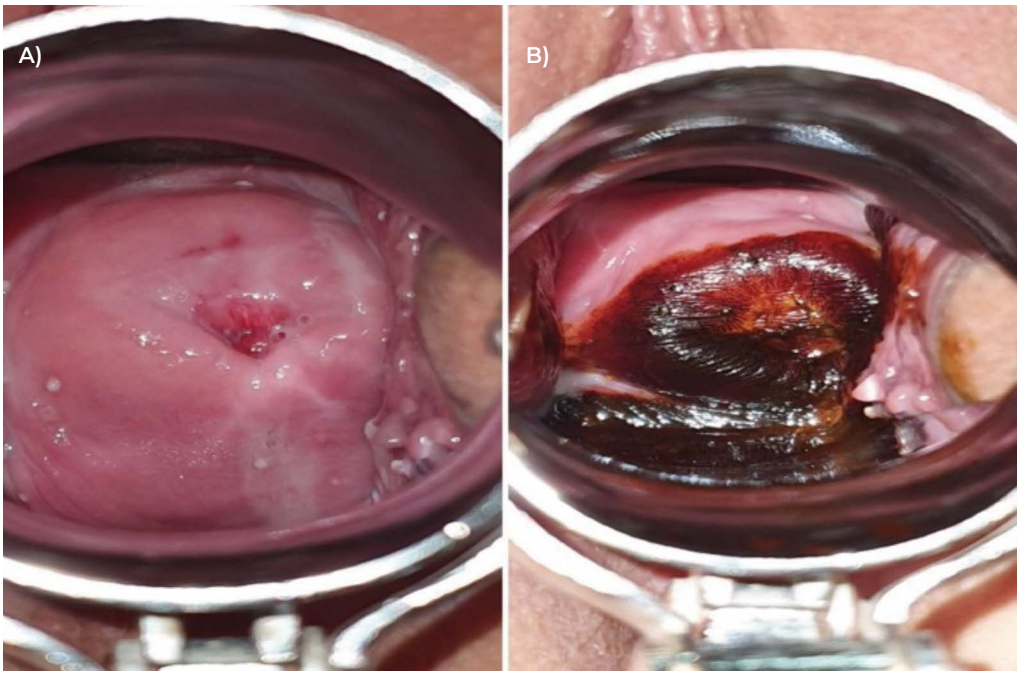

FIGURE 1. A) Six months after re-loop excision. B) Lugol positive exocervix.

Final histopathological findings was HSIL on ectocervix and endocervix forth months after initial treatment.

TREATMENT AND EVOLUTION

Re-Loop excision with endocervical curettage (ECC) was performed, 28.02.2022.

Final histopathological findings was HSIL with focal positive ectocervical surgical margins and ECC was negative on displasia.

Because of re- treatment and nulliparity we suggest patients conservative approach with Papilocare® gel every evening for 21 days, pause during menstruation and repeated for next two menstrual cycles 1x1, 21 days, overall three months.

Six months after the treatment control PAP smear was NILM such as HPV was negative. Colposcopy findings on exocervix was negative, with Lugol positive (Fig. 1).

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The relationship between endocervical and ectocervical margin status and residual or recurrence after cervical intraepithelial neoplasia (CIN) resection has been controversial. Feng H et al investigated the relationship between the excision margins and residual/recurrence to assess indicators for the scope of resection and the risk of treatment failure by using meta-analysis.

A total of 11 studies were included in this study, 8 studies were at low risk of bias and 3 studies were at high risk of bias. Authors concluded that positive endocervical margins, but not external cervical margins, are risk factors for residual/recurrence of CIN after resection, so more aggressive treatment and frequent follow-up are needed for patients with positive endocervical margins[3]. After surgery therapy, the strategy and procedures of follow-up represent a critical point for risk stratification, because HG-CIN recurrence is a major marker for progression to invasive cancer. HPV detection, and particularly genotyping, has an adequate high rate of sensitivity and specificity (along with an optimal reproducibility), for accurately predicting treatment failure, allowing for an intensified monitoring activity. Women with a negative HPV-test, 6 months after therapy, have a very low risk for residual/recurrent disease, leading to individualized follow up schedule, which allows gradual return to the normal screening scheme. In post-treatment follow-up of CIN 2+ patients for early detection HPV testing should be routinely included[4]. Papilocare® has shown significant and consistent rates of HR-HPV clearance ranging from 50% to 70% in the 6 different studies[5-7]. Also have to point that treatment of CIN lesions is associated with labor dystocia as well as a higher rate of spontaneous abortions in the first and second trimesters. Studies show that there is a direct positive correlation between the depth and volume of conus and the incidence of adverse pregnancy outcomes. So have to be careful with treatment and reexcision in these group of nulliparous even with positive surgical margins[8,9].

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TREATMENT OF A 25-YEAR-OLD WOMAN PRESENTIG WITH A LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL) AND HPV 16

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ABSTRACT

This case report describes the clinical management of a 25-year-old woman who presented with low-grade squamous intraepithelial lesion (LSIL) cytology and a positive human papillomavirus (HPV) test. The patient was treated with Papilocare® Vaginal Gel, a dietary supplement formulated to support the immune system's response to HPV infections. Follow-up assessments were conducted to monitor her progress.

PALABRAS CLAVE

HPV. CIN 1. Papilocare®.

INTRODUCTION

Human Papillomavirus (HPV) is a prevalent sexually transmitted infection with over 200 related strains, some of which pose significant health concerns. HPV is primarily known for causing genital warts and various cancers, including cervical, anal, and oropharyngeal cancer. Cervical carcinoma, in particular, is strongly associated with high-risk HPV strains.There are at least 15 high-risk HPV types that are significantly connected with progression of squamous intraepithelial lesion (SIL) into cervical carcinoma[1].

Low-Grade Squamous Intraepithelial Lesions (LSIL) refer to minor cellular changes in the cervical tissue, typically detected through Pap smears. LSIL is often caused by the presence of certain strains of Human Papillomavirus (HPV)[1]. While LSIL itself is generally not cancerous, it requires monitoring and may regress on its own. However, it can progress to High-Grade SIL (HSIL), which carries a higher risk of cervical cancer.

CLINICAL HISTORY

A 25-year-old female, was referred to our gynecology clinic due to an abnormal Pap smear result. Her most recent Pap smear showed LSIL (Low-Grade Squamous Intraepithelial Lesion) and HPV test was positive with HPV 16. She reported no significant medical history or family history of cervical cancer. She is nulliparous and has not been vacci-

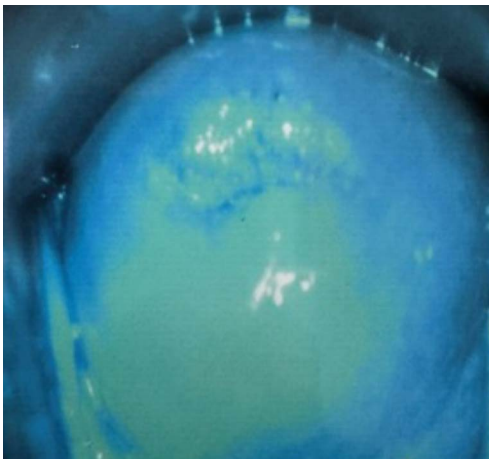

FIGURE 1. Acetowhite with green filter.

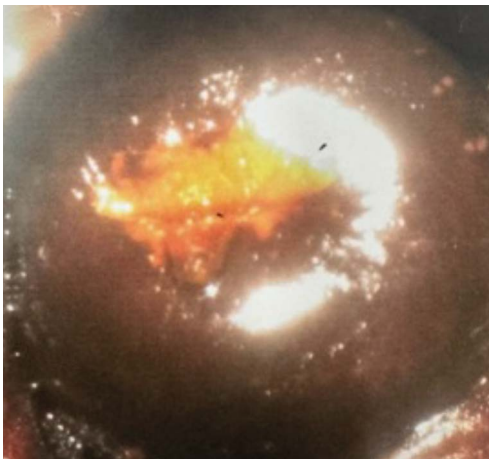

FIGURE 2. After applied lugol

nated against HPV, no steady partner and uses condom.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Pap smear and HPV test: LSIL, HPV 16.

Cervical colposcopy: Given the positive high-risk HPV result, a colposcopy was performed, revealing thin acetowhite epithelium at the squamocolumnar junction. Multiple biopsy samples were taken from the suspicious areas and the histological result is CIN 1/LSIL.

TREATMENT AND EVOLUTION

Given the diagnosis of CIN 1 and the presence of high-risk HPV type 16, we have discussed treatment options with the patient. Considering patient's age, fertility status, and the mild nature of her condition, a non-invasive topical treatment option was chosen. She was prescribed Papilocare® Vaginal Gel for 6 months according to the guideline, daily for 1 month and every other day for at least 3 months. She is also advised to consider HPV vaccination, maintain a healthy lifestyle, including using condom and quitting smoking to reduce the risk of HPV recurrence and progression.

After six months of treatment, the patient underwent a co – test and colposcopy. The follow-up Pap smear showed an improvement in cytology, with a regression from LSIL to normal, the HPV test was negative, indicating the clearance of the high-risk HPV infection and the colposcopic examination was normal. No adverse effects during the treatment period.

FINAL DIAGNOSIS

LSIL/ CIN 1 in young woman, nulliparous, positive HPV 16, after 6 months treated with Papilocare® vaginal gel, co – test showed negative and colposcopy was normal.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Cervical cancer has been previously estimated to be the fourth most common cancer and the fourth most common cause of cancer death for women worldwide in 2012, with an estimated 528,000 new cases and 266,000 deaths annually. In Vietnam, prior estimates suggest it was the fourth most common cancer in women with 5146 new cases and 2423 cervical cancer deaths in 2012[2]. The Vietnamese Ministry of Health has issued guidelines for the screening, diagnosis, and treatment of pre-cancerous cervical lesions, incorporating various screening techniques such as: VIA, cytology and HPV testing in 2011. In the guideline, cytology and VIA testing are recommended for women between the ages of 21 and 70, with a particular emphasis on those aged 30 to 50[3]. HPV test is a highly sensitive and specific screening method for detecting pre-cancerous cervical lesions. In many high-income countries, HPV test can be performed alone, without cervical cytology as a primary method to screen cervical cancer[4]. In Vietnam, HPV testing has been widely used in cervical cancer screening in recent years. This has yielded significant results in altering disease patterns and leading to an increased detection rate of early-stage cervical cancer.

CIN is a premalignant squamous lesion of the uterine cervix diagnosed by cervical biopsy and histologic examination. It is typically divided into three grades or levels of severity: CIN 1, CIN 2, and CIN 3. CIN 1 is a low-grade lesion that has a low potential for progression to malignancy and a high potential for regression, while CIN 2,3 is a high grade lesion that has a higher potential for progression and a lower potential for regression. There are two general approaches to management of CIN, that are close observation with co – testing and treatment with excision or ablation of lesions.

The preservation treatment approach in young female patients, nulliparous, and have cervical lesions of LSIL/CIN 1 in this case should be prioritized. This reduces the risk of cervical damage and lowers the risk of preterm birth, low birth weight or premature rupture of membranes. Papilocare® Vaginal Gel has been widely used in Vietnam over the past year, it is a good optionfor the treatment of LSIL and helping to enhance HPV clearance within 6 months. In the PALOMA study, overall HPV clearance after 6 months visitwas achieved by a greater number of patients treated with Papilocare® compared with those without treatment, especially high – risk HPV ones (62.5% vs 40.0%)[5]. Another study, PAPILOBS study showed that 68% of patients (121/178) had negative Pap smear and concordant colposcopy. HR-HPV clearance was observed in 57.4% of patients (101/176) after 6 months treatment with Papilocare®[6]. However, further research is needed to demonstrate the treatment efficacy of Papilocare®.

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TREATMENT WITH PAPILOCARE® IN PATIENT WITH CERVICAL CONDYLOMA, HPV CERVICITIS AND ANOGENITAL WARTS

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ABSTRACT

Conservative approach to patients, nulliparous at the age of 18 to 22, with LSIL (cervical condyloma ,cervicitis chronica vorpsa and anogenital warts). It is especially important for these patients who have not given birth to children, that they can be treated conservatively, without invasive surgical techniques.

KEY WORDS

HPV cervicitis. Cervical condiloma. Anogenital warts.

CLINICAL HISTORY

A 21-year-old patient who comes to the examination because of extensive anogenital warts.

HPV vaccination: No.

Family history is negative, the patient is nulliparous, she comes to the gynecological examination for the first time. At the same time, she is suffering from Ulcerative Colitis and receives appropriate therapy for it. She gives information about irregular menstrual cycles and does not receive hormonal therapy.

PHYSICAL EXAMINATION

Gynecological examination: In the ano-genital region, numerous condylomatous growths are noted, spreading to the gluteal region as well.

Examination under the speculum: PVU is very red in color, with a large growth on the posterior lip of the cervix.

Colposcopic findings: On the native image, the transformation zone type 1 is noted, and on the front and back lips of the cervix, a growth that extends over the entire back lip. On coloring with acetic acid, it is extremely white, Aceto-white epithelium +++. And the Schiller's test is positive, no coloring with Lugol's solution in that area.

The result of PAP smear was CIN 1, the HPV test was positive on HPV 31 (high-risk HPV) and 6 (low-risk HPV).

Although the colposcopy finding corresponded to LSIL, Biopsy and ECC of the Cervix uteri was performed, and the Pathohistological result was obtained: Cervicitis chronica virosa. Con-

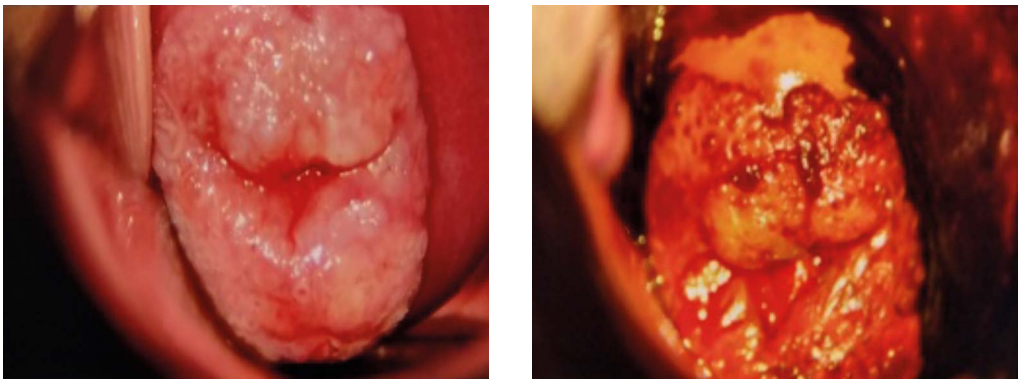

FIGURE 1. Colposcopy pictures before the treatment.

dylomata acumminata (December, 2022 year).

We decided to treat the patient conservatively, by applying Papilocare® Vaginal Gel for 21 days, at night before bed, every day, and a seven-day break during the menstrual cycle.

At the follow-up after three months, we have a visible improvement in the colposcopy picture.

At the check-up after 6 months, a PAP test was taken again, and the result was NILM. HPV test was negative. Condylomas in the anogenital region are also lost.

TREATMENT AND EVOLUTION

Biopsy PVU et ECC were performed and the histopathological finding was Cervicitis chronica virosa and Condylomata accuminata

Because of nulliparity HPV infection, anogenital warts and cervical condyloma, without HSIL, we suggest patients approach with Papilocare® gel every evening for 21 days, pause during menstruation and repeated for next five menstrual cycles 1x1, 21 days, overall six months.

Six months after the treatment control PAP smear was NILM and HPV was negative.

Our recommendations to the patient were to stop smoking cigarettes, to receive vitamin therapy (to maintain immunity at a high level), to be vaccinated against HPV and to come for gynecological check-ups every 6 months.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Human papillomavirus infection is the most commonly diagnosed sexually transmitted disease, with more than 630 million affected men and women in the world, and an average of one in every 10 people.

The highest incidence of HPV infections is in women aged 20 to 24 (44.8%) compared to 24.5% in adolescence (14 to 19) and 27.4% in women aged 25-29.

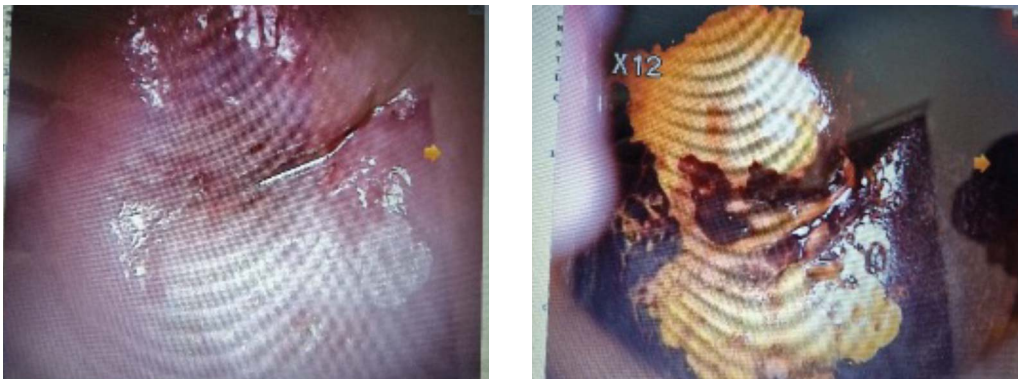

FIGURE 2. Colposcopy pictures six months after the treatment.

The probability of transmission per partner is 60% for HPV 16 and 60% for low-risk types that cause genital warts.

Almost 80% of sexually active women will get an HPV infection at some time during their life, which is usually transient and asymptomatic.

HPV is transmitted through contact with infected genital skin and mucous membranes. As genital warts are highly infectious due to their high virus content, sexual contact will result in HPV infection in 65% of cases.

The usual incubation period for clinical condylomas is three weeks to eight months, an average of 2.9 months.

Cervical condyloma is not common and is present in about 6% of women with vulvar condyloma. This finding raises the suspicion of simultaneous coinfection with high-risk types, since 20% of these changes are associated with cervical intraepithelial lesions.

The most common cause of genital condylomas is infection with HPV types 6 (38.7%) and 11 (36.3%), while in the remaining 25% condylomas are caused by multiple infections with types 6, 11, 16, 18 and 31.

The finding of genital warts is associated with a significantly higher risk of anogenital cancer, primarily cancer of the vulva, vagina, penis and anus, but not cancer of the cervix.

Cervical condyloma is the most common form of low-grade SIL, which is diagnosed in 43% of cervical condyloma. Overall, in 30% of cervical intraepithelial lesions, cervical condyloma is confirmed by pathohistological analysis, and this percentage rises to 99.6% in women under 20 years of age.

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NATIONAL WINNER

MEDICAL TREATMENT OF HIGH-GRADE CERVICAL DYSPLASIA WITH PAPILOCARE®

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Hospital Público Álvaro Cunqueiro, Vigo

ABSTRACT

A 28-year-old woman with CIN 2 and HPV 82 treated with Papilocare®, achieving HPV clearance and regression of the lesion in six months.

KEY WORDS

HPV. Papilocare®. CIN 2. Expectant management.

CLINICAL HISTORY

28-year-old woman.

Nulligravid, with no medical or surgical history of interest and no relevant family history.

Vaccinated against HPV in childhood (Cervarix®).

Asymptomatic, diagnosed with AGUS in cervical cancer screening cytology, referred for cervical pathology consultation for this reason in March 2023.

PHYSICAL EXAMINATION

Colposcopy in March 2023 (Figs. 1 and 2):

- Transformation zone: type 1.
- Vascularisation: typical.
- Acetowhite: thick mosaic and thin mosaic.
- Schiller's test: positive.

Compatible with major changes.

Directed biopsies were performed with diagnostic pathology showing cervical tissue (exo-endocervix) with minimal focal lesion with morphological and immunohistochemical findings consistent with high-grade squamous intraepithelial lesion (HSIL) / CIN 2 and p16 immunostaining: + intense.

HPV detection by PCR on the tissue was requested and the result was positive for HPV 82 (possible high risk).

Endocervical curettage was negative for malignancy.

DIFFERENTIAL DIAGNOSIS

This is high-grade cervical dysplasia caused by a proven HPV infection not

FIGURE 1.

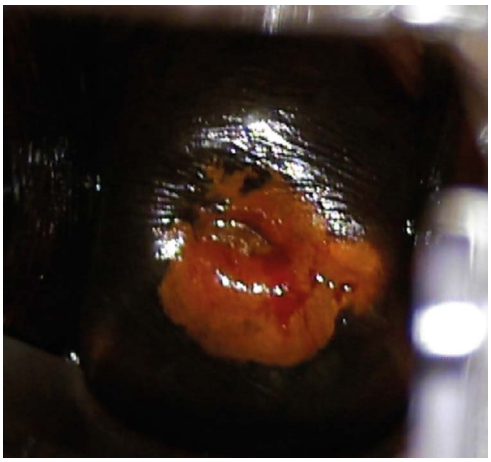

FIGURE 2.

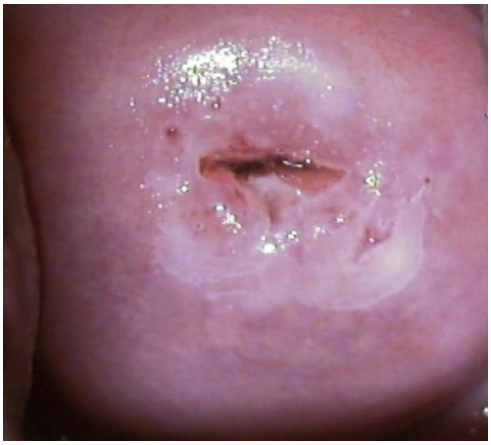

FIGURE 3.

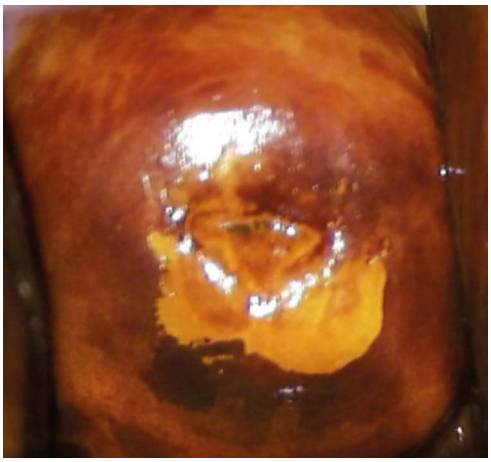

FIGURE 4.

present in the vaccination received by the patient. No other differential diagnosis is possible.

TREATMENT AND PROGRESS

In the case of a nulligravid patient, under 30 years of age and with a localised lesion, excisional treatment or conservative management with topical treatment with vaginal Papilocare® was considered, and conservative management was decided upon.

Colposcopy in September 2023 (Figs. 3 and 4):

- Transformation zone: type 1.
- Vascularisation: typical.
- Acetowhite: late onset faint uptake of stain on posterior lip with a fine mosaic pattern.

- Schiller's test: positive in 60% of the cervix.

Compatible with minor changes (improvement noted vs previous test).

Cervical biopsy and cytology + HPV determination.

FINAL DIAGNOSIS

Cervical biopsy: cervical tissue (exo-endocervix) with focal lesion with minimal changes suggestive of low-grade squamous intraepithelial lesion (LSIL)/CIN 1.

Citology: negative.

HPV: negative.

Lesion regression and HPV clearance in the first six months of follow-up.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

The treatments currently available for cervical cancer severely compromise a woman's reproductive health. In a Cochrane systematic review, Kyrgiou et al. reported an increased risk of prematurity in women with cervical intraepithelial neoplasia, a risk that increases with ablative and excisional treatments. This has led to questions about the systematic treatment of all patients.

Untreated HSIL/CIN 2 lesions are now known to regress, persist or progress to HSIL/CIN 3 in 50%, 32% and 18% of cases, respectively. The highest regression rate is observed in the first 12 months of follow-up and especially in women under 30 years of age (as is the case with our patient).

Although HSIL/CIN 3 lesions have a higher risk of progression, it is now accepted that overall they constitute a heterogeneous group with variable risks of progression/regression.

As previously mentioned, the main reason to follow up HSIL/CIN 2-3 lesions is to avoid overtreatment of lesions with the potential for regression and the consequent obstetric morbidity associated with such treatments.

When considering expectant management, we must not forget the anxiety-inducing component of "doing nothing" for the patient. This component is significantly reduced by providing adjuvant treatment such as the application of Papilocare®, which favours the cure of low-grade lesions (and high-grade in our case), the elimination of HPV and improves the patient's perception of the disease.

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ADJUVANT TREATMENT WITH PAPILOCARE® IN HIGH-GRADE CERVICAL LESIONS

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ABSTRACT

Human Papillomavirus (HPV) is the most common sexually transmitted virus. More than 200 genotypes have been described, some of which are involved in benign lesions, but many others are responsible for malignant tumours, most notably cervical cancer[1].

KEY WORDS

Human Papillomavirus (HPV). Genital lesions. Cervical cancer. Conisation. Colposcopy.

CLINICAL HISTORY

A 26-year-old woman, with no medical or surgical history of interest, except for hypothyroidism, which is being treated with Eutirox 25 micrograms. Non-smoker and no other toxic habits. Her gynaecological-obstetric history includes being nulligravid, eumenorrhoea and not being vaccinated against HPV. She uses condoms as a contraceptive method.

Diagnosed in the primary care screening cytology with a low-grade squamous intraepithelial lesion (LSIL), for which she was referred to the general gynaecology department.

PHYSICAL EXAMINATION

In addition to completing the patient's medical history, a general gynaecological and physical examination was performed at the general gynaecology clinic. The patient reported being asymptomatic.

Examination revealed eutrophic external genitalia and vagina, with normal discharge and a well-epithelialised cervix with no obvious macroscopic lesions.

A 26-year-old woman was referred to the cervical pathology clinic due to a finding of LSIL. A colposcopy was performed in addition to the cytological study, which proved adequate. A lesion was observed at 12 o'clock, occupying 25% of the cervix in the supero-external quadrant. The lesion was classified as high-grade due to the dense staining of rapidly appearing acetowhite epithelium. Two directed biopsies were performed with pathology findings indicating

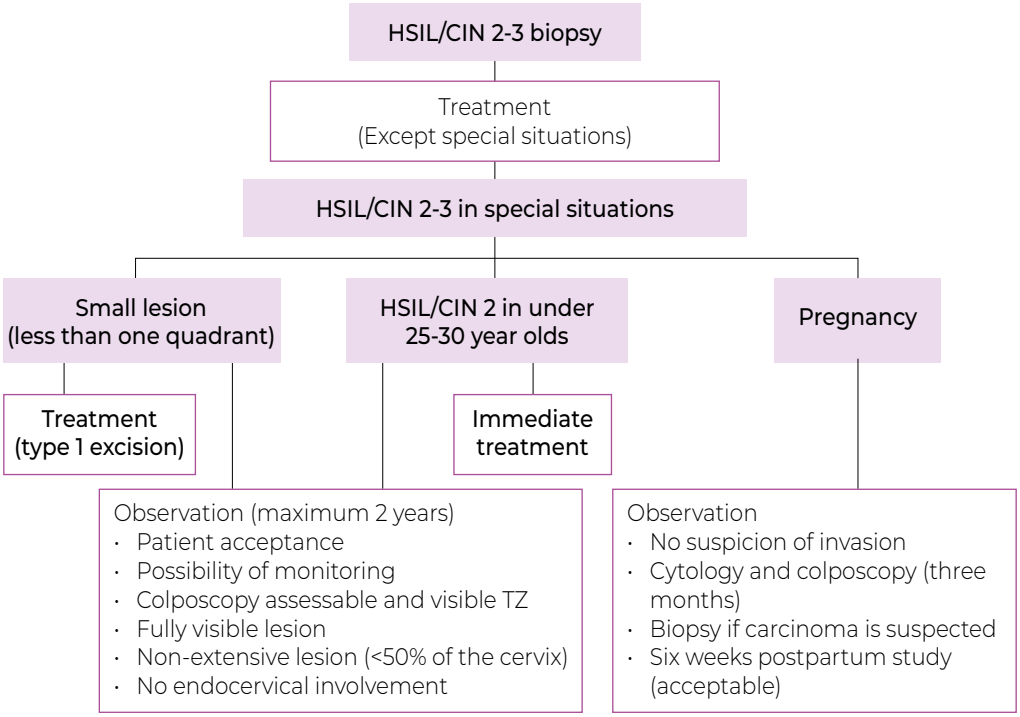


FIGURE 1. Complete algorithm for HSIL/CIN 2-3 informative biopsy results, developed by the Spanish Society of Cervical Pathology and Colposcopy.

a high-grade squamous epithelial lesion (HSIL/ CIN 2-3).

Based on the recommendations of the *Spanish Society of Cervical Pathology and Colposcopy,* immediate excisional treatment was chosen (Fig. 1).

TREATMENT AND PROGRESS

Fifteen days after the colposcopy pathology report was obtained, LLETZ diathermic loop conisation was performed, guided by Lugol's iodine staining (Fig. 2). After infiltration of paracervical anaesthesia with 10 cc of Mepivacaine at four points, Lugol's iodine was applied, observing an iodine-negative area at 12 o'clock, followed by conisation with a diathermy loop (Figs. 3 and 4), obtaining a cone that was sent for pathology. Finally, the bleeding surgical site was coagulated with a coagulation electrode. The patient did not require antibiotic or thromboembolic prophylaxis. On the same day of the operation she was discharged home, where she was instructed to complete the surgical treatment with Papilocare® Vaginal Gel applied once daily for 21 days.

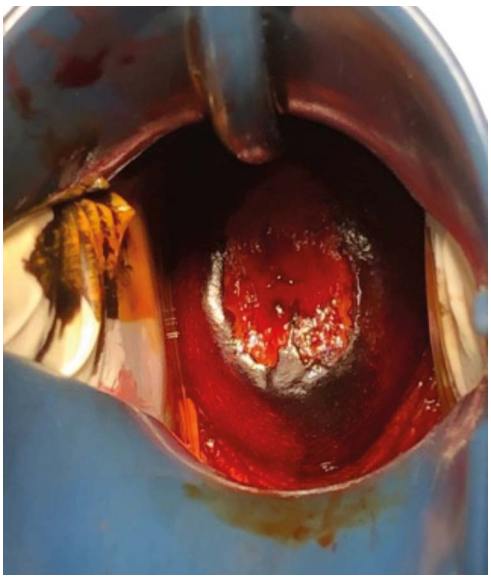
FIGURE 2. Macroscopic view of the uterine cervix prior to cervical conisation.

FINAL DIAGNOSIS

One month after surgery, the patient was assessed at the cervical pathology clinic. The definitive pathology result of the conisation was reported as high-grade cervical intraepithelial neoplasia (CIN 3) of the uterine cervix focally affecting the endocervical resection margin, with a lesion-free exocervical resection margin. Additionally, there was squamous metaplasia extending to the endocervical glands.

A physical examination of the uterine cervix was performed to assess the patient's progress with the prescribed treatment and an HPV DNA test. Her postoperative status was very favourable, with good healing and no macroscopically evident cervical lesions.

Currently, the patient continues to be followed up at the cervical pathology clinic, having completed the full HPV vaccination regimen and having been treated with Papilocare® gel, one application every other day for five



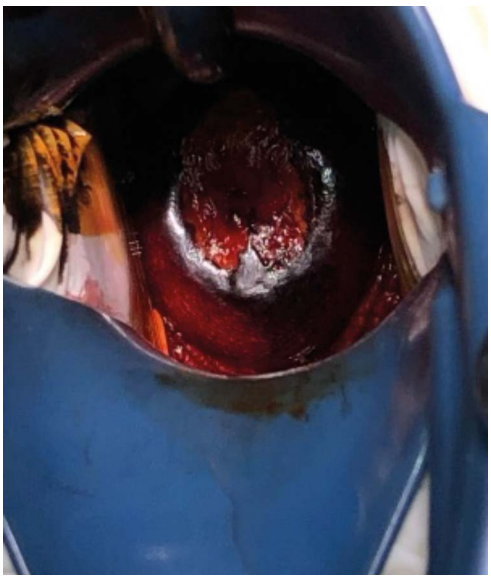


FIGURE 3 AND 4. Application of Lugol's iodine solution. Also known as Schiller's test, prior to loop diathermy conisation

months after the postsurgical check-up.

She is currently asymptomatic. Physical examination revealed a macroscopically healthy cervix. The HPV test, which was positive for HPV 16, was negative at six months and subsequent cytology showed no neoplastic lesions or lesions suspicious for malignancy.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

HPV infection is the main causative factor involved in the development of cervical cancer and its precursor lesions, as well as other lesions including cancer and pre-cancer of the vulva, vagina, penis and anus, oropharyngeal carcinoma, anogenital warts and recurrent respiratory papillomatosis. HPV causes warts and malignant disease in both men and women, although the overall burden of HPV-related cancers in men is about one-third lower than that observed among women. While warts are the most common clinical symptom, neoplasms are the most serious manifestation. The percentages of cancers caused by HPV vary by anatomical site, with virtually 100% of cervical cancers, 90-93% of anal canal cancers, 12-63% of oropharyngeal cancers, 36-40% of penile cancers, 40-64% of vaginal cancers and 40-51% of vulvar cancers being attributable to papillomavirus infection. Cervical cancer is the most important HPV-associated outcome, but the incidence of other cancers, including anal and oropharyngeal cancer, vulvar cancer and skin cancer, is increasing in Western countries[4].

HPV is considered a necessary but not sufficient cause of cervical cancer, which is a global health problem. It is estimated to be the fourth most common malignant disease in the female population, and considering health disparities, cervical cancer is the third most common cause of death for women living in underdeveloped countries[3]. Current figures report that each year 527,624 women are diagnosed with cervical cancer and 265,672 die from the disease[3,4].

With regard to cervical cancer screening, smear testing or cytology has been the standard method of secondary prevention. Since its implementation, comprehensive coverage has significantly reduced mortality due to cervical cancer. Subsequently, advances in the understanding of carcinogenesis of the virus have led to the emergence of the HPV test as a more sensitive method than cytology screening. However, given the high prevalence of the virus in the population, HPV testing has a high number of false positives, which has an important impact on the physical and mental health of patients, given the subsequent overdiagnosis and overtreatment that it entails. Therefore, new cervical cancer screening strategies are currently being developed based on molecular markers of the virus and the patient's genome[4].

However, the best available method of prevention is prophylactic HPV vaccination, which should be targeted at females between the ages of 10 and 14 years, before the onset of sexual activity5. Since they came onto the market in 2006, the different HPV vaccines avai-

lable have been successful in reducing the prevalence of anogenital warts and high-grade cervical lesions caused by genotypes included in the vaccine, as well as cross-protection for other genotypes not included[4,5].

Persistence of the virus is estimated to occur in only 10% of infected women, and only 1% of these will develop HPV-associated neoplastic lesions[6]. In cases where the persistence of the virus is clinically apparent, early diagnosis is common. Management of the early stages of the disease is usually conservative. Conisation of the uterine cervix is the procedure of choice for diagnostic and therapeutic purposes. It is indicated in the treatment of severe cervical dysplasia (CIN 2 and 3 and carcinoma in situ), as well as in the early stages of cervical cancer if the patient wishes to preserve her fertility, and finally, for diagnostic purposes when there is a discordance between the results obtained in the complementary tests[7].

Occasionally, patients are able to complement excisional treatment with a topical treatment that helps to eliminate the virus and the lesions caused by it. To this end, Papilocare®, a *Coriolus versicolor*-based vaginal gel, has been evaluated for its efficacy in HPV-related low- and high-grade cervical lesions[8,9]. In 2021, a multicentre trial was conducted in 91 HPV-positive women with low-grade alterations. The results concluded that Papilocare® treatment is safe and effective in treating low-grade cervical lesions as well as eliminating the virus[8]. In the same year, Criscuolo et al. conducted a retrospective observational study to evaluate the efficacy and safety of this gel in women with high-risk HPV. The test results showed HPV clearance in 67% of the treated patients compared to 37.2% of the controls, so the authors conclude that this treatment is safe and effective based on the evidence examined[9].

It can be concluded, based on the literature reviewed and the clinical case report, that early management at specialised clinics is essential in the treatment of HPV lesions. The current understanding of the virus' aetiopathogenesis and carcinogenesis is improving the diagnosis and treatment of processes in which the virus is involved. As a result, adjuvant treatments such as Papilocare® vaginal gel, which has shown a beneficial effect as an adjunctive treatment for high-grade cervical lesions, are now available.

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VULVAR, VAGINAL AND CERVICAL CONDYLOMATOSIS IN PREGNANT PATIENTS: NON-PHARMACOLOGICAL TREATMENT WITH A GOOD, EARLY RESPONSE

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ABSTRACT

We present the case of a 32-year-old pregnant woman with a history of a single sexual partner who was referred for consultation for vulvar, perineal and cervical condylomatosis, with the aim of treating said condition.

KEY WORDS

Condylomatosis. Pregnancy. Human papillomavirus (HPV). Colposcopy. *Molluscum.*

CLINICAL HISTORY

A 32-year-old woman, 12 weeks pregnant based on the date of her last menstrual period, was referred by a fellow obstetrician to the cervical pathology unit for evaluation of treatment for genital condylomatosis. The patient is a primiparous woman with a history of first trimester miscarriage a few months earlier, treated by curettage, with no other diseases of interest; the only relevant information is that she is allergic to acetylsalicylic acid. The patient has no family history of interest. She is a non-smoker. She denies immunisation for human papillomavirus (HPV) through vaccination. She says that she has always worked as a shop assistant, but since she got married a year ago she has been doing housework. She tells us that her husband has been her only sexual partner, denying pre-marital relations.

PHYSICAL EXAMINATION

On lithotomy examination, the vulva, vulvar fourchette and perineum show mixed lesions: Small rounded nodules with a smooth umbilicated surface extending over the vulva and inguinal regions, as well as warty lesions that coalesce into plaques, more localised in the perineal and perianal area (Fig. 1). Vaginal and cervical examination was performed by speculoscopy with a standard speculum, and warty lesions with a hard, whitish surface were observed on the vaginal walls and surface of the cervix (Fig. 2). These plaques were friable and bled when rubbed with the speculum. An attempt was made to complete the examination by performing a colposcopy and 2% acetic acid was applied to the cervix with a swab, but the test had be suspended as it was not assessable due to the bleeding.

FIGURE 1.

FIGURE 2.

FIGURE 3.

FIGURE 4.

DIFFERENTIAL DIAGNOSIS

Molluscum contagiosum and perineal, perianal, vaginal and cervical condylomatosis.

TREATMENT AND PROGRESS

Given the initial examination, it was decided that the best approach would be conservative treatment of the cervical lesions by applying Papilocare® vaginal gel for 21 consecutive nights, continuing three times a week thereafter. For the external lesions, Papilocare® cream was indicated, applied several times a day to the condylomatous plaques. Treatment was completed with the application of 10% potassium hydroxide

solution on the suspected molluscum lesions.

The patient was scheduled for a further attempt at colposcopy after one month. After that time, the patient showed an improvement in the lesions identified as condylomata in the perineal area, which was noted on examination: The molluscum vesicles persisted, but the condylomata acuminata plaques in the perineum and perianal area had disappeared, with some very small isolated warty lesions persisting in that location (Fig. 3). The vaginal condylomata had also disappeared, but the cervical condyloma persisted with the same appearance and size (Fig. 4). A colposcopy was performed, taking a sample to determine HPV and a cervical biopsy that resulted in a diagnosis of infection by HPV 56, 6 and 42 and cervical condyloma.

She was given an appointment for a check-up after two months, during which time she continued with Papilocare® cream and vaginal gel at the same dosage. This examination revealed complete disappearance of the small perianal warts that still persisted and of the cervical condyloma that had remained visible until the previous colposcopy. The disappearance of the molluscum was also achieved thanks to the application of potassium hydroxide.

After delivery, the patient was re-examined and at first glance she no longer had any visible condylomata or molluscum lesions. A co-test was performed, in which HPV 51 and 53 (high risk) were identified, and a colposcopy was performed, which was negative.

At this point, we lost the patient because she moved to another autonomous community.

FINAL DIAGNOSIS

- Condylomatosis.
- High- and low-risk HPV infection.
- *Molluscum contagiosum*.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Human papillomavirus (HPV) is a DNA virus that infects epithelial tissues, of which about 200 genotypes are known, and it is responsible for squamous cell carcinoma in different locations[1]. It is the most common sexually transmitted infection, with an average prevalence in Spain of around 14% and rising, which depends on numerous risk factors[2]. This infection has been linked to numerous complications in pregnancy, such as miscarriage, premature delivery, placental abnormalities or even IUGR, although the evidence of causality is unclear. Condylomatosis is one of those situations caused by infection that has been shown to have a major impact on pregnancy outcome: Cases of neonatal infection by vertical transmission to the foetus (such as juvenile recurrent respiratory papillomatosis) or the impossibility of vaginal delivery due to obstruction of the birth canal caused by large condylomata have been reported[3].

HPV infection diagnosed during pregnancy is a challenge for the spe-

cialist, who is faced with the challenge of regular monitoring of tissues that are constantly changing. The performance of diagnostic tests and the use of surgical therapies are limited by pregnancy, so in many cases we must carry out more conservative actions. In addition, pregnant patients are very sensitive to the use of drugs or surgical treatments at this time in their lives. Using products that are compatible with pregnancy is the key to success, especially if they are products designed to prevent the risk of HPV integration into the epithelial cells of the cervix, vulva and vagina, and which, as in this case, avoid the need for more aggressive therapies that may justify the risk or discomfort for the pregnant woman[4,5].

The diagnosis of condylomatosis in pregnancy requires active management to resolve the condition, either completely or partially, in order to minimise the complications associated with this condition and improve the neonatal and maternal prognosis[5].

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ENDOCERVICAL LSIL. NOT JUST A MATTER OF WAITING

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ABSTRACT

Complete remission of endocervical LSIL following application of Papilocare® vaginal gel.

KEY WORDS

HPV. LSIL. *Coriolus versicolor*. Papilocare®.

CLINICAL HISTORY

A 35-year-old woman attended the Cervico-Vaginal Pathology Unit due to abnormal cytology findings compatible with LSIL (low-grade squamous intraepithelial neoplasia). She had undergone her gynaecological check-up, which revealed HPV (Human Papillomavirus) infection positive for HPV 18.

Reflex cytology was conclusive with LSIL.

History

Her history indicated that this was a woman with a parity of 1-0-0-1, one birth five years ago by caesarean section. No other interventions, illnesses or toxic habits were reported. She highlighted the use of oral contraceptives as a method of family planning since the caesarean section. She did not report having been vaccinated for HPV.

Current situation

She did not report any genital discomfort or altered menstrual pattern, although on occasion she had had a little intermenstrual bleeding. The previous gynaecological examination was five years earlier, at which time a cytology was performed with a normal result.

PHYSICAL EXAMINATION

The patient was well hydrated and perfused, weight 62 kg and height 168 cm.

No macroscopic changes were observed in the genital region. Colposcopy showed a type 3 transformation zone with small glandular orifices and no acetowhite or iodine negative lesions (Fig. 1). Vaginal and vulvar examination also revealed no pathological findings. A study of the cervical canal was carried

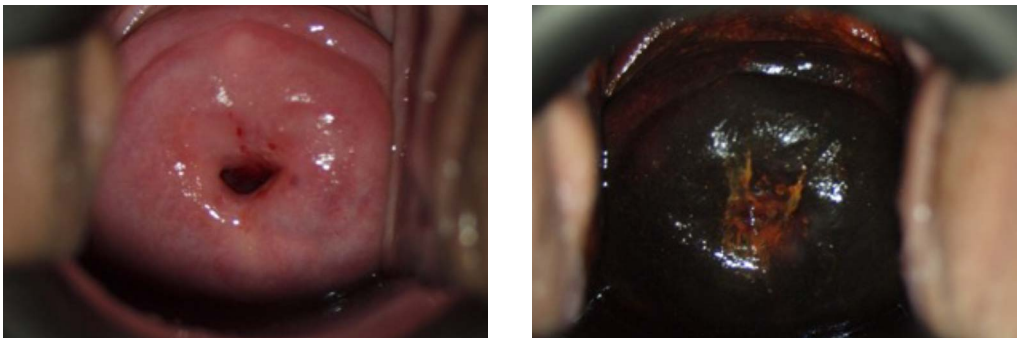

FIGURE 1. Colposcopic imaging prior to treatment

out by brushing and ECC (endocervical curettage) with a small endocervical curette.

Transvaginal ultrasound was performed to rule out associated organic disease as the patient reported occasional intermenstrual bleeding. The result of the ultrasound did not reveal any alterations detectable by ultrasound.

The histological result of the brushing and ECC was endocervical LSIL/CIN 1 (cervical intraepithelial neoplasia 1) (Fig. 2). Mature epithelial cells were observed with nuclear alterations (increased nuclear size, anisonucleosis, irregular chromatin distribution, irregular nuclear silhouette giving a "wrinkled" or "sultana" appearance), cellular keratinisation, with dense, eosinophilic cytoplasm and koilocytosis.

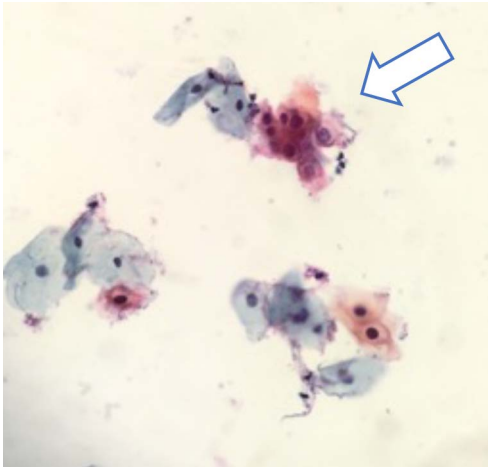

FIGURE 2. Mature epithelial cells with nuclear alterations, cellular keratinisation, with dense, eosinophilic cytoplasm and koilocytosis (arrow) (Courtesy of Dr A. Puche).

DIAGNOSIS

Endocervical LSIL/CIN 1.

Differential diagnosis

The differential diagnosis should be carried out with other lesions affecting the cervix, especially to rule out a high-grade lesion or an occult neoplastic lesion. It is also important to rule out exocervical lesions, condylomata or benign pathologies unrelated to HPV, such as cervical polyps or cervicitis, which could be related to cytological abnormalities.

FIGURE 3. Treatment plan.

TREATMENT

The patient was treated with Papilocare® Vaginal Gel *(Coriolus versicolor)* for six months, starting with 21 consecutive days of daily vaginal treatment, resting for the week of menstruation and continuing with the treatment every other day for five more months (skipping the week of menstrual bleeding). The patient reported good tolerance to the treatment, with no adverse side effects (Fig. 3). Concomitantly, she was fully vaccinated with three doses of Gardasil® (vaccination schedule 0-2-6 months). She stopped oral contraception and continued to use condoms for contraception, and her menstrual pattern became more regular and the intercycle bleeding disappeared.

After six months of treatment, the patient was re-evaluated. Macroscopic examination revealed no lesions. Colposcopy showed a type 3 transformation zone, with no acetowhite or iodine negative lesions. Epithelialisation of the glandular orifices seen at the previous colposcopy was observed (Fig. 4). A cytology study was performed with meticulous endocervical sampling with brushing, and the result was normal. The HPV test was negative.

At 12 months, cytology and HPV testing were repeated and remained negative for malignant cells and HPV negative.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

HPV infection is the most common sexually transmitted infection and it is estimated that 80% of women are infected in their lifetime[1]. Infection with certain high-risk genotypes (HR-HPV) is a necessary factor for the development of most cervical cancers and their precursor lesions[1]. Although only 1.7% of smears in cytology-based screening

FIGURE 4. Colposcopic image six months after treatment.

programmes are consistent with LSIL, it should be noted that, based on the new guidelines and protocols for cervical cancer screening, in which HPV testing has been shown to have better clinical performance, women with a positive HPV test will have LSIL in 13.6% of cases[2].

We present a case of endocervical LSIL associated with HPV 18 infection, one of the HR-HPVs associated with cervical cancer oncogenesis and with an increased risk of progression. Not all HR-HPVs carry the same oncogenic risk. Between 10% and 25% of women infected with HPV 16 or 18 will have HSIL (high-grade squamous intraepithelial lesion) at three years compared to 3% if infected with other types of HR-HPV[3,4]. Therefore, it seems important that in the event of an HR-HPV infection, and especially one of those with the highest oncogenic potential, follow-up and treatment protocols should be established to ensure that it is negative as soon as possible.

In the case in question, it should be noted that it is a lesion affecting the endocervical canal, attributed to HPV 18, and given that it is not visible by colposcopy, it is important to have a histological study of the lesion to rule out a high-grade lesion or the possibility of an occult neoplastic lesion. We know that HPV 18 can be more frequently associated with adenocarcinoma of the cervix and that cytological sensitivity is lower in these cases[2,5]. At the same time, it is important to rule out endocervical contamination from an exocervical lesion[2]. In this case, colposcopy did not reveal any lesions and the endocervical study was carried out under careful colposcopic vision.

Classically, due to the complexity of follow-up of an endocervical lesion, excision was indicated, but nowadays, based on the low risk of progression and the high rate of regression of these lesions, abstention from excision and monitoring of these patients is justified[2]. Based on the current cervical cancer prevention guidelines, the situation in question would merit monitoring after one year by co-test and endocervical examination, accompanied by watchful waiting on the part of the patient[2]. However, despite an 80-90% regression rate in

these cases, this situation makes many women anxious, stressed, anxious and uneasy during the waiting period. Treatment with Papilocare® vaginal gel *(Coriolus versicolor)* has shown a clinical benefit in these patients with LSIL, both in efficacy for the treatment of low-grade cervical lesions and in HPV clearance after six months of treatment[6,7]. Improved cervical re-epithelialisation, reduced perceived stress and high adherence to treatment have been reported, even in women over 40 years of age[8]. We also know that the main factor in the development of cervical cancer and its precursor lesions is the persistence of HPV infection, so early clearance of the virus can reduce this persistence with a beneficial effect for the patient. It therefore seems debatable, based solely on the spontaneous regression rate of LSIL, to maintain watchful waiting alone, especially if the beneficial effect of *Coriolus versicolor* on these patients is known, with its good tolerance and low rate of associated adverse effects[6]. In the case in question, after six months of treatment with Papilocare® vaginal gel, the cytology result normalised, HPV was negative and, despite being a type 3 transformation zone, changes were observed in the cervical re-epithelialisation of the glandular orifices. Although it is true that the patient concomitantly received a complete vaccination regimen, we know that to date the potential therapeutic role of this has not been established[9]. Therefore, this treatment can be a useful tool for our patients during the waiting period, improving cervical re-epithelialisation, clearing the virus and reducing stress for the patients, without detracting from the importance of the other usual approaches such as vaccination.

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LSIL-CIN 1 TREATED WITH *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL (PAPILOCARE® VAGINAL GEL) AND IMMUNITY BOOSTER (PAPILOCARE® IMMUNOCAPS) IN AN IMMUNOCOMPROMISED PATIENTS. VIRAL CLEARANCE AND RESOLUTION OF THE CERVICAL LESION

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ABSTRACT

Genital infection with human papillomavirus (HPV) is the causative agent of almost all cases of cervical cancer and its precursor lesions. Specifically, high risk oncogenic HPV genotypes (HR-HPV) 16 and 18 account for 70% of cases of cervical cancer and ten other types (HPV 45, 31, 33, 52, 58, 35, 59, 56, 51 and 39) account for 25-35% of the remaining cases. More than 90% of HPV infections are transient, i.e. they disappear spontaneously. However, a higher persistence of HR-HPV infection has been demonstrated in women aged 30 years and older, which is a risk factor for progression of premalignant lesions. Studies of *Coriolus versicolor*-based vaginal gel are extremely promising as they have provided clinical evidence of improved viral clearance, re-epithelialisation, re establishment of the vaginal microbiota and increased immunity to HPV.

KEY WORDS

HPV. *Coriolus Versicolor*. Viral clearance.

CLINICAL HISTORY

43-year-old patient referred by haematology for a gynaecological check-up following a recent diagnosis of Hodgkin's lymphoma, for which she is currently receiving chemotherapy treatment. Last gynaecological check-up six years ago, coinciding with her last pregnancy. Cytology result was LSIL associated with HR-HPV 39 and 58. Not vaccinated against HPV.

PHYSICAL EXAMINATION

She was offered colposcopy +/- possible biopsy. Thin acetowhite epithelium was evident at the level of the squamocolumnar junction. After

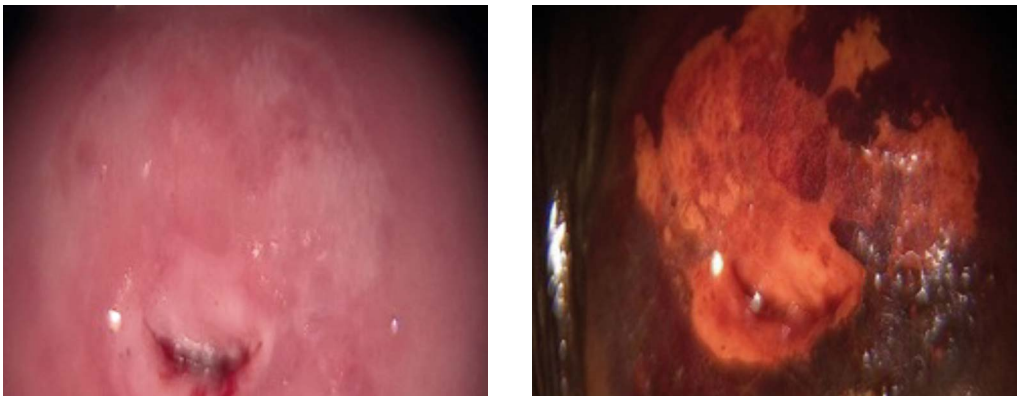

FIGURE 1.

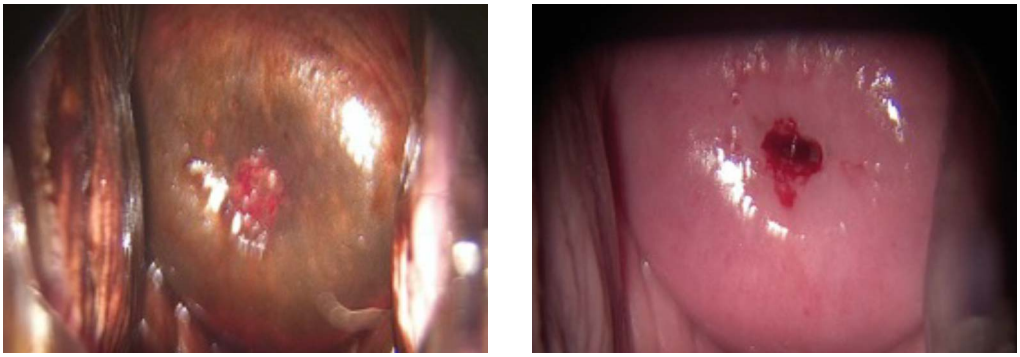

FIGURE 2.

staining with Lugol's iodine, the same area was iodine negative. A biopsy was performed, giving a histological result of LSIL/CIN 1 (Fig. 1).

TREATMENT AND PROGRESS

Treatment was offered with Papilocare® Vaginal Gel and Papilocare® Immunocaps for six months according to the regimen recommended in the summary of product characteristics, with re-evaluation after completing the treatment. Healthy lifestyle habits, regular use of condoms and nonavalent HPV vaccination were recommended. After six months, another cytology was performed and LSIL persisted, the colposcopic findings were similar to the previous ones and the result of the biopsy was LSIL/CIN 1. The same treatment was repeated for a further six months to complete the full year, with a subsequent follow-up visit. At the next examination, a co-test was performed, which was negative and the colposcopic examination was normal (Fig. 2). The patient reported good adherence to

treatment and excellent tolerance, not reporting any side effects.

FINAL DIAGNOSIS

LSIL-CIN 1 treated with *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal Gel) and immune reinforcement with Papilocare® Immunocaps in a patient who is immunocompromised due to cancer and chemotherapy, with complete resolution of the cervical lesion and viral clearance.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Papilocare® is a medical device in the form of a gel for vaginal application based on *Coriolus versicolor* and other phytotherapeutic ingredients. *Coriolus versicolor* is a fungus of Chinese origin containing β-glucan polysaccharides with known immunostimulant properties and antimicrobial and antitumour activity. This fungus acts as an immunomodulator and its β-glucans can cause selective apoptosis on dysplastic cells without affecting healthy cells. In patients with HPV infection, a regression effect of low-grade squamous intraepithelial lesions of the cervix has been observed in addition to viral clearance. The PALOMA clinical trial has demonstrated normalisation of ASCUS/LSIL lesions caused by HPV (cytological normalisation and concordant colposcopy) after six months of treatment in 85% of women treated with Papilocare® vaginal gel compared to 65% in the control group. The PALOMA study has also demonstrated viral clearance after six months of treatment in 63% of women with high-risk HPV compared to 40% in the control group. All patients (and especially the subgroup of immunocompromised patients) may benefit from treatment with Papilocare® Immunocaps to improve the microbiota, boost immunity and enhance viral clearance.

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HPV-POSITIVE ASCUS AND CONDYLOMATA IN A YOUNG WOMAN

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ABSTRACT

30-year-old woman with cytology results of ASCUS, non-16/18 HPV and genital condylomata treated with Papilocare® vaginal gel and Papilocare® external genital gel.

KEY WORDS

ASCUS. HPV. Condyloma. Papillomavirus. Papilocare®.

CLINICAL HISTORY

A 29-year-old woman visited our clinic with no medical history of interest but a cytology result of: ASCUS and non-16 or 18 high-risk HPV, asymptomatic. She had been vaccinated for HPV with Gardasil® 9.

PHYSICAL EXAMINATION

The examination revealed four millimetric lesions in the perineum compatible with condylomata.

The cervix showed mild cervical ectropion. The rest of the examination was normal.

DIFFERENTIAL DIAGNOSIS

The cytology results and the finding of lesions compatible with condylomata were explained to her.

TREATMENT AND PROGRESS

The patient was concerned about the ASCUS cytology result, so she was offered treatment with Papilocare® vaginal gel followed by an annual check-up with cytology and HPV testing.

In addition to recommending condom use and a healthy lifestyle and diet, treatment was started for condylomata with 5% imiquimod three times a week for 16 weeks[1].

The lesions were followed up by the nursing staff at our clinic.

She was re-evaluated after six months, and the condylomata persisted, of a similar size to the one observed at the first consultation. In addition, the patient had pruritus.

Papilocare® external genital gel was prescribed.

At the annual check-up, the external lesions had disappeared. Another Pap

smear and HPV test were performed. The result was negative.

FINAL DIAGNOSIS

ASCUS and non-16 or 18 high-risk HPV. Genital warts.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

This case is a common example of a young patient in whom adjuvant treatment with Papilocare® vaginal gel and Papilocare® external genital gel has been successful.

Human papillomavirus (HPV) is a virus that affects the mucous membranes and skin, and there are many types of HPV. High-risk HPVs are those capable of causing cancer precursor lesions. Low-risk HPVs are responsible for non-malignant lesions such as genital warts.

Up to 75% of women and 85% of men are infected with HPV in their lifetime, with the majority (90%) being transient infections[2].

Cytology with atypical squamous cells of undetermined significance (ASCUS) is the most common cytological abnormality, representing 3.6% of these cases.

The prevalence of human papillomavirus infection in women with ASCUS is high, especially in young patients, reaching 70% in those under 25 years of age[3].

In the presence of a cytology with ASCUS, HPV testing allows an estimation of the risk of a high-risk lesion (HSIL or CIN 3). It can also be performed on the same sample (reflex) without the need for the patient to visit again[4].

The risk of an HSIL or CIN 3 lesion is low if HPV is negative[5].

If it is positive for HPV, the risk will vary depending on the genotyping, with the immediate and five-year risk of HSIL/CIN 3 in women with ASCUS cytology and HPV 16/18 positive being 9% and 13% and decreasing to 2.8% and 4% if negative for HPV 16/18, respectively[6].

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VULVAR, PERIANAL AND CERVICAL CONDYLOMATOSIS IN A PREGNANT WOMEN. EFFICACY OF ADJUVANT TREATMENTS

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ABSTRACT

Pregnant woman with vulvar, perianal and cervical condylomatosis. Treatment with trichloroacetic acid and adjuvant treatment with *Coriolus versicolor*-based external genital gel during pregnancy and a Reishi extract-based food supplement in the postpartum period. Resolution of all condylomatous lesions at 35 weeks and no recurrence throughout pregnancy. Finally, ventouse delivery without incident. Puerperium also without recurrence.

KEY WORDS

Vulvar condylomata. Cervical condyloma. Pregnancy. Puerperium. Papilocare® external genital gel. Papilocare® Immunocaps.

CLINICAL HISTORY

Age: 36 years.

Family history: None of interest.

Personal history: No known drug allergies. Crohn's disease. Surgical interventions: Dilation and curettage (VTP). Regular medication: Yodocefol. No toxic habits.

Obstetric and gynaecological history: Menarche: 12. Menstrual bleeding/cycle: 4-5/28-30. LMP: 20/07/2022. EDD: 20/04/2023. G2 P0 (current pregnancy in progress) A1(VTP). Previous cytological screening within the normal range. HPV vaccine: no.

Pregnant woman who starts check-ups at the Cervical Pathology Unit of our centre for vulvar and perianal condylomatosis and suspected cervical condylomatosis, diagnosed in the gynaecology emergency department at 28+4 weeks.

PHYSICAL EXAMINATION

Examination by gynaecology emergency department: External genitalia with 5-6 condylomatous lesions in the introitus, approx. 6-8 condylomatous lesions on both labia majora and 3-4 condylomatous lesions in the right perianal region. Vagina normal, no lesions. Cervix with a lesion suspicious of cervical condyloma measuring approx. 1.5 cm on the posterior lip.

Vaginal examination: no findings except induration at the level of suspected cervical condyloma, closed cervix.

1st visit to Cervical Pathology Unit at 29+3 weeks: Vulvar, perianal and cervi-

cal condylomatosis as described in the previous examination by the emergency department. Colposcopy (with acetic acid) and exocervical biopsies showed cervical condylomatosis with no other findings of malignancy or dysplasia. Biopsies of vulvar lesions found to be condylomata.

DIAGNOSIS

Vulvar, perianal and cervical condylomatosis in a pregnant women.

TREATMENT AND PROGRESS

Treatment with trichloroacetic acid (TCA) at 80 and 90% at vulvar, perianal and cervical level was proposed to the patient, who agreed to the treatment. She attended weekly sessions from 29+3 to 32 weeks. Disappearance of vulvar and perianal condyloma at 31 weeks, but persistence of cervical condyloma. At the 32-week check-up (one week without external TCA), eight new vulvar condylomata appeared and it was decided that treatment should be resumed with weekly TCA, prescribing Papilocare® external genital gel (two applications per day).

It was necessary to continue with the prescribed treatment until 35 weeks, at which time the complete disappearance of both vulvar and cervical lesions was achieved. We recommended that the patient should continue to use Papilocare® external genital gel until the end of pregnancy.

The patient had no recurrence of vulvar or cervical lesions from 35 weeks until delivery.

Delivery

Vaginal delivery with ventouse at 39+4 weeks. Episiotomy.

Newborn: Female. Weight 3280 grams. Apgar 8/10.

Puerperium

Within normality. Breastfeeding.

One week after delivery, for the patient's comfort (due to extensive episiotomy), Papilocare® external genital gel (two applications per day) was replaced by Papilocare® Immunocaps (one oral capsule after meals). HPV vaccination was recommended, with follow-up by the Cervical Pathology Unit. She was also referred to General Surgery for proctological evaluation.

FINAL DIAGNOSIS

Resolution of vulvar and perianal condylomata and cervical condyloma after treatment with TCA and synergistic treatment (during pregnancy, Papilocare® external genital gel and during the postpartum period, Papilocare® Immunocaps).

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Condylomata are the clinical expression of infection with certain types of HPV, primarily HPV types 6 and 11 (both low risk).

The cervical location is the least common and is usually associated with condylomata in other locations, as in the case we present at the vulvar and perianal level.

There is a higher frequency of condylomatous lesions during pregnancy due to alterations in the immune system.

In pregnancy, an increase in the size of the lesions is typical, as are recurrences. Condylomata can be transmitted from mother to newborn and can lead to certain complications such as laryngeal papillomatosis.

The recommendation with regard to treatment is to achieve the disappearance of the condylomata before the onset of labour, since the risk of viral transmission is also lower if there are no lesions, even if it does not disappear completely. The first-choice treatment is 80-90% trichloroacetic acid. It should be applied locally by the physician, two to three times a week for a maximum of three weeks. It is effective and is not absorbed systemically.

In this case, the usefulness of treatment with Papilocare® external genital gel as an adjuvant to trichloroacetic acid is demonstrated and it has no contraindications in pregnancy. The usefulness of treatment with Papilocare® Immunocaps is also demonstrated, which likewise has no contraindications in the postpartum period.

Papilocare® external genital gel: non-hormonal gel with moisturising and re-epithelialising properties. Seven ingredients of natural origin, including *Coriolus versicolor* extract and Bioecolia®, a prebiotic that promotes the growth of beneficial bacteria such as *Lactobacillus crispatus;* hyaluronic acid; beta-glucan; Centella asiatica; neem extract and aloe vera extract. Two applications per day, one of which should be at night, before going to bed.

Papilocare® Immunocaps: a Reishi extract-based food supplement that contributes to the normal functioning of the immune system and mucous membranes. It helps to normalise the vaginal microbiota and strengthen the body's natural defences. The recommended daily dose is one capsule per day. No contraindications in the postpartum period or for breastfeeding.

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EFFICACY OF *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL (PAPILOCARE®) IN THE TREATMENT OF LSIL-CIN 1 CERVICAL LESIONS

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ABSTRACT

The prevalence of HPV infection in Spain is estimated to be 14.3% (CLEOPATRE study). This figure rises to 28.8% among women aged 18 to 25 years[1].

Squamous intraepithelial lesions (SIL) and cervical cancer caused by HPV infection are a major public health problem and are of growing public concern.

Most lesions caused by HPV infection are low-grade squamous intraepithelial lesions (LSIL) with low potential for progression to invasive cancer. However, the relatively long time it takes to cure them and the lack of reliable indicators to predict which lesions are likely to progress are reasons for patients to demand some form of treatment or measure to accelerate the clearance of HPV infection.

The current therapeutic option for which we have the most evidence and experience for these clinical situations is *Coriolus versicolor*-based vaginal gel (Papilocare®).

KEY WORDS

HPV. Squamous intraepithelial lesion (SIL). *Coriolus versicolor*.

CLINICAL HISTORY

A 44-year-old patient referred to the lower genital tract pathology clinic for screening cytology with findings compatible with **low-grade squamous intraepithelial lesion (LSIL).** The patient also provided a positive HPV test for variant 16. She denied drug allergies. No associated medical conditions. Two previous obstetric curettages, two caesarean sections and one tubal blockage. G4P0C2A0. She was not taking any medication and was using barrier methods. She had no gynaecological or medical symptoms. Stable partner. Not vaccinated for HPV.

PHYSICAL EXAMINATION AND ADDITIONAL TESTS

Good general condition. Vulva and vagina normal. Colposcopy adequate,

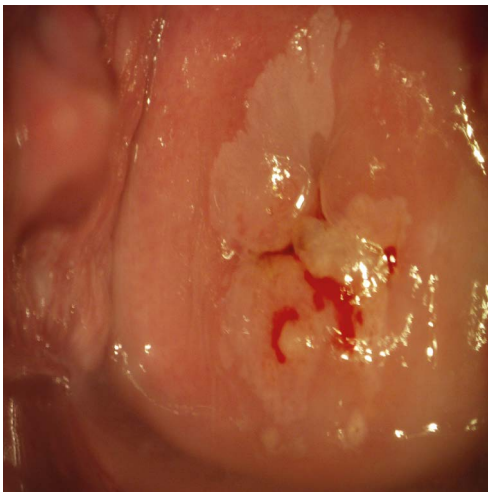

FIGURE 1. Colposcopy at initial visit.

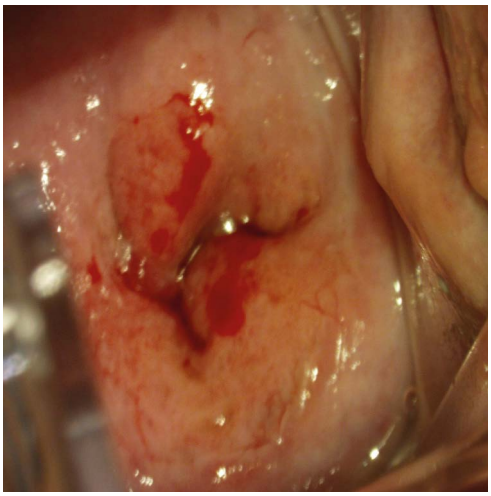

FIGURE 2. Colposcopy following treatment with Papilocare®.

satisfactory TZ 2. Fine acetowhite lesions at 1, 6 and 11 o'clock (Fig. 1). Lugol's iodine staining negative at these locations. Colposcopic changes consistent with low-grade HPV infection, G1. Biopsies were taken from these lesions, with a result of LSIL/CIN 1.

TREATMENT AND PROGRESS

Annual screening, condoms and HPV vaccination were recommended. However, the patient expressed her anxiety about the diagnosed lesion and asked for a more active therapeutic approach. We proposed starting treatment with Papilocare® vaginal gel, with one daily vaginal application for 21 days and then one daily application every other day for up to six months. She was asked to attend a six-month check-up to assess the response to treatment. At this check-up, the colposcopy and cytology performed showed no abnormal changes (Fig. 2). However, an HPV test that was performed was still positive for HPV 16. We recommended that the patient should continue with Papilocare® for a further six months and we would see her after completing the treatment. At this third check up, all the tests performed, colposcopy, cytology and even the HPV test were negative, so we could inform her that the LSIL and HPV infection had been completely cured. These findings were confirmed in two successive annual check-ups by co-testing, and the patient was discharged from our unit and returned to routine cervical cancer screening.

FINAL DIAGNOSIS

Low-grade squamous intraepithelial lesion due to HPV 16 with cytological histological resolution at six months and microbiological resolution at 12 months after the application of Papilocare® vaginal gel.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Currently, around 370,000 low-grade lesions (LSIL or ASCUS) and 2,500 cases of cervical cancer are diagnosed each year in Spain. Approximately two million women test positive for HPV[1].

Spontaneous clearance of HR-HPV occurs in approximately 29% and 41% of cases at 6 and 18 months, respectively[2].

The approach to HPV infection in young patients with low-grade lesions is generally follow-up and informing the patient about lifestyle recommendations that may facilitate earlier clearance of the virus.

It is common for many women to feel uneasy when they learn of their infection and demand an active attitude that does not condition future pregnancies and does not expose them to risky procedures such as cervical conisation. A safe, non-surgical treatment that can help repair low-grade lesions and improve viral clearance could be very useful in these circumstances.

Papilocare® is the first and only treatment indicated in Europe to prevent and treat low-grade HPV-dependent lesions[3].

Papilocare® (Procare Health, Valencia, Spain) is a *Coriolus versicolor*-based vaginal gel that combines ingredients with known properties such as hydration, tissue regeneration and balancing of the vaginal microbiota (hyaluronic acid, Centella asiatica, aloe vera and α-glucan oligosaccharide), some of them contained in niosomes and phytosomes, with other ingredients with proven positive effects on both HPV-dependent cervical lesions and HPV clearance (*Coriolus versicolor*, Azadirachta indica and carboxymethyl-β-glucan)[4].

The PALOMA clinical trial has demonstrated efficacy in the normalisation of ASCUS/LSIL HPV lesions (cytological normalisation and concordant colposcopy) after six months of treatment in 85% of women treated with Papilocare® vaginal gel compared to 65% in the control group. The PALOMA study has also demonstrated viral clearance at six months of treatment in 63% of women with high-risk HPV compared to 40% in the control group[4].

The PAPILOBS study is a clinical practice-oriented study, pending publication, whose main objective is to evaluate the effectiveness of Papilocare® in the repair of low-grade cervical lesions caused by HPV (normalisation of ASCUS or LSIL cytological alterations with concordant colposcopic imaging) in HPV-positive women over 25 years of age.

Intermediate results for 97 patients evaluated showed that after six months of treatment, 66% of the patients had normal cytology and negative concordant colposcopy, reaching 91% normalisation at 12 months. On the other hand, HPV clearance at six months occurred in 63% of patients, reaching 82% clearance at 12 months[5].

The case described here would be prototypical of the PAPILOBS study. In daily clinical practice, treatment with Papilocare® in patients with low-grade cervical lesions can promote lesion repair and even clearance of HPV infection as early as six months and, importantly,

prolonging treatment up to 12 months can further improve the chances of lesion repair and clearance of viral infection.

Therefore, the use of products such as Papilocare® can have a clear impact on the short-term normalisation of the clinical situation of women with low-grade cervical lesions caused by HPV with the consequent benefit in terms of the physical and psychological health of our patients.

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TREATMENT OF VULVAR CONDYLOMATOSIS WITH PAPILOCARE® EXTERNAL GENITAL GEL AND IMMUNOCAPS.. A CASE REPORT

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ABSTRACT

Condylomata acuminata or genital warts are the clinical expression of infection by certain types of human papillomavirus (HPV) that are considered to be of low oncogenic risk. A 45-year-old female patient consulted about vulvar lesions of three months' duration. The external genitalia showed multiple condyloma-type lesions with a raised, hyperpigmented, broad-based plaque (sessile) covering both labia majora. Adjuvant treatment was offered with Papilocare® external genital gel *(Coriolus versicolor*-based) and Papilocare® Immunocaps. After three months, the patient came for a check-up and the vulva was observed to be free of lesions. She returned to the clinic after four months with a 7-week pregnancy and further genital lesions, and again external genital gel was prescribed, with a complete improvement of the symptoms in two months.

KEY WORDS

Condylomata acuminata. Genital warts. HPV. Papilocare®.

CLINICAL HISTORY

The patient is 45 years old, TPAL 0-0-1-0, not vaccinated against HPV, with no personal or family history of interest, non-smoker, currently in a stable relationship, with a desire to become pregnant. Last gynaecological check-up at our centre one year ago, which was normal. Consultation for vulvar lesions of three months' duration.

PHYSICAL EXAMINATION

Genitals: External genitalia with multiple, broad-based (sessile), raised, hyperpigmented, plaque-like condyloma-type lesions covering both labia majora. Vulvoscopy was performed with acetic acid and the result was acetowhite lesions. It was decided that a gynaecological examination should be carried out, leading to the following findings:

- Cervical cytology: satisfactory, negative for malignancy.
- Cervical HR-HPV genotyping: positive for 39, 51, 56, 73 (high risk) 6, 42 (low risk).
- Colposcopy: transformation zone type 2, normal with acetic acid and

Lugol's iodine. No evidence of cervical condylomata.

- Vaginoscopy: normal with acetic acid and Lugol's iodine. No evidence of vaginal condylomata.

Perianal condylomata were ruled out in the patient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should be made with vulvar papillomatosis, a physiological finding that differs in morphology, as it presents papillae with separate bases, whereas condylomata acuminata are acetowhite lesions that have a common base. Other papular lesions include *molluscum contagiosum* and seborrhoeic keratosis.

TREATMENT AND PROGRESS

Given the diagnosis of vulvar condylomatosis, the patient was offered the option of conservative management, which she accepted. Prophylactic HPV vaccination was indicated, and adjuvant treatment with Papilocare® external genital gel *(Coriolus versicolor*-based) and Papilocare® Immunocaps was offered. Three months later, the patient came for a check-up. She has undergone full treatment, reporting no adverse effects. Physical examination revealed no lesions on the vulva, and complete regression of the lesions was evident. She was told to return after three months for an HPV typing test. She was found to be clear from the virus and no lesions were found upon physical examination. She returned to the clinic after four months with a 7-week pregnancy and further genital lesions. Physical examination revealed five condylomatous lesions measuring 3 mm in diameter; external genital gel was prescribed again, with complete clinical improvement in two months.

DISCUSSION AND SIGNIFICANCE OF THE CASE

Papillomavirus infection is an infection that involves the entire anogenital area. CO_2 laser is one of the treatments indicated for this condition, especially if it covers large areas. However, it is a technique that may not be within the reach of some patients. This is why the use of Papilocare® external genital gel was suggested in this case, as its components have been shown to improve genital lesions, combining the benefits of hydration, tissue regeneration, balancing of the vaginal microbiota and viral clearance, combined with Immunocaps® to improve the patient's immune system.

Pregnancy favours the appearance of condylomata in the anogenital region, mainly the vulvoperineal area. During pregnancy, genital warts grow and spread considerably due to increased vascularisation and humid conditions, as well as oestrogen concentration and decreased immunity.

Although prospective studies with an adequate sample size are needed, adjuvant treatment of vulvar condylomatosis with these products seems appropriate, both to facilitate healing of the lesions and because of their likely stimulation of HPV clearance from the genital mucosa.

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FLORID VAGINAL CONDYLOMATOSIS IN AN IMMUNOCOMPROMISED PATIENT. ADJUVANT TREATMENT WITH PAPILOCARE®

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ABSTRACT

We present the case of an immunosuppressed patient with florid vaginal condylomatosis.

KEY WORDS

Immunosuppressed patient. Condylomatosis. Papilocare®.

CLINICAL HISTORY

36 year-old patient monitored at the rheumatology clinic for systemic lupus erythematosus (SLE), on treatment with Dacortin and belimumab and Tromalyt.

She was referred to the cervical pathology clinic because her partner had condylomata on his penis and she reported noticing nodules in her vagina. Smoker of 10 cigarettes/day.

PHYSICAL EXAMINATION

On speculum examination, multiple wart-like formations are observed on both lateral surfaces and the vaginal fundus.

Liquid-based cytology was performed, the result of which was LSIL, in addition to an HPV 16 (HOR) and HPV 6 (LOR) test.

Colposcopy: adequate for assessment. No abnormal acetowhite changes. Schiller's test was negative. No cervical condylomata.

Vaginoscopy: multiple wart-like formations were observed on both lateral surfaces and the vaginal fundus, turning acetowhite after application of 3% acetic acid.

Vulvoscopy (5% acetic acid) has two tiny condylomata in the introitus, smaller than 0.5 cm.

TREATMENT AND PROGRESS

Topical treatment with trichloroacetic acid (TCA) on the vaginal condylomata was started and was well tolerated. Treatment with Papilocare® was also recommended as adjuvant therapy and to prevent recurrences (for six months) and HPV vaccination was advised. Two separate TCA sessions were required over a period of one month. Finally, the patient presented complete remission

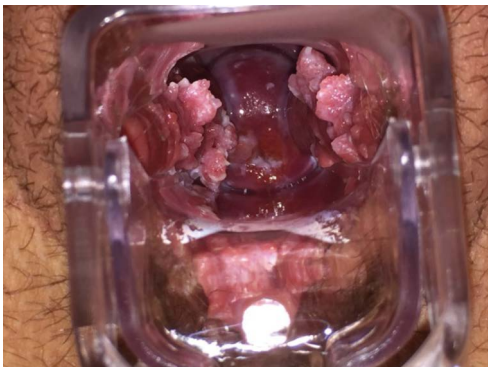

FIGURE 1.

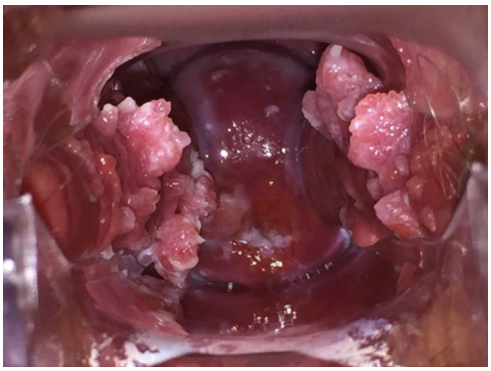

FIGURE 2.

of the condylomata, which has been maintained to date.

FINAL DIAGNOSIS

Florid vaginal condylomatosis in an immunocompromised patient resolved with trichloroacetic acid and Papilocare®.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Women with florid condylomatosis may require combination therapies, not only destructive but also to prevent recurrence, which can occur in 30% of cases. The treatment approach in immunocompromised patients does not differ from the approach in immunocompetent patients. However, treatment of the warts is less successful in immunocompromised patients. Longer courses of treatment and closer monitoring may be necessary.

It should be noted that in the case of condylomata acuminata on vaginocervical and/or anal mucosa, the use of podophyllotoxin, imiquimod and sinecatechins should be avoided due to the risks of severe mucositis and possible systemic absorption of these drugs.

Immunosuppressed patients are highly susceptible to persistent HPV infection and are at increased risk of developing premalignant and malignant cervical lesions and condylomata acuminata. The prevalence of HPV in these populations often exceeds 30% and a high proportion of cytological abnormalities is also observed. Condylomata acuminata in these patients are more frequent, larger, occur in rare locations and are resistant to treatment and recurrent. Therapies that activate the immune system (imiquimod and sinecatechins) may be less effective, while trichloroacetic acid and destructive treatments (cryotherapy, CO_2 laser) are more effective. Excisional therapy is indicated in cases where histological examination is required to rule out neoplastic lesions associated with condylomata, which are common in this group of patients. Sometimes, the severity and refractoriness of the lesions make it necessary to use multiple treatments

sequentially or in combination, or experimental or novel treatments, as was done in the patient in the clinical case with Papilocare®, achieving a very good response. Although more studies are needed, it appears that adjuvant treatment of vulvar lesions caused by HPV may be a good option as an adjunct to destructive topical treatments.

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RECURRENT VULVOVAGINAL CONDYLOMATOSIS

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ABSTRACT

We present the case of a patient diagnosed with persistent, recurrent vulvar and vaginal condylomata.

Genital warts are the most common clinical manifestation of HPV. In Spain, 22,000 new cases are diagnosed in women each year, while at European level it is estimated that approximately 8% of the population has been diagnosed with this lesion at least once in their lifetime[1]. Condylomata acuminata or genital warts are the clinical expression of infection by certain types of human papillomavirus (HPV) that are considered to be of low oncogenic risk (6 and 11). They are now considered one of the most common sexually transmitted diseases, with an increasing incidence in most populations [2].

There are multiple forms of presentation and spread of the lesions (from very localised forms with little disease volume to very extensive forms with multicentric involvement of the anogenital tract). Sometimes, the absence of a single effective therapy for all patients forces us to choose between the different procedures available (excisional, destructive, topical, etc.) on an individual basis.

We must not forget the high rate of recurrence after treatment due to the appearance of new lesions in treated or untreated areas[3]. Genital HPV infection is one of the most common sexually transmitted infections. However, condylomata acuminata are not included in most countries' surveillance systems, so global epidemiology data are limited.

KEY WORDS

Condyloma. HPV. Wart. Vulva. Immunosuppression.

CLINICAL HISTORY

26-year-old patient from Mexico, who came to us with warty lesions that had appeared on her vulva six months ago.

No family or personal history of interest.

Her gynaecological-obstetric history indicated that she had started appropriate cervical cancer screening with the last cytology in 2022: signs suggestive of HPV infection. Candidiasis.

Treated in her country with sinecatechins (Veregen®) ointment twice a day but they failed to disappear. The patient has a negative memory of this treatment due to intense stinging, local itching and discomfort, which is why she is asking about alternative therapies.

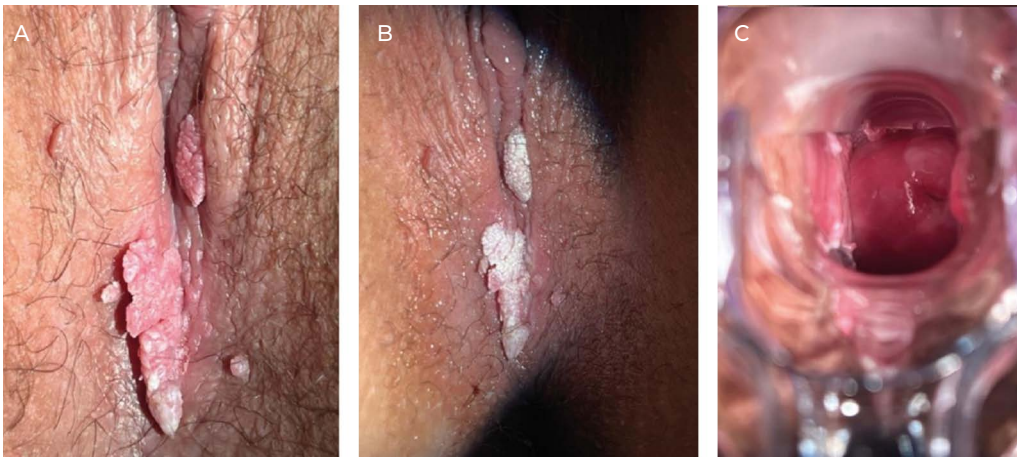

FIGURE 1. A) Multiple vulvar condylomata. B) and C) After application of Verrutop.

Non-smoker, started sexual intercourse at 16 years of age, not using contraception and not vaccinated against HPV, but she has decided to start now.

PHYSICAL EXAMINATION

We observed five raised warty lesions, some pinkish and some dark and more pigmented, ranging in size from 2 mm to 30 mm (Fig. 1).

Vulvoscopy was performed with colposcopy and staining with 2% acetic acid. Vaginoscopy and colposcopy were also performed, revealing multiple condylomata in the vagina and cervix (Fig.2).

Physical examination is the *gold standard* in the diagnosis of this condition.

Lesions should not be biopsied performed in a standardised manner, only if the response to treatment is not as expected, if signs of malignancy are suspected or in girls with suspected sexual assault[5].

DIFFERENTIAL DIAGNOSIS

Condylomata acuminata (CA) are the clinical expression of infection with certain types of HPV that are considered to be of low oncogenic risk, mainly HPV types 6 and 11. Condyloma acuminatum is a common and highly infectious STI, which can be psychologically distressing to patients because of its tendency to recur after treatment, to cause malignancy and to be transmitted to sexual partners[6].

The differential diagnosis should also be made with vulvar vestibular papillomatosis, a physiological finding that differs from CA in that its papillae are not acetowhite and each of them has an independent base, whereas CA have a common base with a cockscomb surface. Other papules include molluscum contagiosum and seborrhoeic keratosis[7].

TREATMENT AND PROGRESS

Before starting a treatment plan, an adequate explanation is necessary

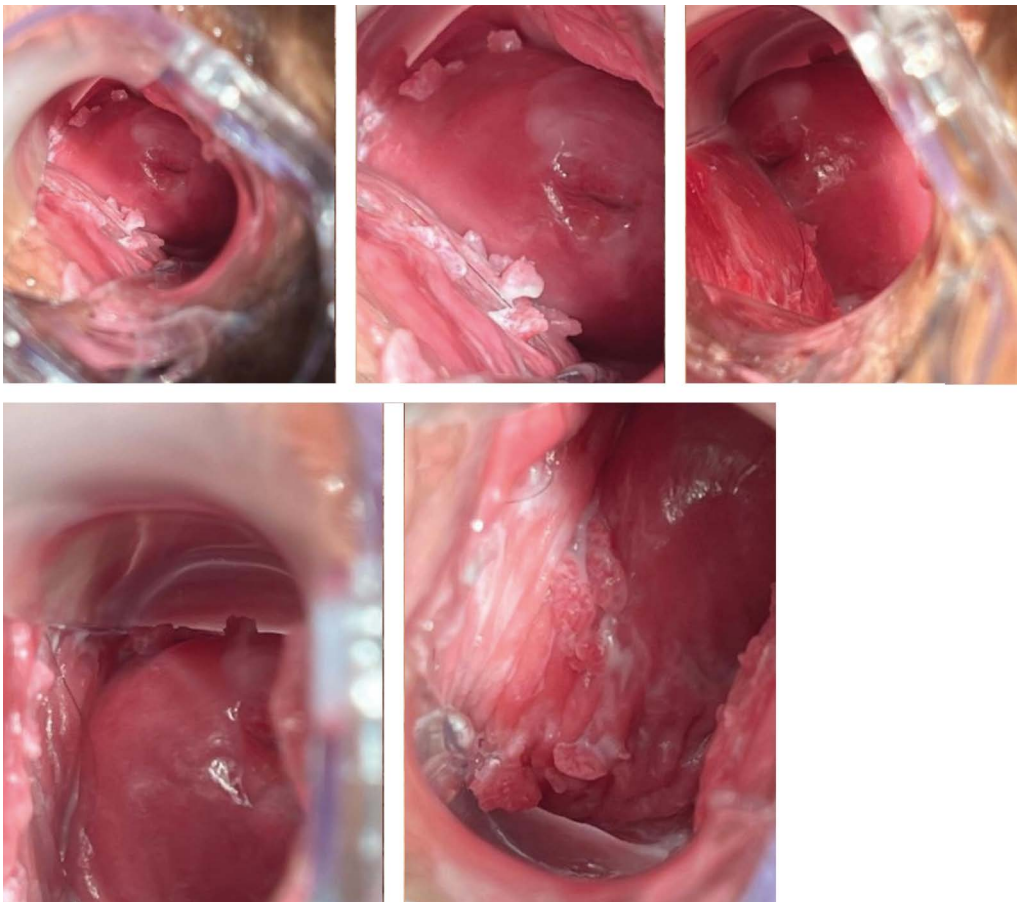

FIGURE 2. Vaginal and cervical condylomata.

so that the patient understands: the evolution of the process, the purpose of treatment and the therapeutic possibilities, the possible adverse effects and the cure and recurrence rates.

In the case of this patient, we started the first session by applying Verrutop® (Nitrizinc Complex (TM): Organic acids (acetic, lactic and oxalic), inorganic acids (nitric), copper and zinc salts) to the vulvar area on the condylomata. This product allows for one or two more applications in the same session, if necessary. We also applied Aldara® (imiquimod) locally to the vaginal and cervical condylomata. This patient underwent a second round of combined condyloma treatment and the vast majority of the condylomata remitted.

On her third visit, the patient stated that she had intercourse without a condom with her partner, who had developed condylomata. She asked for information about the most effective and quickest therapeutic alternative. In this regard, she was informed about laser

therapy and the possibility of complementary adjuvant treatment with *Coriolus versicolor*-based vulvar gel (Papilocare®) for five weeks, applied at night, except during menstruation, in the area treated for condylomata. It was emphasised that the purpose of such adjuvant therapy is that it helps to re-epithelialise and protect this area.

She travelled to her home country and underwent definitive laser therapy for three persistent vaginal condylomata. At the end of the treatment, the patient was clinically re-evaluated and the lesions had disappeared completely and no new warts were observed.

The main therapeutic objective is to achieve their disappearance in order to improve the emotional, psychosocial and psychosexual impact, as well as possible local symptoms, and to reduce transmission, probably without eradicating HPV infection[7].

Final diagnosis: Recurrent vulvar condylomata.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Although experience with the use of Papilocare® vulvar gel is positive, studies with larger numbers of cases are needed to draw statistically significant conclusions regarding its adjuvant and preventive role.

There is no scientific evidence to show that one treatment is clearly superior to another. Treatment must always be individualised. Many variables must be taken into account when choosing the most appropriate treatment, such as: number and size of lesions, area of lesions, presence or absence of keratosis, the doctor's personal experience, possibility of adherence to treatment, toxicity, economic cost, side effects, etc.

In this clinical case, the combination of laser therapy with Papilocare® vulvovaginal gel was appropriate for this patient, who made satisfactory progress with total elimination of the lesions and absence of recurrences six months after treatment.

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PERSISTENT HUMAN PAPILLOMAVIRUS. A CHALLENGE IN ONCOLOGY PATIENTS

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ABSTRACT

A 58-year-old patient with a history of squamous cell carcinoma of the anal canal in complete remission in follow-up at our centre due to abnormal cytology findings and human papillomavirus (HPV) infection. After treatment with conisation with free margins, the virus persisted despite normal cytology results. The patient was treated with Papilocare® and the HPV infection disappeared in successive check-ups.

KEY WORDS

Persistent HPV. History of cancer. Viral clearance..

CLINICAL HISTORY

58-year-old patient who came to our clinic following an abnormal cytological finding. She provides cytology from February 2018: ASC-H HPV positive, low risk: 70.

Family history: none of interest.

Personal history:

- HPV vaccination: no.
- Ethnicity: Hispanic.
- Personal history: differentiated squamous cell carcinoma of the anal canal in 2017 treated with chemoradiotherapy, in complete remission.
- Smoker: no.
- Initiation of sexual relations: aged 18 years.
- Number of sexual partners: not sure.
- Stable sexual partner: yes.
- Previous pregnancies: G2 EE1 (ectopic pregnancy treated by laparoscopic salpingectomy) P1.
- Contraceptive method: none.

**The patient has been informed and consents to the publication of her clinical case and the dissemination of images and clinical data for teaching purposes while respecting her anonymity, having signed the informed consent form.*

PHYSICAL EXAMINATION

In the lithotomy position, a thorough colposcopic examination of the vulva and vagina was performed. Staining with 2% acetic acid of the entire cervical and vaginal region, followed by application

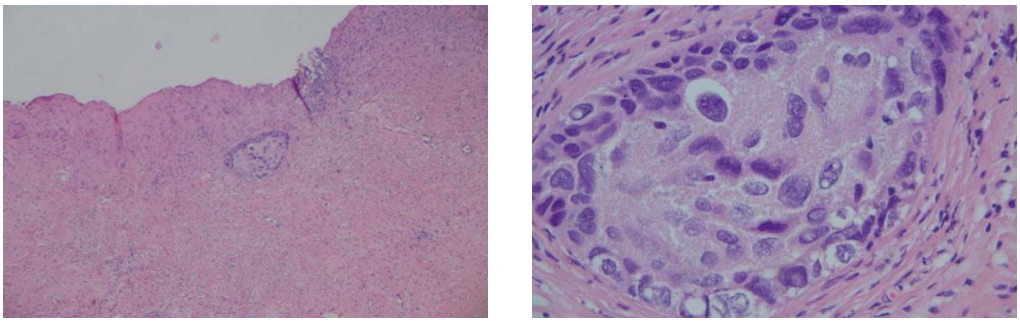

FIGURE 1. Conisation specimen observed under the microscope at 10x and 40x magnification. Histologically, extensive ulceration of the lining epithelium is observed, identifying an endocervical gland in the chorion whose columnar epithelium is replaced by squamous epithelium with high-grade dysplasia (HSIL).

of 2% Lugol's stain. The vulvoscopy and vaginoscopy were normal and the cervix showed a type 1 transformation zone with isolated cervical ulceration, the biopsy result of which was "inconclusive".

DIFFERENTIAL DIAGNOSIS

Cervical ectopia: Cervical erosion, also known as cervical ectopia or cervical ectropion, occurs when there is loss of tissue or eversion of the endocervix exposing columnar epithelium in the vagina.

Atrophy: Thinning of the walls of the vagina due to a decrease in oestrogen levels, causing dryness and inflammation of the area.

Cervicitis: Cervicitis is an inflammation of the cervix. It tends to be caused by an infectious agent, usually sexually transmitted.

Cervical polyp: an excrescent lesion of the cervix, mostly benign, of unknown aetiology, usually asymptomatic.

Cervical condyloma: Benign lesions (usually warts or raised lesions) caused by HPV infection (low oncogenic risk). The most common location is the vulva but they can also be seen in the anal, vaginal or cervical area.

TREATMENT AND PROGRESS

It was decided that a cervical conisation should be performed due to the patient's history and inconclusive biopsy. Anatomical pathology result of conisation specimen (February 2018): HSIL-CIN 3, free margins.

The patient continues to be followed up in our practice. A follow-up cytology was performed at six months, the findings of which were ASCUS, HPV-positive, low risk: 70; Colposcopy was normal.

The importance of HPV vaccination was explained to the patient again, with initiation of vaccination at her primary care centre.

Another cytology was repeated six months later, with the result being "benign cell changes, low-risk HPV positive: 70" and colposcopy was again normal.

After normal cytology and colposcopy with persistence of HPV, treatment with Papilocare® was proposed, with a daily vaginal application for 21 days, with seven days off, for one month, followed by an application every other day for five months to complete six months of treatment.

At the end of treatment (July 2020), co-testing was performed, with normal cytology and negative HPV and normal colposcopy. Co-testing was repeated one year later (July 2021), with normal cytology and negative HPV, again negative one year later (2022) and the patient is currently undergoing regular screening.

FINAL DIAGNOSIS

HSIL treated with conisation, persistent HPV in successive controls treated with a *Coriolus versicolor*-based vaginal gel in a patient with a history of cancer. Complete remission.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

HPV includes a family of viruses with cutaneous and mucosal tropism that cause the most common sexually transmitted disease. The natural history of the virus associates HPV infection, particularly persistent infections, with malignancies such as anogenital (cervical, vulvar, vaginal, penile and anal) and head and neck cancers[1,2].

Through population-based screening we can detect HPV before it causes malignant lesions and propose appropriate treatment[3]. Cytological cervical screening in patients with a history of anal cancer in remission does not differ from the general population[3,4]. In our case, screening in a patient with a history of cancer showed the presence of the virus that had already caused a high-risk lesion (HSIL-CIN 3) and, subsequently, the persistence of the virus in the cervical mucosa despite normal cytology and colposcopy.

Persistent HPV infection with oncogenic types is responsible for approximately 5% of human cancers. Although the genotype carried by our patient (70) is not one of the most aggressive and the patient was not immunosuppressed, she developed a premalignant lesion and her immune system was not able to eliminate the virus in successive check-ups[5,6].

Papilocare® *Coriolus versicolor*-based vaginal gel is currently available on the market for the treatment of women with high-risk HPV, which acts by re-epithelialisation and rebalancing of the vaginal microbiota[7].

In our clinical case, the difficulty of managing persistent infection despite vaccination and lifestyle changes is noteworthy. Expectant management is the norm although, in general, and especially in patients with risk factors for persistence of the virus, Papilocare® has been shown to help eliminate the virus with a simple treatment regimen and, in this case, without any adverse effects.

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USE OF PAPILOCARE® GEL IN THE POST-SURGICAL PHASE OF CONISATION

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ABSTRACT

Conisation is the treatment of choice for high-grade cervical dysplasia caused by HPV. *Coriolus versicolor*-based vaginal gel after surgery speeds up the re-epithelialisation process, reduces the risk of bleeding, promotes healing and improves viral clearance rates.

KEY WORDS

HSIL (CIN). *Coriolus versicolor*. Conisation. Re-epithelialisation.

CLINICAL HISTORY

43-year-old patient who came to our clinic from the cervical pathology unit of Hospital Juan Ramon Jimenez (Huelva), referred from primary care for cytology result showing ASCUS. The patient reports recurrent vaginosis and irregular menstrual periods.

Ethnicity: Caucasian .

Personal history: no chronic diseases of interest. Smoker. Yes

(10-12 cigarettes a day). 3 pregnancies. Bilateral tubal ligation

First sexual intercourse: aged 16 years.

Number of sexual partners reported: 5.

Stable sexual partner: currently yes

Contraceptive method: No

Family history: none of interest

Cytology findings: ASCUS.

Determination of HPV: 16 +

HPV vaccination: No.

PHYSICAL EXAMINATION

In the normal lithotomy (gynaecological) position, an exhaustive examination was carried out using colposcopy; staining the entire cervical and vaginal area with 2% acetic acid as well as staining with Lugol's iodine.

Colposcopy (Fig. 1): Areas of acetowhite epithelium on the anterior lip between 10 and 12 o'clock and on the posterior lip between 6 and 8 o'clock; both seem to extend slightly towards the endocervix. Schiller's test was concordant.

A directed cervical biopsy was performed and a diagnosis of high-grade squamous intraepithelial lesion CIN 3 was made.

DIFFERENTIAL DIAGNOSIS

Treatment and progress: Before starting a treatment plan, an adequate

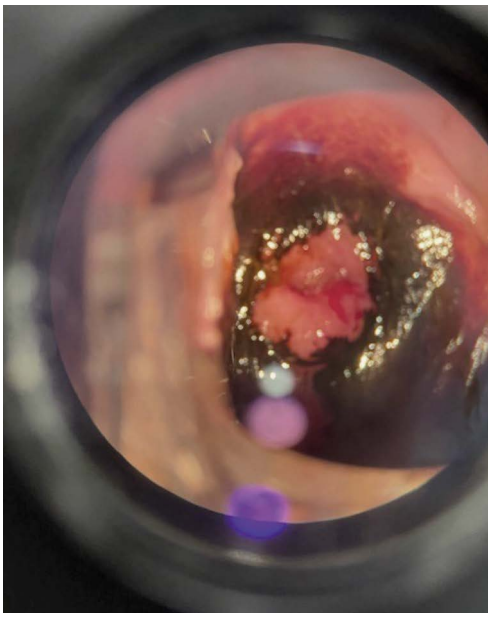

FIGURE 1.

FIGURE 2.

FIGURE 3.

explanation is necessary in order for the patient to understand: The evolution of the process, the purpose of treatment, the possible adverse effects that may occur, the cure and recurrence rates.

It was decided that a LEEP cervical conisation should be performed on an outpatient basis. The definitive diagnosis of the specimen issued by anatomical pathology describes a high-grade squamous intraepithelial lesion CIN 3, concordant with the pre-treatment biopsy, with free surgical resection margins and HPV 16 positive after conisation.

Papilocare® vaginal gel was prescribed once daily at bedtime for three consecutive weeks, and every other day for the following five months.

The patient was scheduled for an appointment after one month to evaluate its effect on the re-epithelialisation of the cervical mucosa. Re-epithelialisation was assessed during the consultation at one month (Fig. 2) and six months (Fig. 3), as was viral clearance, which was measured at six months; in

both aspects, an excellent response to treatment was observed over the following weeks, with HPV negativation and good healing.

FINAL DIAGNOSIS

After excisional treatment with a diagnosis of a high-grade cervical lesion, Papilocare® vaginal gel was prescribed for three weeks consecutively, and on alternate days for the following five months. There is evidence of improvement and rapid epithelialisation of the cervix thanks to the treatment, as well as viral elimination with cytological normalisation, which is evident in the co-test carried out at six months.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

In Spain the prevalence of HPV in women between 35 and 65 years of age is around 15% depending on the test used and the population studied[1]. This means that in primary screening with HPV testing we should perform a triage test on approximately one in ten women. The choice of triage tests in HPV-positive women should take into account the following: 1) the acceptable risk of HSIL/CIN 3+ in the short term (2-3 years), 2) the performance (efficacy and effectiveness) of such tests in detecting premalignant lesions, and 3) the availability and efficiency in a given healthcare setting.

The risk of developing transforming lesions varies greatly between HPV types. Among the 14 types of HPV associated with premalignant lesions and cervical cancer, genotypes 16 and 18 are the ones with the highest capacity for persistence and, therefore, the highest oncogenic risk (between them they cause 70% of all cases of cervical cancer)[2].

Women with HSIL/CIN 2-3 biopsy have a high probability of having or developing cervical cancer. This diagnosis has classically been considered the threshold for indicating excisional treatment of premalignant cervical lesions[3].

The aim of post-treatment follow-up of a cervical lesion is to ensure early diagnosis of any persistence or recurrence of said lesion or HPV-related lesions in the lower genital tract. Lesions detected in the first year of post-treatment follow-up are arbitrarily referred to as persistent lesions. It is assumed that, in these cases, such persistence may be explained as an incompletely excised or treated lesion. Lesions detected after the first year of treatment are referred to as recurrent lesions. In these cases, it is assumed that it may be a new lesion.

The risk of developing cervical cancer among women treated for SIL/CIN is 3-12 times higher than that of the general population over the next 10-20 years[4]. The recommendation for follow-up will depend on the status of the margins.

The recommended use of *Coriolus versicolor*-based vaginal gel after conisation is a patient-friendly strategy with many benefits[5].

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CASE SERIES: EFFICACY OF *CORIOLUS VERSICOLOR* BASED VAGINAL GEL IN WOMEN WITH CIN 2 LESIONS UNDER CONSERVATIVE MANAGEMENT

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ABSTRACT

Through the implementation of protocolised cervical cancer screening, the incidence and mortality of cervical cancer has been significantly reduced. In addition, pre-invasive lesions (CIN) have been appropriately treated and identified.

LSIL/CIN 1 lesions are recognised as initial viral replication and should therefore be treated conservatively. On the other hand, CIN 3 lesions, being an invasive precursor with a high probability of progression to cancer, should be treated by excisional treatment[1]. Despite the major differences in clinical course between CIN 2 and CIN 3, the latest WHO histopathological classification, published in 2014, continues to consider both as a single pathological entity: HSIL. The clinical course and behaviour of CIN 2 lesions is less well understood. Due to the high likelihood of developing cervical cancer, the diagnosis of CIN 2 has classically been considered the cut-off point for excisional treatment by cervical conisation in this group of women[2]. Recently, the possibility of untreated observation for up to two years in women diagnosed with HSIL/CIN 2 with a desire to become pregnant or a lesion smaller than two quadrants, or women with HSIL/CIN 3 under the age of 30 and a lesion smaller than one quadrant has been added. There is a greater likelihood of regression in HSIL/CIN 2-3 lesions in women younger than 30 years, lesions occupying less than two quadrants, if there is HPV clearance or if there is an absence of HPV16+ infection[3].

It is of great importance to avoid overtreatment, especially in young patients, as cervical conisation increases the risk of preterm delivery and third trimester foetal loss.

KEY WORDS

HPV. Papilocare®. CIN 2. Regression.

CLINICAL HISTORY

The cases of patients with a diagnosis of CIN 2 with a desire to become pregnant or a lesion occupying less than two quadrants, in whom a conservative approach has been agreed at our centre (level II hospital) during the last year, have been compiled. The criteria used to reach a consensus on a conservative approach in a woman diagnosed with CIN 2 are as follows[1]:

- Patient acceptance
- Possibility of proper follow-up.
- Adequate colposcopy and visible TZ.

TABLE I. Clinical characteristics, follow-up approach to be followed and use of Papilocare®

	HPV	Age	Follow-up	Approach to follow	Use of Papilocare®
Case 1	16	38	Colposcopy in six months: Grade 2. Biopsy: HSIL/CIN 3. ECC: unchanged. Cytology: negative.	Conisation carried out in primary care: HSIL	No
Case 2	16 58	27	Colposcopy in six months: HSIL/CIN 2. ECC: unchanged.	Continue monitoring	Yes
Case 3	16	28	Colposcopy in six months: Grade 2. Biopsy: HSIL/CIN 2. ECC: unchanged.	Continue monitoring	Yes
Case 4	16 73	37	Colposcopy in six months: Grade 2. Biopsy: HSIL/CIN 3. ECC: unchanged. Cytology: negative.	Conisation carried out in primary care: HSIL	Yes
Case 5	16	29	Colposcopy in six months: Grade 2. Biopsy: HSIL/CIN 2. ECC: unchanged. Colposcopy in 12 months: Grade 1. Biopsy: LSIL/CIN 1. ECC: unchanged. Cytology: negative.	Continue monitoring	Yes
Case 6	16	32	Colposcopy in six months: Grade 1/2. Biopsy: HSIL/CIN 2. ECC: unchanged. Colposcopy in 12 months: Grade 1. Biopsy: LSIL/CIN 1. ECC: unchanged. Cytology: negative.	Continue monitoring	Yes

- Fully visible lesion.
- No endocervical involvement.
- Follow-up cytology-colposcopy every six months.

As mentioned above, it is of particular interest in young women, as the likelihood of lesion regression is higher.

In addition, in women who become pregnant after excisional treatment by conisation, certain obstetric complications, such as premature delivery, may increase[4].

It should be noted that the maximum follow-up time for these patients is two years. If, after two years of follow-up, the lesion persists or progresses during follow-up, excisional treatment will be performed.

PHYSICAL EXAMINATION

A selection of cases has therefore been made, with a total of six women meeting the criteria described above. All the women selected expressly authorised their inclusion in the present study.

The results are shown in the table I.

TREATMENT AND PROGRESS

Of the total cases collected in our case series, we observed that two pa-

tients (33.3% of the total) progressed to CIN 3 during follow-up. In both cases, the approach to be followed was excisional treatment by cervical conisation and endocervical curettage. The pathology results of the surgical specimens confirmed CIN 3 on both occasions, which is consistent with the colposcopy previously performed.

With regard to the other four patients included (66.6% of the total), we note that none of them completed the entire follow-up in terms of duration, described as two years. Specifically, we can observe that in two of the cases included (33.3%), there was persistence at six months follow-up, with HSIL/CIN 2 being reported again in the colposcopy.

Therefore, follow-up had to continue according to the protocol and, if after two years the persistence persisted, cervical conisation would be performed. On the other hand, in two of the patients included (33.3%), it was seen that in the second follow-up colposcopies with biopsy performed at 12 months, the results showed LSIL/CIN 1, which means that regression had occurred. In this case, the approach to be followed would be to perform another control at six months and, if confirmed, to follow up according to the specific protocol according to the test results (cytology, HPV test, biopsy). All the patients were recommended to use Papilocare® vaginal gel with the aim of achieving cervical re-epithelialisation, as it is capable of increasing viral clearance rates as well as HPV-dependent lesion reversal.

The treatment was applied by five of the patients (83.3%), while one patient did not use this treatment (16.6%).

FINAL DIAGNOSIS

We summarise the findings:

- Regression to LSIL: 33.3% (two cases).
- Persistence of HSIL/CIN 2 at six months: 33.3% (two cases).
- Progression to HSIL/CIN 3: 33.3% (two cases).

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

In the literature, it is described that half of the cases of CIN 2 lesions will regress within two years of follow-up, while one fifth of the cases will progress. In our study, we found that it has progressed in one third of the cases. All the cases that progressed were women older than 35 years, while women who continue to be followed up without progression or those who experience regression to LSIL/CIN 1 were younger than 35 years.

We can conclude that age is one of the factors most frequently associated with progression or regression. This is in line with the data found in the literature, where it is described that an age younger than 25-30 years implies a higher probability of regression[5].

HPV 16+ was found in all the patients included in our study. Based on the data reviewed in previously published studies, there is a greater likelihood of lesion regression if there is HPV clearance. However, none of our patients have yet been re-tested for HPV.

With regard to the use of Papilocare® in our patients, we observed that all the patients who continue to be followed up (due to persistence at six-month follow-up or in those whose lesions regressed) have continued treatment with this vaginal gel. Its components include hyaluronic acid, β-glucan, alpha-glucan oligosaccharide, *Coriolus versicolor*, Centella asiatica, Azadirachta indica and aloe vera. The aim of their use is to promote cervical re-epithelialisation, increasing viral clearance rates as well as reversing HPV-dependent lesions[6]. On the other hand, we observed that in patients in whom lesion progression to HSIL/CIN 3 was documented, 50% underwent treatment with Papilocare®, while the other 50% did not.

Coriolus versicolor-based vaginal gel could therefore be considered as a possible agent that favours the vaginal microbiota and local immunity, which could have an effect on increasing regression in high-grade CIN 2 intraepithelial cervical lesions or favouring viral clearance. Its use should be combined with general recommendations aimed at increasing viral clearance, such as smoking cessation and condom use.

It should be noted that further studies with larger sample sizes are needed to draw further conclusions, as the studies conducted to date are limited. This is an issue of great importance, as the possibility of follow-up in selected patients would avoid a not inconsiderable percentage of conisations, thereby preventing the comorbidity that this entails.

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USE OF PAPILOCARE® IN A PATIENT WITH LSIL/VaIN I AND PERSISTENT HPV POSITIVITY AFTER CERVICAL CONISATION

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ABSTRACT

Human papillomavirus is the most prevalent sexually transmitted infection and it can cause precancerous lesions in the lower genital tract. The use of Papilocare® is a therapeutic option when surgical treatment fails to eliminate the infection or when the infection does not resolve spontaneously.

KEY WORDS

Papilocare®. HPV. Conisation.

CLINICAL HISTORY

A 39-year-old woman came for consultation due to LSIL cytology result and positive non-16/18 high-risk human papillomavirus (HPV).

Personal history:

- Allergy to isothiazolinone.
- Diseases: no.
- Interventions: no.
- No regular treatments.
- Non-smoker.

Obstetric and gynaecological history:

- Menarche 12.
- Menstrual bleeding/cycle 5/30.
- Nulligravid.
- Contraceptive method: condom (oral contraceptives for two years).
- Not vaccinated for HPV.

The patient has reported occasional bleeding during intercourse for the last two months. She is otherwise asymptomatic.

The last cytology was carried out four years earlier with negative results.

PHYSICAL EXAMINATION

Normal external genitalia. Normal vagina. Macroscopically normal cervix with slight periorificial ectopia. Vaginal examination: no palpable findings.

Colposcopy: adequate, TZ 2. After application of acetic acid, grade 2 changes were observed in a small area of the anterior lip of the exocervix between 10 and 12 o'clock. With Lugol's iodine staining, this same area showed up as iodine negative.

It was decided that we should perform a biopsy of the exocervical area described and an endocervical study.

Vaginoscopy: no changes with acetic acid. With Lugol's iodine, a small area on the right side of the vagina was visualised as iodine negative. Vaginal biopsy was performed.

DIAGNOSIS

Exocervical HSIL/CIN 3.
LSIL/VaIN 1.

TREATMENT AND PROGRESS

As for the VaIN 1, we decided to wait and see.

Cervical conisation was performed as a treatment for HSIL.

Prophylactic HPV vaccination with Gardasil® 9 and use of Papilocare® vaginal gel was indicated.

One month later, the surgical site had healed well and the patient returned to the hospital for a check-up. The pathology results showed an HSIL lesion with an affected endocervical border, and she was advised to undergo colposcopy, cytology and HPV testing after three months.

Colposcopy at three months showed TZ 2. No changes were visualised with acetic acid or Lugol's iodine.

Cytology showed a negative result and she tested positive for non-16/18 high-risk HPV. An endocervical study was carried out and was negative.

Vaginoscopy showed no changes with acetic acid or Lugol's iodine.

At the annual check-up, the patient continued to use Papilocare® vaginal gel and had already received three doses of the HPV vaccine.

Cytology, HPV and vaginoscopy were all negative.

Cytology and HPV tests were carried out one year later, with negative results.

The patient has now been discharged from our lower genital tract pathology clinic.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

This is a case of a patient with a high-grade cervical lesion and a low-grade vaginal lesion with positive HPV.

HPV causes premalignant lesions mainly at the cervical level but it can sometimes occur in other areas, as in this case at the vaginal level.

After surgical treatment of the high-grade cervical lesion, HPV infection persisted, but with the application of Papilocare® following an appropriate regimen and vaccination, clearance was achieved within approximately one year.

In the case of VaIN, expectant management together with the application of Papilocare® achieved regression of the lesion without the need for further treatment.

Recent studies show that the majority of patients following the Papilocare® regimen have achieved remission of high-risk HPV after six months of treatment as well as normalisation of low-grade lesions.

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SEVERE FOCAL DYSPLASIA (VaIN 3) IN A PATIENT HYSTERECTOMISED DUE TO CERVICAL CANCER

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CLINICAL HISTORY

65-year-old patient undergoing follow-up in the Lower Genital Tract Unit due to cytology results showing HSIL and HPV positive 33 after hysterectomy.

Background

- No known drug allergies.
- **Medical and surgical history:** Arterial hypertension, Cholecystectomy, Atrial fibrillation with electrical cardioversion, Hysterectomy + double adnexectomy, Left knee prosthesis.
- **Obstetric and gynaecological history:** G4P3A1. Normal revisions until 2015.
- **2015:** Conisation HPV+ (non-16/18), CIN 2. Subsequently: ASCUS cytology and persistence of HPV+, non-16/18, with normal follow-up tests, even with negative cytology and negative HPV in 2017.
- **2018:** Cytology showed HSIL and HPV+ (non-16/18). Biopsies were taken, showing→ CIN 3 → 2nd Conisation → Pathology results: CIN 3 in contact with surgical resection borders and ECC with exocervical epithelium showing CIN 3 → Hysterectomy + Double adnexectomy by LPS.
- **Pathology results:** Coderately differentiated infiltrating squamous cell carcinoma of the cervix (Stage IB1).
- **Dec. 2018:** Bilateral pelvic lymphadenectomy.

GYNAECOLOGICAL EXAMINATION

Vaginoscopy: On application of acetic acid, whitish areas with superficial vascularisation were observed in the right vaginal angle. Schiller's test was negative.

A colposcopy-directed biopsy was performed.

Additional tests: Vaginal vault biopsy: severe focal dysplasia (VaIN 3).

Following these results, the patient was referred to the reference hospital for treatment with laser vaporisation.

FINAL DIAGNOSIS

Severe focal dysplasia (VaIN 3) in a post-hysterectomy patient with stage IB1 cervical cancer.

TREATMENT

Vaginoscopy: Extensive, ill-defined, dense acetowhite lesion covering the entire vaginal vault.

The vaginal vault was stained with Lugol's iodine and no lesions were evident.

Laser vaporisation was performed of the entire surface of the vaginal fundus.

Follow-up

In January 2020: ASC-H cytology results, unable to exclude HSIL and persistent HPV 33.

Vaginoscopy: On application of acetic acid, a slightly acetowhite area was observed on the vault, with a bare area in the right corner. Generalised low uptake after application of Lugol's iodine.

Biopsies were taken under colposcopic vision.

Additional Tests

Vaginal vault biopsy: Severe focal dysplasia (VaIN 3)

Following these results, the patient was again referred to the reference hospital (HVV in Seville) for treatment with laser vaporisation.

Follow-up

In October 2020: Persistent ASC-H Cytology and persistent HPV 33.

Vaginoscopy: On application of acetic acid, a discreetly acetowhite area was visible on the left lateral surface, with no uptake of Lugol's iodine stain.

Biopsies were taken under colposcopic vision.

Additional Tests

- Vaginal vault biopsy:
  - Biopsy on the left lateral side at 3 o'clock: Moderate focal dysplasia (VaIN 2)

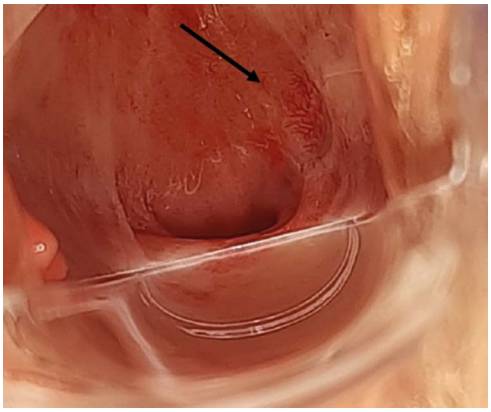

FIGURE 1. Vaginoscopy, superficial vascularised area where directed biopsy was performed.

  - Biopsy of the posterior aspect of the vagina at 4 o'clock: Mild focal dysplasia (VaIN 1)
  - Biopsy of the anterior aspect of the vagina at 1 o'clock: Mild-moderate focal dysplasia (VaIN 1-2)

Following these results and after two failures with laser vaporisation, it was decided that it should be treated with excision of the vaginal lesion.

Findings: Generalised staining of the entire vagina, with no areas of decreased uptake identified. Grade 2 rectocele, which, together with severe atrophy and fibrosis, made it difficult to identify and dissect planes properly.

Technique: Resection was carried out by parts:

- Anterior lip of the vagina → Pathology result: no alterations.
- Posterior lip of the vagina → Pathology result: no alterations.
- Right angle → Pathology result: no alterations.
- Left angle → Pathology result: High-grade dysplasia (VaIN 3).

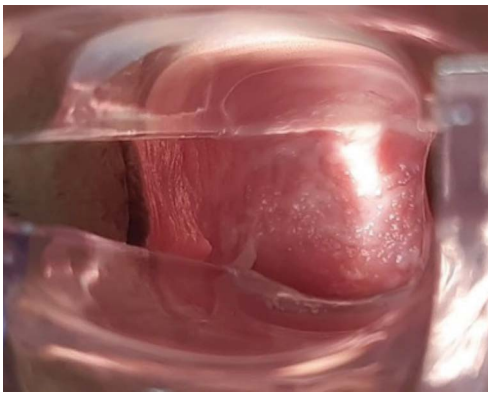

FIGURE 2. Vaginoscopy, on application of acetic acid, a discreetly acetowhite and raised area was observed, from which biopsies were performed under vision

Follow-up

Following the above results, a consensus was reached in the section committee, follow-up of the patient.

In 2021: Negative Cytology, HPV persistent for type 33.

Vaginoscopy: after application of acetic acid, a discreetly acetowhite area was observed on the left lateral surface of the vagina, grade 1 changes, with incomplete uptake of Lugol's iodine. It was decided that no biopsies would be taken.

Subsequent Vaginoscopies with similar characteristics.

May 2023:

- Vaginoscopy:
  - Atrophic vagina. Difficult to examine due to tissue laxity.
  - After application of acetic acid: Atrophic squamous epithelium, with changes due to atrophy. On the anterior surface of the vagina (it looked like the same area when previous biopsies were performed), faint acetowhite was observed with grade 1 changes, but with small ulcerous areas that bleed when rubbed.
  - After application of Lugol's iodine: decreased uptake of Lugol's iodine stain in the area in question.
  - A biopsy was taken from this area → High-grade VaIN (VaIN 2).
- Contrast CT scan of the abdomen and pelvis: No notable findings.
- Chest X-ray: No notable findings.

Following the pathology results, VaIN 2, she was informed of the possible treatment options. Due to her circumstances (age and comorbidities), it was agreed that she should try imiquimod at a weekly dose of 250 mcg with a vaginal cannula for 12 weeks, although from the previous description it seems that it may be a resectable lesion if she needs it in the future.

Currently being treated with Imiquimod.

DISCUSSION

- Vaginal intraepithelial neoplasia, also known as VaIN, is considered the precursor lesion to vaginal cancer.
- HPV infection, as in this case, is involved in up to 90% of cases of VaIN, justifying that these lesions are associated with multicentric lesions. The most frequent types of HPV associated with VaIN are 16, 18 and 33, the latter being the one present in our patient.
- It is estimated that 20-30% of patients with VaIN were previously treated for cervical cancer.

- Clinical symptoms: It usually presents with an absence of symptoms, and is diagnosed, as in the case mentioned above, through abnormal cytology and/or HPV+ test.
- In the follow-up of a patient previously treated for cervical disease, careful Vaginoscopy is required, as well as biopsy, if necessary. It is especially important to carefully examine the angles of the vaginal vault after hysterectomy, as these are the most common areas of recurrence.
- Differential diagnosis:
  - Vaginal papillomatosis
  - Congenital transformation zone.
  - Vaginal adenosis.
  - Vaginal candidiasis, trichomoniasis inflammation.
  - Vaginal lichen planus.
  - Changes due to radiotherapy.
  - Vaginal atrophy.
- There is no agreement on the best method of treatment. It must be individualised, depending on each patient's characteristics, the type of lesion, previous treatments.
- First-line treatments in multifocal disease are local excision, laser ablation and medical therapy with topical agents.
- Although cure rates with laser vaporisation are high (80%), in this case, the expected result was not achieved, so the lesion was excised, with subsequent follow-up. As the lesion persisted, topical treatment with imiquimod was started, as it allows treatment of the entire vaginal mucosa with good coverage of persistent multifocal disease.
- In recent studies, imiquimod has demonstrated a lower recurrence rate and regression of disease, in turn facilitating higher HPV clearance.
- After treatment of previous cervical disease in a hysterectomised patient, careful examination of the vagina is particularly important, with biopsies taken from suspicious lesions for histological examination.
- HPV infection is involved in up to 90% of cases of VaIN. Specifically, VaIN is associated with CIN in 40% of cases and there is previous cervical cancer in 20-30% of cases.
- The management of VaIN must be decided on a case-by-case basis.
- In patients with localised and visible lesions, destructive or topical treatment can be considered.
- Surgical excision is the mainstay of treatment and should be performed if invasion cannot be excluded.
- Topical agents are useful for persistent multifocal lesions or for patients who cannot undergo surgical treatment.
- Imiquimod was associated with the lowest recurrence rate, the highest HPV clearance and may be considered the best topical drug approach.

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RESOLUTION OF HPV AND LSIL-CIN 1 WITH PAPILOCARE® AND IMMUNOCAPS

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Clínica Mileniun-Dent

ABSTRACT

Human Papillomavirus (HPV) is the most common sexually transmitted infection worldwide, affecting up to 90% of sexually active people.

KEY WORDS

Papilocare®. HPV.

CLINICAL HISTORY

A 26-year-old patient came to our office at CLINICA MILENIUN-DENT in June 2022 for an Annual Gynaecological Check-up. The patient reported having no symptoms or disease of note to comment on since the last check-up in 2021.

Ethnicity: Spanish .

Personal history: no chronic diseases of interest.

Smoker: No.

First sexual relations: 16 years.

Number of sexual partners reported: 4 .

Stable sexual partner: not currently.

Previous pregnancies: No

Contraceptive method: No

Family history: none of interest

Vacunación contra el VPH: no.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient attended the gynaecology clinic for an annual gynaecological check-up. She had no external symptoms and her external genitalia were normal.

Speculoscopy: slight erosion of cervix.

Cytology and transvaginal ultrasound performed in consultation: uterus and adnexa normal for her cycle.

Breast ultrasound, CBC and Transvaginal ultrasound with Doppler were requested. The patient was scheduled for an appointment after 30 days to collect the results.

After 15 days, the patient was called to the clinic due to pathological findings:

Cytology: LSIL-CIN 1, mild dysplasia) Suggestion that HPV should be ruled out.

Colposcopy: Ectropion with signs of atypical transformation.

PCR requested for HPV.

PHV Positive for 39 (High Risk) and 62/81 (Low Risk).

The patient was informed of the treatment to be followed.

GENETICS

STUDY REQUESTED:	HPV DETECTION AND TYPING
MOLECULAR BASIS:	High-risk HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. Probable high-risk HPV gen-otypes: 26, 53, 66, 70, 73, 82. Low-risk HPV geno-types: 6, 11, 40, 42, 43, 44, 54, 55, 61, 62, 67, 69/71, 72, 74, 81, 83, 84, 89.
TYPE OF SAMPLE:	EXUDATE
TECHNIQUE:	Automatic DNA extraction from the sample re-ceived. Determination and identification of viral DNA from part of the L1 region of the HPV virus by multiplex PCR and reverse hybridisation. This PCR amplifies most of the known genotypes simultaneously, which would prevent the identifica-tion of certain genotypes present in a co-infected sample, due to primer competition during PCR.
RESULT:	The following HPV genotypes were detected in the sample analysed: 39 and 62/81.

FIGURE 1. Initial HPV

COLPOSCOPY REPORT

DESCRIPTION:
Ectopia invading more than half of the ectocervix, with small-grained papillae, grouped in clusters.

When acetic acid is applied, an acetowhite epithelium with fine mosaic areas and base with precise external borders is observed at 11-12 o'clock. Schiller's test was iodine negative.

COLPOSCOPIC DIAGNOSIS:
Ectopia with signs of atypical transformation. ATZ

FOLLOW-UP:
Follow-up by her gynaecologist.

FIGURE 2. Initial colposcopy.

PATHOLOGY REPORT

SAMPLE(S) SENT:
VAGINAL CYTOLOGY

DIAGNOSTIC PATHOLOGY RESULT:

BETHESDA System 2014
TYPE OF SAMPLE:
TRIPLE (endocervix, exocervix, vagina)
ASSESSMENT OF THE SMEAR:
SATISFACTORY with endocervical cells and/or squamous metaplasia.
INTERPRETATION:
Low-grade squamous intraepithelial lesion (LSIL-CIN 1, mild dysplasia).

Pathologist:

Report Date: 19/05/2022
Issue Date: 20/05/2022
Validation Date: 20/05/2022

DESCRIPTIONS AND COMMENTS:
VAGINAL CYTOLOGY (T-8X210).

FIGURE 3. Initial cytology.

COLPOSCOPY REPORT

DESCRIPTION:
Medium-sized ectopia, with small-grained papillae, signs of re-epithelialisation, leaving numerous glandular orifices, some of them cornified. The acetic acid test shows an acetowhite epithelium at 12 o'clock with superimposed irregular mosaic pattern and precise external borders. Lugol's test was iodine negative. Congestion of both epithelia.

COLPOSCOPIC DIAGNOSIS:
Ectopia with signs of atypical transformation (mosaic pattern, cornified orifices) ATZ.
Colpitis.

FOLLOW-UP:
Follow-up by her gynaecologist.

Madrid, 05 April 2023
Signed: Dr F. VAQUERO MORENO

FIGURE 4. Colposcopy six months later.

TREATMENT

Treatment with Papilocare® Vaginal Gel for HPV and Immunocaps was prescribed for the partner for six months, with check-up in six months

Patient attended after six months of treatment and underwent PCR, cytology and colposcopy.

We insisted upon and recommended as part of her treatment:

- Smoking cessation (if a smoker).
- Start HPV vaccination.
- Always use a barrier method.

SAMPLE OBTAINED FROM: Vagina, ectocervix and endocervix.

MICROSCOPIC DESCRIPTION:

A) Cell morphology: Atypical pavement cells of undetermined significance.

B) Microbiology: Intense inflammation and colonies of coccoid bacteria.
Absence of endocervical component / transformation zone.

C) Cytohormonal assessment: Not assessable.
Coccal infection.
ASCUS.

Signed: Dr F. Vaquero Moreno

FIGURE 5. Cytology six months later.

- Another follow-up visit six months after starting treatment.

RESULTS

Cytology: Coccus, ASCUS.

Colposcopy: Ectropion with signs of atypical transformation (colpitis).

HPV Negative.

PROGRESS

The patient was told that the papillomaviruses had disappeared, that ASCUS on cytology did not require specific treatment on its own.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

In this case, it is striking how, after only six months of treatment with Papilocare® Vaginal Gel and Immunocaps for the partner, a recovery in the cytology (LSIL-CIN 1) to ASCUS is observed, as well as the clearance of HPV 39 (High Risk) and 62/81 (Low Risk).

MOLECULAR MEDICINE UNIT

STUDY REQUESTED: HPV detection

TYPE OF SAMPLE: EXUDATE

MOLECULAR BASIS: Human papillomaviruses (HPV) are diverse groups of DNA viruses belonging to the Papillomaviridae family.
It is one of the most common sexually transmitted diseases, consisting of a group of more than 200 related viruses, some of which are transmitted through vaginal, anal or oral sex. There are two groups of sexually transmitted HPV: low-risk and high-risk.
Low-risk HPVs cause almost no disease. However, some low-risk types of HPV cause warts in the genital area, anus, mouth or throat.
High-risk HPVs cause several types of cancer. Fourteen high-risk HPV types have been described, including the following: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Two of these, HPV16 and HPV18, cause most HPV-related cancers.

TECHNIQUE: Automatic DNA extraction from the sample received. Screening using a real-time PCR technique designed for the qualitative detection of the DNA of 14 genotypes of the human papillomavirus (HPV) considered to be of high oncogenic risk.
The assay can specifically identify HPV genotypes 16 and 18 and at the same time detect genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 at clinically relevant levels of infection. It also detects the human beta-globin gene as an internal control of the quality of the starting material and amplification.

RESULT: No HPV DNA from any of the strains tested was detected in the sample analysed.

FIGURE 6. HPV six months later.

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CONSERVATIVE MANAGEMENT OF CIN 2 IN A YOUNG WOMAN

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ABSTRACT

29-year-old patient diagnosed with CIN 2 by cervical biopsy. Conservative management, follow-up and evolution.

KEY WORDS

Young woman. CIN 2. Conservative management. HPV. Papilocare®.

CLINICAL HISTORY

29-year-old female patient with an ASCUS cytology finding in routine cervical screening with HPV determination positive for HR 39 and 68. (August. 20).

Medical/surgical history: She has no diseases. No known allergies. Elective caesarean section due to breech presentation and augmentation mammoplasty. Contraception: Oral contraceptives. Smoker of 5 cigarettes/day.

Previous negative cytologies according to screening.

PHYSICAL EXAMINATION

Given the cytology finding of ASCUS and positivity for HR HPV 39 and 68, she was admitted to the cervical pathology clinic in October 20. Colposcopic examination: satisfactory. There was evidence of a type 1 TZ, with a minimal fine mosaic pattern at 5 o'clock outside the TZ, which was not biopsied as it was compatible with type 1 changes.

Plan: Initiation of intravaginal Papilocare® for six months, and vaccination with Gardasil® 9 was recommended. Smoking cessation was encouraged.

Sept. 21: At the next check-up, the patient had stopped taking oral contraceptives and was using a condom. She had been treated with Papilocare® for six months with good adherence and had completed vaccination with Gardasil® 9. She wishes to have children.

Examination: another Co-test was taken. Colposcopy was performed: Satisfactory. Type 1 TZ. After acetic acid application, a fine mosaic pattern was visualised on the anterior lip at the 2 o'clock position in contact with the TZ. Cervical biopsy was taken.

The results were: cytology showed Parakeratosis. HR HPV + 39, 68. Cervical biopsy: CIN 1-2. P16 diffuse intense positivity. Ki67: positive in the lower third and focally in the middle third of the squamous epithelium.

Plan: Given the patient's age (<30 years), the existence of a small cervical lesion, visible by colposcopy and the absence of HPV 16, it was decided that she should be offered conservative management, which was accepted by the patient.

DIFFERENTIAL DIAGNOSIS

Low-grade lesion / High-grade lesion.

TREATMENT AND PROGRESS:

Feb. 22: A follow-up at six months was performed, with another colposcopy and Co-test. At this check-up, the patient had started taking oral contraceptives again and was being treated with oral antidepressants and anxiolytics due to a marital separation. Colposcopy: Satisfactory. Type 1 TZ. After acetic acid application, a very small thin mosaic pattern was observed on the anterior lip at 2-3 o'clock, extending into the canal, which was biopsied. Another area of fine mosaic pattern was observed at 5 o'clock on the posterior lip but away from the TZ (exocervical) compatible with type I changes, which was not biopsied. After staining with Lugol's iodine, both areas described were negative.

RESULTS

Cervical biopsy: CIN 1. p16 Microfocal positive. Ki67 Positive in lower ⅓ and focally in middle ⅓ of squamous epithelium.

Co-test: Parakeratosis. HR HPV + 39.

A further six months of treatment with intravaginal Papilocare® was offered, following the previous regimen. Follow-up by psychology and psychiatry was encouraged.

Sept. 22: A follow-up check-up was carried out at six months and the patient's mood had improved. She had decreased her dosage of antidepressants and anxiolytics, and had reduced her smoking. Co-test and Colposcopy were performed again.

Colposcopy was satisfactory. Type 1 TZ. No evidence of acetowhite lesions. No findings after staining with Lugol's iodine.

Co-test negative. HPV negative.

Sept. 23. An annual check-up with co-testing was carried out, confirming negative results for both, so it was decided that the patient should be discharged and referred back to routine screening for follow-up.

FINAL DIAGNOSIS

29-year-old woman diagnosed with CIN 2.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Cervical cancer is rare in young women under 25 years of age despite the high prevalence of HPV infections or the presence of high-grade histological lesions (especially HSIL/CIN 2) in this population[1]. Therefore, in certain cases, it is possible to offer conservative

management in young patients under 30 years of age with a diagnosis of CIN 2. It is known that in small lesions, it is possible that the biopsy itself may excise most or all of the lesion[2], and sometimes the remaining post-biopsy lesion may regress due to the action of the immune system, associated with the healing process[3]. Hence the importance of boosting the immune system at the local level by applying products whose action is exerted locally and systemically, as well as promoting complete vaccination for HPV and psychological therapies or drugs that help to manage the depressive syndrome better.

In patients with an unfulfilled desire to have children and who meet criteria for conservative management of CIN 2, the aim is to avoid overtreatment of potentially regressive lesions and the obstetric morbidity associated with such treatments[4,5].

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REGRESSION OF HIGH-GRADE CERVICAL LESION TO LOW-GRADE CERVICAL LESION IN A PATIENT USING *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL

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ABSTRACT

31-year-old patient using *Coriolus versicolor*-based vaginal gel in the close follow-up of CIN 2.

KEY WORDS

Papillomavirus. High-grade lesion. *Coriolus versicolor.* Expectant management.

CLINICAL HISTORY

31-year-old patient referred for colposcopy in 2020 due to ASCUS cytology findings with persistent HPV 52 and 58 for three years.

Personal history:

- NKDA
- Personal history: none of interest
- Non-smoker
- Not vaccinated against HPV

Obstetric history:

- Menarche: 14 years
- Obstetric formula: 0
- LMP: 12/01/2020
- Menstrual bleeding/cycle: 4/28
- Age at first intercourse: 16
- Number of sexual partners: 3

A colposcopy was performed which revealed a type 1 transformation zone with very faint minor changes, so a biopsy was not taken. Vaccination and treatment with Papilocare® Vaginal Gel was recommended, but the patient did not apply the treatment.

In 2021, a Co-test was performed, and HPV 52 and 58 remained positive. The cytology was negative. The patient still had not applied the recommended treatment. We insisted on vaccination and treatment with Papilocare® Immunocaps.

In 2022, a Co-test was performed, with the patient testing positive for HPV 35 and 58 and cytology reported as HSIL. A colposcopy was performed, showing a type 1 transformation zone. After administration of acetic acid, a thick mosaic pattern was observed on the anterior lip, a sign of major changes, so a biopsy was taken.

Biopsy results: CIN 2 (p16+ / high Ki67 index).

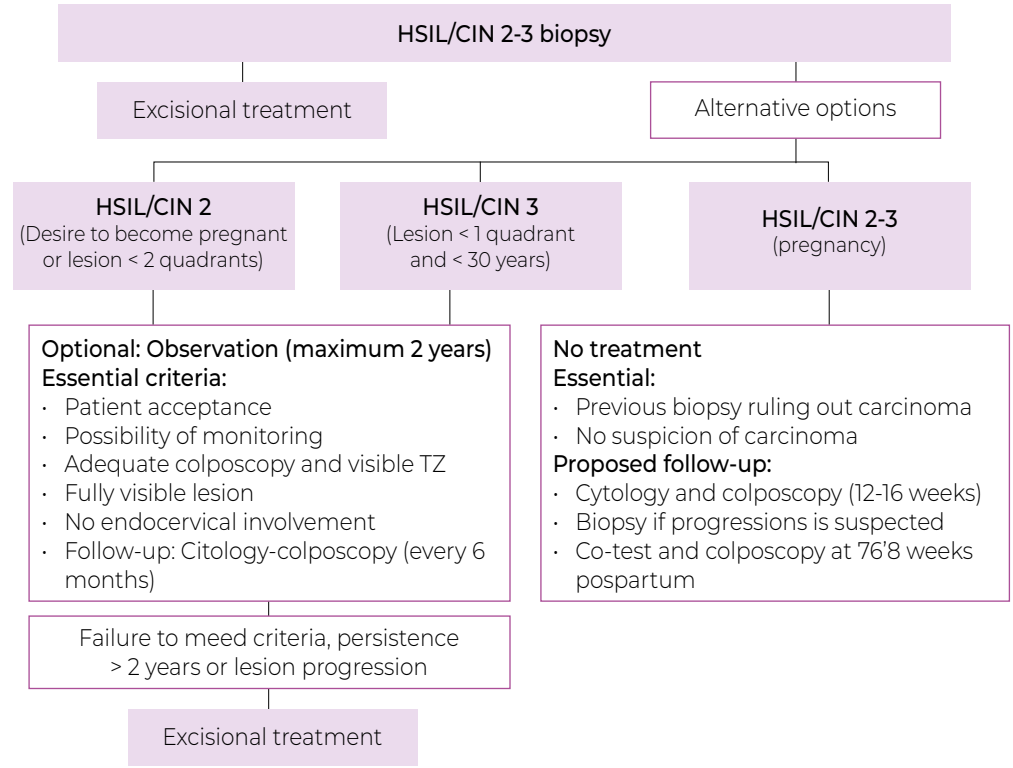

FIGURE 1. Algorithm HSIL/CIN 2-3 biopsy.

The situation was explained to the patient and excisional treatment was offered as opposed to close follow-up. The advantages and disadvantages of each option were explained. The patient opted for closely monitored watchful waiting. We insisted on HPV vaccination and treatment with Papilocare® Vaginal Gel.

After six months, the patient returned for cytology and colposcopy. She had successfully completed the treatment with Papilocare® Vaginal Gel, but was awaiting administration of the HPV vaccine in Preventive Medicine.

Co-test and Colposcopy were performed. Colposcopy showed a type 1 transformation zone. Acetic acid was administered and an acetowhite lesion was seen on the anterior lip. A biopsy was taken and endocervical curettage was performed.

Cytology results: LSIL.

Cervical biopsy result: Low-grade squamous intraepithelial lesion (SIL), CIN 1.

Cervical curettage result: haematic material consisting of loose endocervical cells without significant atypia.

Given the regression of the lesion and the improvement in the patient's

state of anxiety with Papilocare® Vaginal Gel, she decided to continue using it until the next check-up in six months.

SIGNIFICANCE OF THE CASE

Clinical behaviour in response to screening test results is crucial, as the possibility of preventing the risk of cervical cancer largely depends upon it[1].

Women with HSIL/CIN 2-3 biopsy have a high probability of having or developing cervical cancer. This diagnosis has classically been considered the threshold for indicating treatment for premalignant cervical lesions. In recent years, a better understanding of the natural history of these lesions has confirmed HSIL/CIN 3 as the true precursor of cervical cancer as cases of HSIL/CIN 2 constitute a heterogeneous group with a variable risk of progression/regression. The goal of clinical management in this group of women involves identifying cases where there is a risk of progression, which require immediate treatment as a priority option, and recognising the exceptional cases in which spontaneous regression is possible and conservative management may be considered[1].

Overall, HSIL/CIN 2-3 lesions have a higher risk of persistence or progression than regression. There is evidence that treating such lesions reduces the incidence and mortality of cervical cancer[2].

Cervical cancer is the fourth most common cancer worldwide. Women with HSIL/CIN 2-3 biopsy have a high probability of having or developing cervical cancer. This diagnosis has been classically considered the threshold for indicating treatment of premalignant cervical lesions[1].

On the other hand, recent studies have shown that excisional treatment by conisation increases the risk of perinatal death, preterm birth and low birth weight[3].

Among other characteristics, for population-based cancer screening to be beneficial, it is important for it to be accessible to the entire population and to cause as little harm as possible. According to the AEPCC, to keep the harm of screening to a minimum, among other actions, we should avoid overtreatment and minimise the adverse effects of treatment[1].

The main reason for follow-up of HSIL/CIN 2-3 lesions is to avoid overtreatment of lesions with the potential for regression and the obstetric morbidity associated with such treatments.

The regression rate of CIN 2 is higher in women under 30 years of age during the first twelve months. A recent meta-analysis concluded that up to 60% of lesions in this group regress spontaneously[4]. Given that these women are of childbearing age, the choice to opt for close monitoring seems more than justified.

In contrast, women aged 30-35 years showing CIN 2 constitute a more heterogeneous group with a variable risk of regression/progression, within which a high rate will have an unfulfilled desire to have children.

In cases of HSIL/CIN 2-3 where follow-up without treatment is indicated, cytology and colposcopy (possibly

biopsy) should be performed every six months and HPV testing should be performed annually (maximum follow-up period of two years). Treatment with Papilocare® has shown a greater clinical benefit in terms of HPV lesion regression and HPV clearance after six months of use compared to conventional expectant management[5].

Therefore, if the patient decides on close monitoring of the lesion, it would be advisable to use a treatment that favours re-epithelialisation of the cervix and local immunity, such as Papilocare®[6].

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CLOSE MONITORING OF CIN 2 WITH *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL

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ABSTRACT

Use of *Coriolus versicolor*-based vaginal gel in the close monitoring of a patient diagnosed with CIN 2.

KEY WORDS

Coriolus Versicolor. CIN 2. Human Papillomavirus. Conisation.

CLINICAL HISTORY

33-year-old patient referred for colposcopy in 2021 due to the appearance of ASCUS cytology findings and HPV-16+.

Personal history:

- NKDA.
- Personal history: none of interest .
- Smoker of 15 cigarettes a day.
- Not vaccinated against HPV.

Obstetric history:

- Menarche: 12 years.
- Obstetric formula: 20222.
- LMP: 25/02/2021.
- Menstrual bleeding/cycle: 4/28.
- Age at first intercourse: 18.
- Number of sexual partners: 3.

PHYSICAL EXAMINATION

Colposcopy was performed and showed adequate visualisation of the cervix and the squamocolumnar junction with a type 1 transformation zone and absence of lesions, so no biopsy was taken.

TREATMENT AND PROGRESS:

We recommended vaccination with Gardasil® 9, treatment with Papilocare® Immunocaps and smoking cessation.

She returned after 12 months for the Co-test. The patient had been vaccinated and had reduced her smoking to five cigarettes a day. She did not take Papilocare® Immunocaps.

In the Co-test, the cytology was negative with HPV-16+, and colposcopy was performed. It showed adequate visualisation of the cervix and the squamocolumnar junction with type 1 transformation zone. Minor changes were seen on the whole cervix so no biopsy was taken.

Treatment with Papilocare® Vaginal Gel and Papilocare® Immunocaps was recommended for six months.

After one year, she returned for a follow-up appointment at which a Co-test was carried out. The patient continued to smoke five cigarettes/day and had not been treated with Papilocare®.

In the Co-test, we found negative cytology and HPV 16+, so colposcopy was performed. Colposcopy provided adequate visualisation of the cervix and the squamocolumnar junction with a type 1 transformation zone. There was evidence of a grade 2 acetowhite lesion with a mosaic pattern between 6 and 11 o'clock. Complete visualisation of the lesion. Compatible with major changes, so a biopsy was taken.

The biopsy was reported as CIN 2. Close follow-up or excisional treatment was proposed, with the former being the preferred option. We insisted on treatment with Papilocare® Vaginal Gel and Papilocare® Immunocaps.

She returned after six months for colposcopy. The patient had applied with treatment with Papilocare® Vaginal Gel and Papilocare® Immunocaps. Colposcopy with adequate visualisation of the cervix and the squamocolumnar junction with type 1 transformation zone showed a grade 1 acetowhite lesion between 6 and 9 o'clock. At 7 o'clock, there was a small grade 2 mosaic-type plaque, which was biopsied.

The biopsy was reported as CIN 2.

The patient wished to continue with close monitoring, pending a review in six months. Therefore, we insisted on continued treatment with Papilocare® Vaginal Gel, as treatment with *Coriolus versicolor*-based vaginal gel has shown a greater clinical benefit than normal clinical watchful waiting due to a significant improvement in cervical re-epithelialisation, a reduction in perceived stress and high adherence to therapy[2].

DISCUSSION AND SIGNIFICANCE OF THE CASE

Women with HSIL/CIN 2-3 biopsy have a high probability of having or developing cervical cancer. This diagnosis has classically been considered the threshold for indicating treatment for premalignant cervical lesions. In recent years, a better understanding of the natural history of these lesions has confirmed HSIL/CIN 3 as the true precursor of cervical cancer as cases of HSIL/CIN 2 constitute a heterogeneous group with a variable risk of progression/regression. The goal of clinical management in this group of women involves identifying cases where there is a risk of progression, which require immediate treatment as a priority option, and recognising exceptional cases where spontaneous regression is possible and conservative management may be considered.

Overall, HSIL/CIN 2-3 lesions have a higher risk of persistence or progression than regression. Patients with untreated HSIL/CIN 3 have a 50% long-term risk of progression to cervical cancer, while the risk in the group of correctly treated women is 0.7%. Therefore, there is evidence that treating such lesions reduces the incidence and mortality of cervical

cancer. Recently, new data on the natural history of HSIL/CIN 2-3 lesions have called into question the routine treatment of all patients. A meta-analysis and systematic review of the literature shows that untreated HSIL/CIN 2 lesions regress, persist or progress to HSIL/CIN 3 in 50%, 32% and 18% of cases, respectively. Although HSIL/CIN 3 lesions have a higher risk of progression, it is now accepted that overall they constitute a heterogeneous group with variable risks of progression/regression.

The main reason for follow-up of HSIL/CIN 2-3 lesions is to avoid overtreatment of lesions with the potential for regression and the obstetric morbid ity associated with such treatments. However, the reproductive and obstetric complications associated with the treatment of premalignant lesions remain controversial. Some studies show that there is a directly proportional relationship between the risk of preterm birth and the size of the conisation specimen while others, after adjusting for confounding factors, do not confirm this association.

In cases of HSIL/CIN 2-3 where follow-up without treatment is indicated, cytology and colposcopy (possibly biopsy) should be performed every six months and HPV testing should be performed annually (maximum follow-up period of two years). Therefore, in young women with an unfulfilled desire to have children, the follow-up option is more than understandable, and thanks to the use of a treatment that favours re-epithelialisation of the cervix and local immunity, such as Papilocare®[3], we can help the woman during this follow-up period.

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CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN THE TREATMENT OF HPV 16 AND 18 POSITIVE ENDO- AND EXOCERVICAL LSIL IN A PATIENT WITH A HISTORY OF OVARIAN CANCER

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ABSTRACT

A 34-year-old woman positive for HPV 16 and 18 and with normal cytology with ovarian cancer and conservative surgery due to unfulfilled desire to have children. A colposcopy was performed with results showing LSIL, so she was prescribed HPV vaccination and Papilocare® for six months and she was recommended to stop smoking. A year later, a repeat co-test was performed with negative cytology and HPV diagnosis.

KEY WORDS

HSIL. HPV. *Coriolus versicolor*. Vaginal gel.

CLINICAL HISTORY

A 34-year-old female patient attended our lower genital tract (LGT) clinic at Hospital Materno Infantil Torrecárdenas in Almería in 2022, presenting positive tests for HPV 16 and 18 and normal cytology.

As an additional point of interest, the patient underwent a left adnexectomy in the same year at the nearby regional hospital, with a diagnosis of mucinous adenocarcinoma, and was referred to our hospital to complete the surgery.

The woman had not fulfilled her desire to have children, so our tumour committee decided to perform pelvic and para-aortic lymphadenectomy, omentectomy, appendectomy and parietal biopsy, preserving the uterus and contralateral adnexa, to allow for future pregnancy.

Other personal history: smoker of 20 cigarettes a day. No known drug allergies.

Obstetric and gynaecological history:

- Obstetric formula: 0.
- Menarche: 13 years.
- Menstrual formula: regular 5/28.
- Contraceptive method: condom.
- Not vaccinated for HPV.
- Stable male partner.

PHYSICAL EXAMINATION

At the LGT consultation prior to surgery, a physical examination was car-

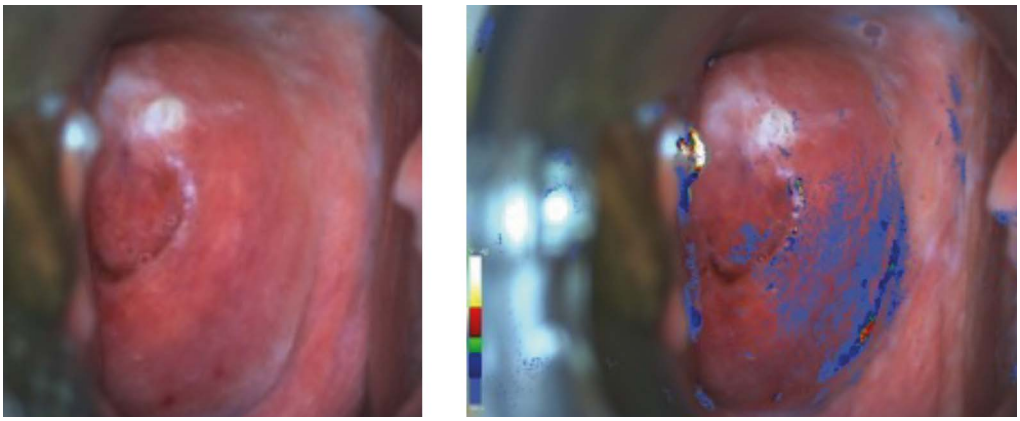

FIGURE 1. Colposcopy.

ried out, which was normal. Colposcopy was performed and a dense acetowhite epithelium was visualised at 11 o'clock, which was biopsied and endocervical curettage (ECC) was performed, showing a result of a low-grade squamous intraepithelial lesion (LSIL) in both samples.

REATMENT AND PROGRESS

After surgery for ovarian cancer, the definitive pathology result revealed mucinous adenocarcinoma of the ovary with areas of mucinous borderline tumour and negative peritoneal fluid, Stage IC1, and it was therefore decided that she should undergo follow-up at an onco-gynaecology clinic, without other adjuvant therapies.

With regard to the result of the cervical biopsy, follow-up was indicated and treatment was prescribed with HPV vaccination and Papilocare® vaginal gel for six months. She was also recommended to stop smoking.

FINAL DIAGNOSIS

One year after the first cytology, the patient returned to the LGT clinic for another co-test, the result of which was negative for cytology and HPV. The patient continues to be followed up by the LGT and onco-gynaecology clinics with no signs of recurrence at the present time.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Human papillomavirus (HPV) is the most common sexually transmitted infection among young sexually active individuals. There are more than 200 types of HPV, which can be subdivided into cutaneous or mucosal categories according to their tissue tropism. Persistent infection with an oncogenic type of HPV is the major risk factor for the development of cervical dysplasia and HPV-associated cancer. HPV is associated with approximately 100% of cervical cancer cases.

Among the circumstances that may be related to HPV clearance or persistence, type 16 and 18 positivity is clearly a risk factor for cell integration and associated oncogenic risk.

Squamous intraepithelial lesions of the cervix are the precursors of cervical cancer. Screening for cervical pathology by cytology and detection of high-risk human papillomavirus leads to early diagnosis of numerous low-grade intraepithelial lesions that represent a high cost of care.

Coriolus versicolor-based vaginal gel accelerates the re-epithelialisation process and improves viral clearance rates.

Papilocare® vaginal gel is presented as a possible treatment for this type of lesion, while waiting to repeat the co-test one year later, as indicated in our cervical cancer prevention guidelines. In addition to *Coriolus versicolor* extract, this gel contains hyaluronic acid (moisturising effect), beta-glucan (anti-inflammatory effect), Bioecolia® (prebiotic), *Centella asiatica* (regenerating effect), *Azadirachta indica* extract (re-epithelialising agent) and Aloe vera.

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TREATMENT WITH *CORIOLUS VERSICOLOR* -BASED VAGINAL GEL IN PERSISTENT HPV ASSOCIATED WITH LSIL/ ASCUS. A CASE REPORT

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ABSTRACT

We present the case of a patient diagnosed with histological LSIL and persistent HPV infection managed conservatively with vaginal gel containing *Coriolus versicolor* extract.

KEY WORDS

LSIL. ASCUS. Persistent HPV. Conservative treatment. *Coriolus versicolor*.

INTRODUCTION

Persistent human papillomavirus (HPV) infection is a risk factor for the development of both low-grade (LSIL) and high-grade (HSIL) dysplastic cervical lesions. For immunocompetent patients with cytological LSIL, the clinical guidelines of the Spanish Association of Cervical Pathology and Colposcopy[1] recommend referral for colposcopy for all women with cytological LSIL at primary screening. In cases where co-testing has been performed, they recommend referral for colposcopy if the HPV test is positive in the absence of genotyping. If genotyping is available, patients should be referred for colposcopy only in cases of type 16/18. In patients who are HPV negative or non-16/18 HPV positive, they recommend co-testing after one year. On the other hand, in patients with cytological HSIL, direct referral for colposcopy is recommended.

CLINICAL HISTORY

We present the case of a 28-year-old nulligravid patient referred to the lower genital tract pathology clinic for a history of histological LSIL lasting more than two years (previous test in a private clinic).

Her personal history includes: being a smoker, excision of genital warts in 2015 and a complete vaccination schedule with Cervarix in 2016. She reports using condoms as a method of contraception and having a steady partner.

The patient is gynaecologically asymptomatic.

PHYSICAL EXAMINATION

Co-testing and colposcopy were performed, revealing an adequate type 1 transformation zone, faint acetowhite epithelium at 12 o'clock and 6 o'clock, iodine negative after application of Lugol's iodine, which was biopsied.

The test results obtained showed infection with HPV 52 (high risk) and cytology reported ASCUS .

Cervical biopsies were reported as negative for dysplasia. The biopsy at 12 o'clock position identified cells with hyperchromatic and enlarged nuclei suggestive of viral infection.

DIFFERENTIAL DIAGNOSIS

LSIL or histological ASCUS with persistent HPV infection. It is necessary to rule out progression to a high-grade lesion.

TREATMENT AND PROGRESS

Due to the persistence of HPV infection, cytology result indicating ASCUS and a personal history of long-standing LSIL in a young patient of childbearing age, treatment with Papilocare® vaginal gel was offered for six months, together with follow-up.

Two months after starting treatment, the patient presented with acute abdominal pain in the right iliac fossa radiating to the lumbar region lasting several hours, hyporexia and low-grade fever, for which she went to the general emergency department. After ruling out acute appendicitis, the patient was referred to the gynaecology emergency department for evaluation due to the finding of an abdominal mass with suspected primary ovarian neoformative process with a maximum axis of 20 cm (probably benign or with a low degree of malignancy) in the abdominopelvic CT scan. After assessment in the emergency department, the patient was referred to the gynaecological oncology department. Tumour markers were: CA-125 214 U/ml and CA-19-9 57 U/ml. The case was presented to a multidisciplinary committee and it was decided that surgery should be performed.

FINAL DIAGNOSIS

During the operation, a median laparotomy was performed, revealing a large (20 cm) adnexal mass dependent on the right adnexa, with a chocolate-like liquid content compatible with endometrioma and a cyst measuring approximately 4 cm in the left adnexa, compatible with left endometrioma. The patient also had severe adhesive symptoms. Right adnexectomy was performed due to the impossibility of conservative surgical management, together with left ovarian cystectomy. The pathology study confirmed the diagnosis of endometriosis with no evidence of malignancy. The patient had an uneventful postoperative course.

Six months after starting treatment, the patient was reviewed at the lower genital tract pathology clinic. The gynaecological examination was normal. A co-test was performed, which was negative, in addition to colposcopy, which was normal.

The patient's endometriosis is currently being controlled with oral contraceptives.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

HPV infection is the most common sexually transmitted infection, and it is estimated that at least 80% of sexually active women will have been infected with some form of HPV in their lifetime[2]. The peak incidence of HPV infection is concentrated in the 15-30 age group, coinciding with the onset of sexual relations, and the percentage of women affected is estimated to be 20-30%. The incidence of HPV infection decreases with age, from 47% among 15 to 19-year-olds to 12% in women over 45[3].

Most HPV infections are asymptomatic and transient, such that during the normal course of the infection itself, spontaneous clearance is achieved in nine out of ten cases within two years of infection[4]. This requires an adequate local immune status (vaginal microbiome) to support viral clearance and cervical re-epithelialisation in case of lesions[5,6].

The development of cervical lesions requires persistent HPV infection[7]. HPV infection is known to be a necessary condition for the development of cervical cancer; however, it takes a long time to progress. Nevertheless, a positive result for HPV or the appearance of a cytological lesion leads to a state of anxiety[8] in the patient that worsens throughout follow-up if the lesions persist. This was one of the reasons why we started treatment in our patient.

The availability of a *Coriolus versicolor*-based vaginal gel with local immunomodulatory and re-epithelialising action[8] has resulted in increased regression of low-grade cervical lesions as well as increased viral clearance rates compared to conservative management[9,10] in studies to date.

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APPLICATION OF *CORIOLUS VERSICOLOR* VULVAR GEL AS ADJUVANT TREATMENT OF VULVAR INTRAEPITHELIAL NEOPLASIA (VIN) IN AN IMMUNOCOMPROMISED PATIENT

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ABSTRACT

Vulvar Intraepithelial Neoplasia (VIN) represents a recognized clinical entity characterized by anomalies in the vulvar epithelium, primarily associated with high-risk Human Papillomavirus (HPV) infections. The most common subtype, common type VIN, manifests as pre-invasive lesions affecting the vulva, often linked to progression towards vulvar squamous cell carcinoma. Understanding the pathogenesis, epidemiology, and associated risk factors of this neoplasia has become crucial in clinical practice, particularly in early detection and therapeutic management. In this context, the identification of specific HPV subtypes and the assessment of molecular markers have enhanced our comprehension of the disease's natural history and facilitated more precise therapeutic approaches. We present a clinical case of common type Vulvar Intraepithelial Neoplasia in an immunocompromised patient, highlighting evidence-based management strategies and proposing the adjunct use of *Coriolus Versicolor* vulvar gel to laser therapy. Studies on *Coriolus Versicolor*-based vaginal gel have shown promising outcomes, providing solid clinical evidence in enhancing clearance, re-epithelialization, restoration of microbiota, and boosting immunity.

KEY WORDS

Vulva. VIN. HPV. *Coriolus Versicolor* gel.

MEDICAL HISTORY

A 59-year-old patient under regular follow-up due to multiple sclerosis and receiving immunosuppressive treatment presented with several vulvar lesions, the largest on the right labium majus, elevated, with a papillomatous appearance and hyperpigmentation.

PHYSICAL EXAMINATION & DIFFERENTIAL DIAGNOSIS

After examination and vulvoscopy with 5% acetic acid, a biopsy of the main lesion revealed VIN 2/ high-grade squamous intraepithelial lesion (HSIL). Considering multiple lesions and following the current evidence-based therapeutic algorithm, we opted for

FIGURE 1.

FIGURE 2.

simple excision of the largest lesion to eliminate it, ruling out invasion, and CO_2 laser vaporization to achieve complete disease eradication. The post-vaporization appearance of the lesions is shown in Figure 1.

TREATMENT

After explaining the diagnosis to the patient and confirming the absence of invasive lesions with resolution of the largest lesion, we proposed adjuvant treatment with *Coriolus Versicolor* vulvar gel. Commencing post-healing, the gel was applied every 12 hours for 3 months. At the one-month follow-up, vulvoscopy revealed the treatment's significant efficacy, displaying visible lesion resolution (Figure 2). The patient exhibited good adherence to treatment and excellent tolerance without reporting any side effects. The psychological impact of the treatment was noteworthy, as it provided the patient, in an immunocompromised state, a sense of greater disease control, reinforcing viral clearance and re-epithelialization processes. A subsequent check at 3 months showed a normal vulvoscopy with complete lesion resolution (Figure 3).

CONCLUSION

Resolution of HSIL vulvar lesion, common type VIN, in an immunocompromised patient using *Coriolus Versicolor* vulvar gel as an adjuvant to excisional treatment and CO_2 laser vaporization. A

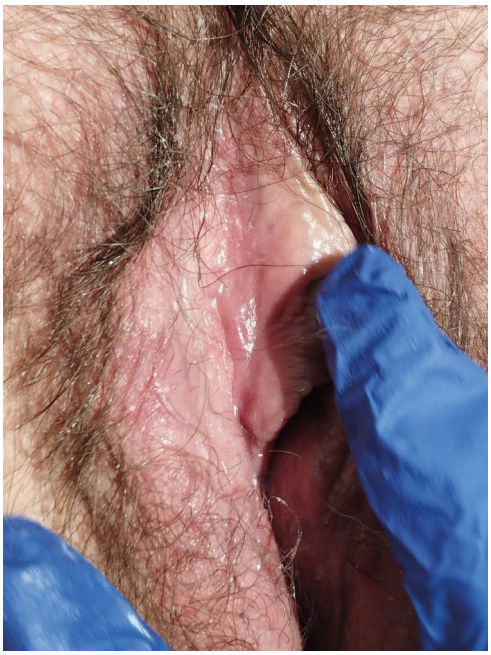

FIGURE 3.

safe and effective alternative satisfying both the patient and gynecologists.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The use of *Coriolus Versicolor* vulvar gel as an adjuvant therapy in common type HSIL VIN lesions holds significant importance for various reasons. Its known immunomodulatory and antitumoral properties could help modulate local immune responses and reduce the progression of high-grade lesions. Applied directly to the affected area, this gel may reduce viral load, promote lesion regression, and potentially prevent recurrence. Moreover, being a topical treatment, it offers a less invasive alternative compared to other procedures. Its ability to enhance the immune system's response specifically in the affected area makes it a promising option as a supplement to conventional management of common type HSIL VIN lesions, offering a more comprehensive and potentially effective therapeutic option to improve patient prognosis and quality of life.

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TREATMENT OF A LOW-GRADE INTRAEPITHELIAL LESION WITH *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL AND CAPSULES CONTAINING REISHI EXTRACT AND LACTOBACILLI IN A PATIENT WITH A DESIRE TO HAVE CHILDREN

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ABSTRACT

Coriolus versicolor-based vaginal gel and capsules with Reishi extract in patients with LSIL and HPV 16 and 52+ and desire to become pregnant, with postpartum clearance.

KEY WORDS

L-SIL. *Coriolus versicolor*. Reishi. Papillomavirus. Pregnancy.

CLINICAL HISTORY

31-year-old female patient referred to the Cervical Pathology Clinic for cytological findings of a low-grade intraepithelial lesion.

In terms of her family history, her mother has rheumatoid arthritis.

The patient is a smoker of about 15 cigarettes a day and had one vaginal delivery and one miscarriage.

From the beginning of the consultation, the patient expressed her concern about the findings and her desire to become a mother again in a short period of time.

Smoking cessation and vaccination against human papillomavirus were recommended, as well as the procedure to be followed for this type of cytological lesions. *Coriolus versicolor*-based vaginal gel was also recommended.

PHYSICAL EXAMINATION

The first step was to perform a human papillomavirus typing test, which was positive for types 16 and 52, and colposcopy was performed (Fig. 1).

As these are high-risk viruses, it is recommended to combine treatment with vaginal gel and adjuvant capsules containing Reishi extract and lactobacilli.

The cervical biopsy confirmed a low-grade intraepithelial lesion (CIN 1), so, in accordance with the Cervical Cancer Prevention Guide, another appointment was made for another annual check-up.

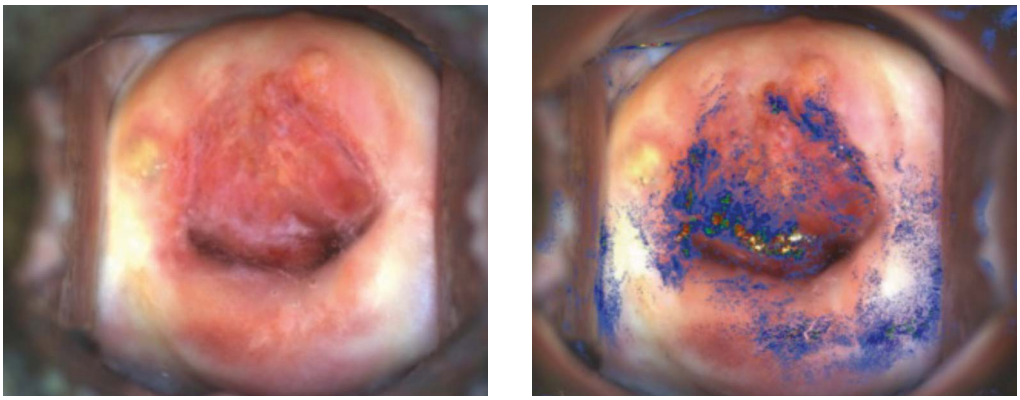

FIGURE 1. Colposcopic image showing thin acetowhite epithelium at 11 12 o'clock, an area that coincides with negative Lugol's iodine staining, from which a biopsy was taken.

TREATMENT AND PROGRESS

The patient was informed that with these data and after completing the vaccination schedule and six months of treatment with *Coriolus versicolor*-based vaginal gel and capsules with Reishi extract and lactobacilli, she would be able to try to become pregnant. And if pregnancy was achieved, cytology and HPV typing would be performed after delivery.

The patient became pregnant eight months after our first visit. She had a normal monitored pregnancy, with vaginal delivery at term, giving birth to a girl weighing 3250 grams.

The patient attended her postpartum check-up, where liquid-based cytology with human papillomavirus typing was performed as planned.

The patient reported having resumed treatment with the vaginal gel and capsules after delivery.

The result of the co-test was negative for malignancy and positive for papillomavirus 52, and was now negative for both the low-grade lesion and the higher-risk virus.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Cervical low-grade squamous intraepithelial lesion is a cellular alteration consisting of atypical changes in the lower third of the epithelium. This lesion is very prevalent and is often associated with human papillomavirus infection. Cytological screening aims to achieve early detection and prevention of progression of cervical lesions to cervical cancer.

In the case of our patient, in the presence of HPV positivity, especially type 16, close follow-up according to the current protocols is of vital importance. In addition, the fact that she wanted to become a mother in a short period of time put us on alert as it was more likely that she would miss her appointments after giving birth.

Since our patient's lesion was histologically confirmed as CIN 1, following

the new AEPCC Guidelines for Secondary Prevention of Cervical Cancer in 2022, follow-up should be with annual co-testing. For this reason, the patient was encouraged to wait for the colposcopic biopsy results before trying to become pregnant.

During the waiting period, in addition to the usual advice on vaccination and smoking cessation, the patient was recommended to take treatment with *Coriolus versicolor*-based vaginal gel(-Papilocare®) and capsules with Reishi extract (Immunocaps®).

Papilocare® vaginal gel is the first treatment with evidence of efficacy in eliminating both human papillomavirus and associated precancerous lesions.

Immunocaps® is a supplement to help normalise the vaginal microbiota and strengthen the immune system, which contains not only Reishi extract, a fungus with antioxidant and immunoregulatory properties, but also different varieties of lactobacilli and a multivitamin compound that improves immune activity, rebalances the vaginal microbiota and improves mucous membranes, with the aim of clearing the virus.

In our case, after a normal pregnancy and delivery, cervical re-epithelialisation was achieved with elimination of the lesion and eradication of the highest risk virus, requiring annual monitoring but with a great improvement in the findings that was conveyed to the patient for her peace of mind.

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ELIMINATION OF LSIL AND HPV 16 IN POST-CONISATION PATIENT WITH UNFULFILLED DESIRE TO HAVE CHILDREN TREATED WITH PAPILOCARE®

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ABSTRACT

In this case, we present a patient with an unfulfilled desire to have children, presenting with high-grade cervical lesions. After conisation, correct HPV vaccination and treatment with Papilocare® for six months, HPV was eliminated and low-grade lesions regressed.

KEY WORDS

Cytology. Colposcopy. HPV. Conisation. Papilocare®.

CLINICAL HISTORY

32-year-old patient with no family history of interest. Her personal medical history includes type 2 DM, obesity and hypertension. Unfulfilled desire to have children.

She was referred to the LGT clinic due to abnormal cytology at her health centre: HSIL and HPV 16 positive.

PHYSICAL EXAMINATION

She came for a consultation and colposcopy is performed: Satisfactory colposcopy. Type 1 transformation zone. Presence of major changes. Schiller's test was positive. Cervical biopsies were taken and reported by anatomical pathology as HSIL/CIN 3. The patient was encouraged to be vaccinated against HPV and a cervical conisation was scheduled.

DIFFERENTIAL DIAGNOSIS

After finding a high-grade lesion, it was decided that conisation should be performed because the lesion occupied > one quadrant and the patient was over 30 years of age.

TREATMENT AND PROGRESS

Cervical conisation was performed and the diagnostic pathology indicated HSIL lesion with free margins. The patient began clinical follow-up at our clinic.

After conisation, the first check-up was performed at six months with Co-test reported as LSIL, HPV 16+.

She returned for another colposcopy, which showed typical post-conisation changes, with no visible lesions. Type 1 TZ.

At this point, it was decided that the patient should undergo clinical follow-up, and treatment with Papilocare® was prescribed for six months.

Again, another co-test was performed one year later and no HPV or cytological abnormalities were detected.

FINAL DIAGNOSIS

After deciding on the approach of clinical follow-up, treatment with Papilocare® and vaccination against HPV, no HPV or cytological abnormalities were detected in the last Co-test. Following these results, the patient started trying to become pregnant.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

The importance of this case lies in the possibility of achieving conservative management of low-grade lesions in young patients with an unfulfilled desire to have children to avoid reconisation and the complications that can develop during pregnancy.

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RECURRENT VULVAR CONDYLOMATOSIS

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ABSTRACT

Case report of a patient with recurrent vulvar condylomatosis despite various treatments, followed up at the clinic for nine years until medical discharge due to non-recurrence of lesions.

KEY WORDS

Condyloma. Papilocare®. Condylomatosis. Recurrence

CLINICAL HISTORY

Family history: mother has Alport syndrome.

Personal history: 31 years of age. No drug allergies. No previous medical-surgical pathology. Menarche: 13 years. Menstrual bleeding/cycle: 7/30. Nulligravid. Never had sex with a male partner (no contraception).

Smoker: 30 cigarettes/day.

Disease: referred from health centre for possible warty lesions on the external genitalia.

PHYSICAL EXAMINATION

External genitalia with lesions suggestive of flat condylomata at the upper level of the vulva, which were stained with acetic acid (biopsy was performed).

Introitus: very lax transverse hymenal remnant observed, which did not prevent insertion of the speculum. No warts visible in the vagina.

Cytology negative, bacterial vaginosis.

Biopsy of vulvar lesion: Condyloma.

Serology: negative.

DIFFERENTIAL DIAGNOSIS

Vestibular papillomatosis (digitiform proliferations of mucosa on the inner surface of the labia minora), molluscum contagiosum (lesion of viral aetiology, poxvirus, contagious), malignant tumours (exophytic, hard, bleeding lesions), Fordyce granules (heterotopic sebaceous glands).

TREATMENT AND PROGRESS

In 2014: vulvar condylomata treated with imiquimod.

In 2015: two new condylomata on external genitalia were removed in clinic.

In 2016: one perianal condyloma. imiquimod was prescribed.

Nov 2019: Laser vaporisation of paraclitoroid and supraclitoroid condylomata (10) and excision with scalpel blade of right perianal condyloma. Biopsy-excision of right perianal lesion: pigmented seborrhoeic keratosis. Smoking cessation.

In 2020: old condylomata on clitoris and two condylomata on introitus. Treatment with trichloroacetic acid + a course of Papilocare® external genital gel. Start of nonavalent HPV vaccination.

November 2021: no lesions. Papilocare® external genital gel is maintained for six months.

November 2023: no lesions. Discharge from clinic.

FINAL DIAGNOSIS

Recurrent vulvar condylomatosis.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Condylomata acuminata are caused by HPV, specifically genotypes 6 and 11 are responsible for 95% of detected cases. Up to 30% may be associated with co infection with HPV genotypes of high oncogenic risk. The incubation period varies according to different publications, ranging from three weeks to eight months and the main route of transmission is sexual contact.

The most effective method for primary prevention of condylomata is vaccination with vaccines containing protection against genotypes 6 and 11 (tetravalent and nonavalent), especially before first sexual intercourse.

At the moment, there is no clearly indicated gold standard for the treatment of lesions, so the emphasis is on individualisation according to the number/size of lesions, location and patient profile.

In this clinical case, we present a young patient, a smoker, who presented recurrent lesions at check-ups despite different treatments (imiquimod, lesion excision, laser therapy and trichloroacetic acid). Finally, the treatment that appeared to be effective in eliminating recurrent lesions was the combination of a destructive treatment (trichloroacetic acid) in combination with Papilocare® external genital gel, after which the patient remained free from recurrence of lesions for three years, achieving medical discharge. It is important to note that throughout the follow-up period, the patient stopped smoking and was vaccinated with three doses of nonavalent HPV vaccine.

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ACLARAMIENTO DE LESIONES Y LESION CLEARANCE AND ERADICATION OF HPV WITH PAPILOCARE®

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CLINICAL HISTORY

We present the case of a 46-year-old patient with a history of recently treated breast cancer, who decided to undergo a complete gynaecological check-up at our centre more than two years after her last evaluation. The patient has no other relevant personal or family history, although she is an occasional smoker. She is nulliparous and premenopausal.

PHYSICAL EXAMINATION

During routine examination, a physical examination was performed and was normal, with a macroscopically normal appearing cervix, but cytology revealed the presence of low-grade dysplasia (LSIL). After informing the patient of this finding, a colposcopy was performed, in which a well-demarcated area of acetowhite epithelium was identified between the 9 and 3 o'clock position, with an associated fine mosaic. After the application of Lugol's iodine, an overall uniform absorption was observed, except in the area described above. The vaginal walls showed normal uptake. A biopsy was performed at the 12 o'clock position, the pathological result of which was consistent with LSIL. (See figures).

In addition, the HPV PCR test was positive for high-risk genotypes 56 and 58.

TREATMENT AND PROGRESS

The patient had a cytology result with low-grade dysplasia (LSIL), confirmed by biopsy. The presence of high-risk HPV (56 and 58) indicates an infection that may be related to the cellular changes observed.

After a detailed explanation of the results and clarification of all the patient's doubts, it was decided that follow-up was needed with cytology and colposcopy in six months. During this period, the patient was recommended to start treatment with Papilocare®, a vaginal gel for the prevention and treatment of cervical lesions associated with HPV. This treatment is spread over six months, with an initial regimen of one vaginal cannula daily for 21 consecutive days, followed by a maintenance regimen of alternate days, stopping treatment during menstruation, until the cycle is complete.

FIGURE 1.

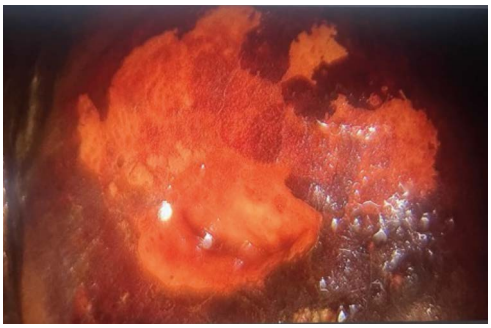

FIGURE 2.

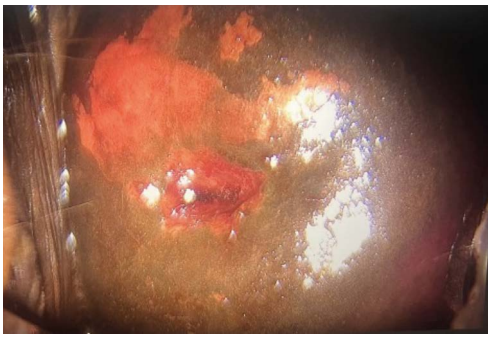

FIGURE 3.

At the end of the six months of treatment, the patient attended her follow-up appointment, showing good tolerance and compliance with the treatment. During this visit, another Pap smear and a colposcopy were performed. The cytology result was satisfactory, indicating an absence of malignancy. Colposcopy showed a normal cervical transformation zone without acetowhite lesions. No minor changes were detected and complete resolution of the previously identified lesions was observed.

FINAL DIAGNOSIS

The use of *Coriolus versicolor*-based vaginal gel can be highly beneficial in the treatment of low-grade dysplasia, as it contributes to its clearance and the elimination of Human Papillomavirus (HPV) infection.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Human papillomavirus (HPV) infection stands out as the most common sexually transmitted infection and, in most cases, it is an infection that is asymptomatic. In about 80% of cases, this infection clears up naturally within about two years without treatment. Although HPV is considered the main risk factor for the development of cervical cancer, the average time lag between HPV infection and the development of cancer is usually two to four decades.

Because of this long window of time, detection of HPV infection, as well as the precursor lesions that HPV can generate at the cervical level, become key targets for screening and early detection of possible future complications.

This approach is crucial for intervening in the early stages of cervical lesions, as it allows preventive and therapeutic measures to be taken that contribute to reducing the risk of developing cervical cancer at later stages.

The current guidelines emphasise that when HPV-positive low-grade dysplasia is diagnosed, the likelihood of developing cervical cancer is quite low. The approach to clinical care for these women seeks to strike a balance between preventing progression of the lesion and avoiding unnecessary treatment. Given the low probability of progression and the high rate of regression of these lesions, a watchful waiting approach is justified, with follow-up and control tests after one year (co-test after one year). However, this strategy can be anxiety-provoking for many women because of the fear of progression without any specific treatment.

In this context, treatment with Papilocare® can be considered as a therapeutic option for these patients. Not only does it focus on helping to eliminate the human papillomavirus, but it has also been seen to help clear premalignant lesions. Papilocare® is a gel for vaginal use composed of a combination of seven components, including *Coriolus versicolor* extract, a medicinal mushroom used in some European countries, China and Japan for its immune-stimulating properties. This gel also contains hyaluronic acid, beta-glucan, Centella asiatica and aloe vera extract, among other elements.

The main objective of applying Papilocare® is to promote re-epithelialisation of the cervical transformation zone, normalise intraepithelial lesions associated with human papillomavirus (HPV), relieve vaginal dryness, restore the balance of the vaginal microbiota and improve overall vaginal health.

Treatment with Papilocare® has been shown to have clinical benefits superior to watchful waiting in HPV-positive patients, demonstrating significant efficacy in the treatment of low-grade HPV-associated lesions, as well as a remarkable ability to increase HPV clearance after a period of six months.

This therapeutic approach can be considered as an integral part of the management of low-grade HPV-positive cervical lesions. However, it is important to note that the effectiveness and inclusion of Papilocare® in the treatment protocol should be evaluated and discussed individually between the physician and the patient.

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RESOLUTION OF CIN 3 LESION AFTER APPLICATION OF VAGINAL GEL CONTAINING *CORIOLUS VERSICOLOR*

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ABSTRACT

Resolution of CIN 3 lesion and HPV 16 infection after six months of treatment with *Coriolus versicolor*-based vaginal gel.

KEY WORDS

CIN 3. Conservative management. *Coriolus versicolor*-based vaginal gel.

CLINICAL HISTORY

28-year-old patient. Personal history: Asthmatic, treated during attacks. No toxic habits. No previous surgeries. OB/GYN history: Menarche: 12 years G2P1(PN)A0. Stable partner, vaccinated against HPV, uses condom. Current pregnancy: Referred from the screening programme due to ASC-H cytology finding, performed in the first trimester of pregnancy. Asymptomatic. Previous cytology in 2019, negative.

CLINICAL EXAMINATION

ASC-H cytology: she has an immediate risk of HSIL that varies according to HPV (26-50% if positive vs 3.4% if negative) and a risk of cervical cancer that does not vary according to HPV. Colposcopy was indicated because of the risk of cervical cancer, regardless of the HPV test result or whether the patient was pregnant (1). She was seen in the cervical pathology clinic at 15 weeks of pregnancy by an experienced gynaecologist, given the difficulty in differentiating cervical pathology from pregnancy-related changes or deciduosis. Colposcopy was adequate, type 1, G1 changes between 12- and 3 o'clock and G2 at 12 o'clock, NO suspicion of micro-invasion. Vaginoscopy was normal, ruling out lesion. Cytology and HR-HPV test were performed. Cytology was reported as HSIL (according to colposcopic findings) and HPV(+): 16.

DIFFERENTIAL DIAGNOSIS

1. Between cervical and vaginal lesion.
2. Between physiological changes of pregnancy and cervical lesion.

3. Between low-grade cervical lesion, high-grade cervical lesion and lesion suspected of invasion.

TREATMENT AND PROGRESS

Results: cytology: HSIL and HPV 16 (+) in a 15-week pregnant woman with NO colposcopic findings suspicious for invasion. We decided on conservative management during pregnancy and re-evaluation after delivery. In the presence of cytological HSIL in a pregnant woman, the aim of colposcopy is to rule out invasion, as treatment of HSIL/CIN 3 will be deferred until postpartum, because the risk of progression is the same as in non-pregnant women[1]. Delivery was eutocic at term: female newborn weighing 4190 g, Apgar 9/10. The patient came for consultation eight weeks after delivery and presented a Colposcopy: adequate, type 1, G2 changes between 12 and 2 o'clock. Cytology was performed: HSIL; HPV 16 (+); Cervical biopsy at 12 o'clock: CIN 3 and ECC(-). As it is a lesion in < one quadrant and patient aged < 30 years old, observation was proposed, in consensus with the patient and following the recommendations of the AEPCC. An appointment was made at six months, recommending the application of *Coriolus versicolor*-based vaginal gel, with the following dosage: one application per day for one month, then every other day, with a break during the week of menstrual bleeding[2]. There were no pathological findings on colposcopy at six months, cytology was negative for malignancy and the HR-HPV test was also negative. Follow-up was by colposcopy and cytology every six months and HPV testing every year for a period of two years. All the results remained negative, confirming resolution of both the infection and the lesion, and she was referred to the screening programme.

FINAL DIAGNOSIS

The application of *Coriolus versicolor*-based vaginal gel for six months in patients with CIN 3 in whom a conservative approach is indicated may contribute to the resolution of the lesion, avoiding the risks associated with conisation.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

CIN 3 has a higher risk of persistence or progression than regression. The long-term cancer risk is 50% in untreated patients compared to 0.7% in treated patients. Conisation is widely accepted as a treatment, but in women of childbearing age it increases the risk of preterm birth, PROM, low birth weight and perinatal mortality. There is little data available on spontaneous regression of CIN 3, as most patients undergo conisation and also often no distinction is made between CIN 2 and CIN 3. However, the time to conisation has shown that in one in four women there was regression of high-grade lesions. It is a priority to identify women who are most likely to regress, avoiding the morbidity of conisation, especially at childbearing age. Regression is more

common in patients aged <30 years and conisation is not without morbidity[3,4]. It is now accepted that CIN 3 is a heterogeneous group with variable risks of progression/regression. A "wait and see" approach may be considered in young women without risk factors (smoking, HIV infection or immunosuppressive treatment), with their consent. The regression rate in women aged <25 years with CIN 3 is 29%, with HPV vaccination at any age and HPV clearance being factors for regressio[5,6].

In patients who meet the criteria set out in the AEPCC guidelines for conservative management of CIN 3, *Coriolus versicolor*-based vaginal gel could contribute to its resolution, as it re-establishes the vaginal microbiota, which favours clearance of the virus, one of the factors involved in the regression of the lesion.

This approach is based on the following facts:

1. Women with persistent HR-HPV infection are known to be at high risk for cervical cancer, but this is not enough and other co-factors are needed, including dysbiosis or disruption of the vaginal microbiota. The vaginal microbiota is important for maintaining the cervical epithelial barrier and preventing HPV entry[7,8].
2. A reduction of *Lactobacillus spp,* or dysbiosis, has been associated with persistence of HPV infection. Long-term use of vaginal probiotics with *Lactobacillus spp* (six months) has been associated with a two-fold clearance of HPV compared to short-term use (three months). Restoration of the vaginal microbiota may help prevent the progression of HPV-related lesions, preventing CIN 2+[9,10].
3. *Coriolus versicolor*-based vaginal gel contains Centella asiatica, beta glucans, alpha glucans, hyaluronic acid and Aloe vera to promote hydration and repair. It also has an anti-inflammatory and immunomodulatory effect that preserves the balance of the vaginal microbiota[2].

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SOCIO-EPIDEMIOLOGICAL PROFILE OF PATIENTS ATTENDING A PRIVATE CLINIC FOR COLPOSCOPY: HOW MUCH DO THEY KNOW AND WHAT ARE THEIR CONCERNS? WHAT CAN WE DO ABOUT LOW-GRADE LESIONS?

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ABSTRACT

We collect socioeconomic and epidemiological data on the patients we see in private practice for lower genital tract pathology (LGTP) with abnormal colposcopy screening, the most frequent questions they ask and the best tolerated therapies with the best results.

KEY WORDS

HPV. Cervical premalignant lesions. Colposcopy. Alternative treatments.

CLINICAL HISTORY

Patients who come for cervical pathology consultation in private practice consult mainly for clarification of concerns about HPV and their abnormal screening test result.

In Spain, the incidence of HPV-associated cervical disease is very significant: ASCUS, LSIL and/or HPV-positive cytology findings account for almost 2.5 million cases diagnosed each year, with cervical cancer being a much rarer entity, with 2500 cases/year[1, 2].

According to the most recent cervical cancer screening guidelines from our scientific societies, the management of persistent non-16/18 HR HPV infection and/or cytology less than or equal to LSIL, as well as histological confirmation of LSIL in non-menopausal patients, is with co-testing every 12 months for two years, given the low probability of rapid progression, or the low risk of major lesions in the following years (risk-based clinical management)[2].

The approach to these situations in our practice is a point of added complexity, not only because of having to report a pathological result, which is not normal and yet which is also a result that does not require excisional or destructive surgical treatment, but rather expectant management. Therefore, when communicating these results to patients, it is of utmost importance to know about adjuvant therapies to HPV

vaccination, condom use or smoking cessation, such as treatment with *Coriolus versicolor* every six months, a well-tolerated therapy with a high level of adherence to treatment by patients, which, according to multiple recent studies, also acts on virus clearance, re-epithelialisation of the cervix and reduction of stress due to the disease and waiting for the next check-up[3, 4].

CLINICAL CASE STUDIES

We reviewed the histories of patients who underwent colposcopy in the last two years in private practice, in whom the mean age at consultation was 37.2 years

With regard to their profession, we find they have higher education or a degree.

More than 50% of the patients who consulted were seeking a second medical opinion regarding HPV positivity or abnormal results in the screening cotest, or to clarify doubts about the disease.

Data are also collected on toxic habits, the method of family planning used, the obstetric formula, whether they are vaccinated against HPV in primary prevention (in patients under 30 years of age), and whether they have followed adequate cervical cancer screening to date with the results of these tests.

During the directed anamnesis, the questions that patients ask after receiving the specific information in their case are recorded in their history, and they are questioned about the extent to which they are aware of the repercussions or treatments for either persistent or transient HPV infection, as well as whether they are aware of the existence of HPV vaccination regardless of age, sexual activity initiated or the existence of established HPV-associated pathology .

Key questions when addressing the issue include: is it cancer? how and when did I catch it? does my partner have to be tested? can I infect him?

Only half of the patients knew that HPV is an STI and none thought that condoms should be used to reduce exposure to the virus if there was a steady partner. Fortunately, many of the patients come forward to initiate HPV vaccination as secondary prevention, and very few are reluctant to be vaccinated after explaining that despite having initiated coital sexual activity or having been in contact with the virus, the benefits of vaccination are greater than those of non-vaccination. They are also very interested when you tell them about non-invasive treatments, including local treatment with *Coriolus versicolor*-based vaginal gel, when you explain to them that the management of their disease consists of expectant management.

The most frequently repeated question, after getting the diagnosis of a lesion less than or equal to LSIL, is: is there no treatment I can do besides vaccination or quitting smoking while waiting for the next test?

In the management and follow-up of these lesions, the recommendations or tests do not differ whether the consultation is carried out in a public or private

FIGURE 1. Most frequently asked questions in the consultation room in case of abnormal screening result and/or HPV positivity.

setting, and although it is true that the recommendations for HPV vaccination and smoking cessation are universal, we have the possibility of offering these treatment alternatives that can help in the fight against HPV during the conservative or non-invasive management of established periodic controls, which are safe and well tolerated[4].

For all these reasons, at our LGTP clinic, we systematically recommend treatment with *Coriolus versicolor*-based vaginal gel for six months according to the usual protocol of daily administration for one month with a one-week break, and thereafter on alternate days up to six months, resting with menstruation after the colposcopy and to all patients who, during the follow-up of their HPV disease, whether persistent infection, cervical lesion or post-conisation, come to us to decide whether to take any treatment while waiting for their next check-up.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

HPV infection is the most common STI (Sexually Transmitted Infection) in the world[5] and is the necessary cause for the development of cervical cancer, as well as other genital and extragenital cancers in both women and men[2].

Vaccination against HPV in primary, secondary and tertiary prevention, together with screening programmes and information campaigns in the media, represent progress in the fight against premalignant diseases and lesions caused by this virus. But the most important role of communicator continues to be that of the specialist, who must provide truthful, understandable

and appropriate information to each patient concerned.

The best strategy to combat HPV infection is to act on modifiable or preventable factors, which can be summarised in three main pillars:

1. Hygiene and dietary habits such as maintaining a healthy and balanced lifestyle and diet, regular physical exercise and avoiding obesity[6], smoking cessation[7], condom use, and the addition of zinc compounds[8].
2. Primary, secondary and tertiary prevention with HPV vaccination.
3. Adjuvant therapies or non-invasive treatments[1, 3, 4, 9] help in the conservative management of mild dysplasia that does not require surgical treatment at this stage, giving the patient a number of tools to cope with and deal with HPV infection. They consist of acting on therapeutic targets such as re-epithelialisation of the cervix, virus clearance and repair of low-grade lesions[3, 4].

In almost 100% of cases, patients are concerned about what they can do to end persistent HPV infection, or what else they can do when they have mild dysplasia or a minor cytological alteration and they have been vaccinated; and in most cases, after having explained the pros and cons, mechanism of action and duration of the different options, local vaginal treatment with *Coriolus versicolor* is the most accepted alternative for women who want to do something else while waiting for their next check-up[3, 4].

In the case of private practice, where the patient generally comes to resolve doubts and obtain a second opinion regarding diagnosis, therapeutic management and follow-up, it is vitally important to have tools that can provide greater peace of mind for patients, to know them and to have up-to-date information on the subject.

Non-invasive treatments based on vaginal application of a gel containing *Coriolus versicolor* as the main compound used as an adjuvant during expectant management have proven to be safe, well tolerated and well accepted, as well as having good adherence and being effective[3, 4, 9].

The stigmatisation of HPV disease and the fact that it is an STI makes the patient feel guilty, vulnerable and insecure, suffer stress[3] and even depression and distortion of their self-image, anguish about the diagnosis and follow-up, etc. All of this leads to impaired psycho-emotional and sexual health, which is why the specialist, by providing clear and up-to-date information, correct follow-up and opening up the possibility of non-invasive treatment, plays a fundamental role in the course of mild HPV-associated disease.

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ADJUVANT AND RE-EPITHELIALISING MANAGEMENT WITH PAPILOCARE® EXTERNAL GENITAL GEL IN VULVAR INTRAEPITHELIAL NEOPLASIA

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ABSTRACT

Vulvar HSIL lesions are associated with persistent infection with high-risk oncogenic HPV genotypes, the most common being 16, 33 and 18.

The risk of progression to vulvar cancer is 6-10%. Treatment should be individualised, taking into account factors such as immunosuppression, multifocality and risk of recurrence.

We present the case of a patient in whom excisional treatment was chosen, followed by Papilocare® external genital gel as an adjuvant and healing agent.

KEY WORDS

Vulvar intraepithelial neoplasia. HPV. *Coriolus versicolor*.

CLINICAL HISTORY

69-year-old woman previously followed up at our lower genital tract clinic.

Personal history: No drug allergies.

Surgical interventions: Type 1 cervical conisation in 2016 for high-grade intraepithelial lesion Laparoscopic total hysterectomy in December 2017 for new onset high-grade intraepithelial lesion with HPV 16.

Subsequent non-regulated follow-up due to the patient's non-appearance

OB/GYN history: G2P2 Last period at 47 years of age She presented with vulvar pruritus that had been refractory to topical antifungal and corticosteroid treatments for several months, accompanied by whitish lesions. No other associated symptoms

Cytology performed in Primary Care one year ago within normality. Non-smoker. No HPV vaccination and no sexual intercourse for five years.

PHYSICAL EXAMINATION

External genitalia with signs of intense lichenification. Predominantly whitish areas in the upper third of the vulva and the region around the clitoris. In the introitus, inner surface of the right lip, erythematous area of approximately 2 cm and isolated whitish area on the left labium minora. No proliferative lesions. Vaginal vault normal without observable alterations.

Liquid-based cytology: Non-neoplastic reactive cellular changes. Atro-

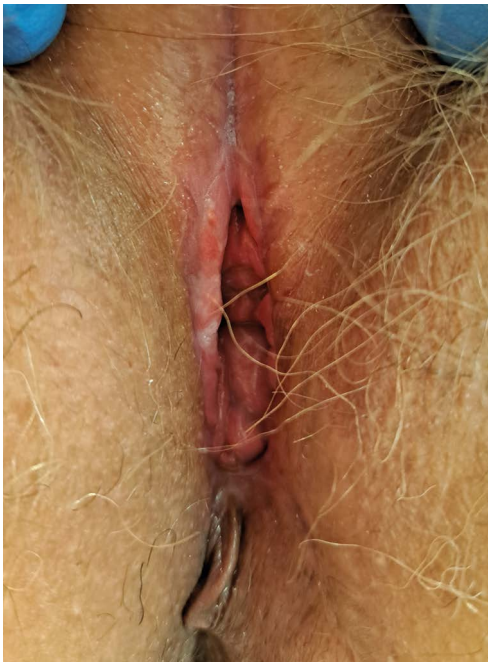

FIGURE 1.

FIGURE 2.

phy. Negative for intraepithelial lesion or malignancy.

HPV Genotype 16 .

Vaginoscopy: Adequate, normal vascularisation. Normal colpotomy scar. Atrophic squamous epithelium. No acetowhite areas .

Vulvoscopy: Adequate, no atypical vessels. Weak acetowhite changes, bilateral. Vulvar biopsies were performed:

A. Lower third of the inner surface of the right labium majus: HSIL-VIN 2.
B. Upper third at the level of the inner surface of the right labium minora: HSIL-VIN 2.
C. Upper third at the level of the inner surface of the left labium minora: HSIL-VIN 2. The p16 study was positive.

FIGURE 3.

FIGURE 4.

FIGURE 5.

DIFFERENTIAL DIAGNOSIS

Given the great variety in the clinical presentation of pre-invasive squamous lesions of the vulva, many vulvar disorders can be confused with these conditions, and histological examination should be performed. The differential diagnosis should be made with conditions such as: condyloma acuminatum, seborrhoeic keratosis, lichen sclerosus, lichen simplex chronicus, lichen planus, psoriasis, contact dermatitis, Paget's disease or candidiasis.

TREATMENT AND PROGRESS

Our patient presented a multifocal lesion, so surgical excision was proposed. A complete and uneventful cutaneous vulvectomy was performed. Closure of the primary defect with direct tension-free reconstruction without the need for skin grafts.

The definitive anatomical pathology findings show:

- High-grade squamous intraepithelial lesion (HSIL/VIN 2-3) located on both labia minora, involving the right peripheral cutaneous border, both medial/internal mucosal borders of the right and the left labia minora and the right deep resection border.
- Low-grade squamous intraepithelial lesion (LSIL/VIN 1) involving the right labium minora and respecting the resection margins.

FINAL DIAGNOSIS

Application of Papilocare® external genital gel once daily was prescribed. The postoperative course was favour-

able and the healing process was correct.

At the three-month follow-up, direct examination and vulvoscopy revealed only one lesion with minor changes on the inner right side, a biopsy compatible with a low-grade intraepithelial lesion (LSIL/VIN 1).

The patient currently remains asymptomatic and shows no signs of recurrence.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Vulvar intraepithelial neoplasia (VIN) is considered a precursor lesion to carcinoma of the vulva. There is no lesion characteristic of VIN, and the clinical findings are highly variable with respect to colour, surface and topography.

Treatment should be individualised and as conservative as possible, if oncological safety permits. We use *Coriolus versicolor*-based gel as an adjuvant because it has been shown to be effective in resolving HPV-associated cervical lesions and promoting hydration and repair of damaged mucosa, enhancing the normal re-epithelialisation process.

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CONISATION *VERSUS* CONSERVATIVE TREATMENT WITH PAPILOCARE®

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Centro médico Alpedrete

ABSTRACT

Papilocare® as an alternative treatment to Conisation

PALABRAS CLAVE

Papilocare®. Conisation.

CLINICAL HISTORY

30-year-old patient. Nulligravid. Stable partner. Tests in public and private clinics.

PHYSICAL EXAMINATION

July 2021. Private clinic:

- Liquid-based cytology: HSIL.
- Colposcopy Normal.
- ECC negative.
- HPV (+) for other HR types.
- Vaccination schedule: Gardasil® 9.
- Conisation was proposed: she wanted expectant management and follow-up in six months.

December 2021. Public clinic:

- Adequate colposcopy, type 1 TZ.
- ECC: CIN 1.
- Definitive study p16 (+): CIN 1.
- Rejects proposed conisation.
- Follow-up in three months.

December 2021. Private clinic:

- Treatment is proposed with six cycles of vaginal Papilocare® and oral Immunocaps for three months.

February 2022. Public hospital:

- Cytology negative.
- Cervical biopsy: negative.
- Subcentimetric condyloma on the right labium majus.

May 2022. Public hospital:

- 5th month of Papilocare® vaginal gel..
- Condyloma smaller than 1 cm on the right labium majus: treated with Vergen for 16 weeks.
- Adequate colposcopy, type 1 TZ.
- Endocervical brushing: LSIL.
- Cervical biopsy negative.
- PCR HPV (+) 31 and 58.
- She was urged to give up smoking.

November 2022. Private clinic:

- No condylomata observed on clinical examination. Negative endocervical brushing
- Liquid-based cytology: negative.
- PCR continued to be (+) for HR.

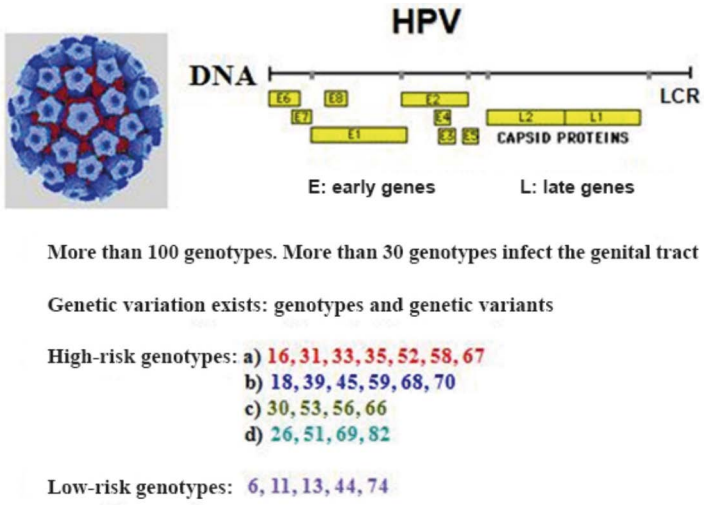

FIGURE 1.

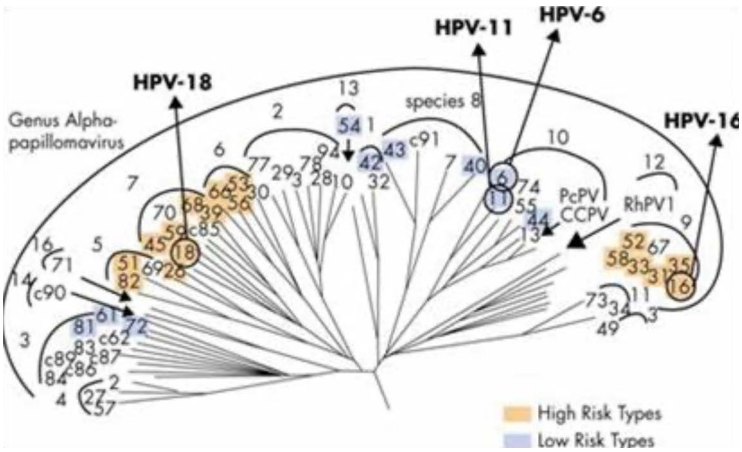

FIGURE 2. Dendrogram of HPV genotypes and phylogeny.

- Colposcopy: satisfactory.
- A second six-month cycle of vaginal Papilocare® was started.
- She was urged to give up smoking.

April 2023. Private clinic:

- Liquid-based cytology: negative.
- HPV typing: negative.
- Annual clinis check-up.

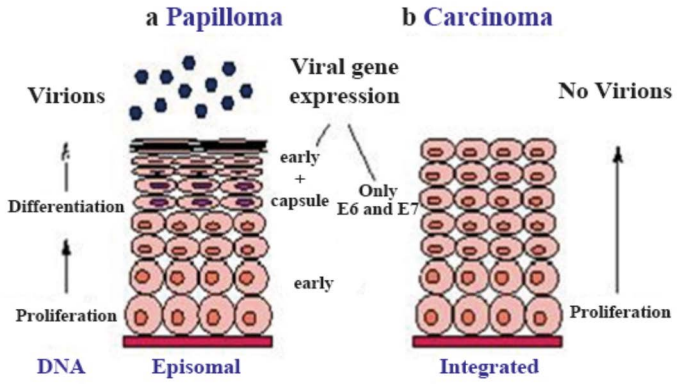

FIGURE 3. Molecular biology of genital HPV infections.

DIFFERENTIAL DIAGNOSIS

A cytological HSIL evolved into LSIL that "tried" to persist and thanks to the perseverance of conservative treatment, regression and HPV "clearance" or negativisation was achieved.

TREATMENT AND PROGRESS

Her evolution was favourable with complete resolution.

FINAL DIAGNOSIS

LSIL in a patient with HPV in the OTHER HR group.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Every year that Procare asks us to present clinical cases, I am pleased to confirm the enormous value of conservative treatment with Papilocare® vaginal gel, despite the reluctance of the public health system.

My experience so far remains satisfactory with two cycles of six months of treatment with *Coriolus versicolor*-based vaginal gel.

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TREATMENT OF CERVICAL HPV-ASSOCIATED LESIONS WITH PAPILOCARE® - A CLINICAL CASE

Dr. Dobrinka Gincheva

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ABSTRACT

Human papilloma virus (HPV) has a crucial role in cervical neoplasia. Koilocyte atypia is considered the morphological equivalent of HPV infection. Papilocare® is a vaginal gel and contains a series of plant ingredients.

Clinical case: A 30-year-old woman visited University hospital "St. Marina" - Pleven, Bulgaria. Colposcopy showed a zone of transformation around the OECC,12 mm in diameter, bleeding on touch. A leukoplakia (L0-1), measuring 10x5 mm. The result of the pap smear was PAP IIIB group. PCR Real Time-study showed positive three oncogenic types of HPV (16, 18, 31). Target biopsy proved cervical intraepithelial neoplasia - CIN 1. The histological result of the cervical cone was: "Glandular ectropion with cervical intraepithelial neoplasia CIN 3. Resection lines - intact". Postoperatively, the patient underwent therapy with Papilocare® according to the scheme.

Results: At the sixth month after treatment, we found a 100% cure. Long-term results show a good trend.

Conclusions: The treatment of HPV-associated cervical lesions should be complex. Definitive treatment of cervical precancers is surgical. The therapeutic regimen with Papilocare® is convenient and provides a high percentage of definitive cures with long-term effectiveness.

KEY WORDS

HPV. Cervical lesions. Papilocare®.

INTRODUCTION

Human papilloma virus (HPV) has a crucial role in the development of cervical neoplasia. Worldwide, HPV causes 5% of all malignant diseases. Cervical cancer is the most common HPV-associated carcinoma in women[1]. More than 200 types of HPV are known, although only a fraction of them have established oncogenic potential. Of the high-risk HPVs, five (HPV types 16, 18, 33, 31, 45) cause 60% of cervical intraepithelial neoplasia (CIN) and 70% of cervical cancers[2]. "Koilocyte atypia" is considered the morphological equivalent of HPV infection. There is enormous variation in disease severity, morphology, host immune response, and potential for progression. It has been shown that approximately 10-15% of women with

HPV-changes of the vulva have an atypical colposcopic finding on the cervix. HPV can affect the duration of the invasion process in malignant lesions. The diagnosis and the type of treatment of precancers and carcinoma of the cervix are established after a comprehensive examination, Pap smear, colposcopy and targeted biopsy. It is necessary to determine predisposing factors before starting treatment:

Viral genotype is a well-known variable that determines cellular integration capacity and associated oncogenic risk.

Immune status of the host - high risk is seen in immunocompromised patients. Improving the local immune status in the area of action of HPV can be considered as a good strategy to facilitate the clearance of the virus.

The balance of the microbiota - guarantees vaginal health. Current evidence suggests that this balance determines the pathogenesis of cervical cancer.

Histological structure of the ectocervix - HPV integrates into cells in the process of mitotic activity. The spare cells in the metaplastic process of re-epithelialization fulfill this condition and represent ideal conditions for the attachment of HPV.

Therefore, a good epithelialization of the cervix with squamous epithelium, with limited or nonexistent transformation zones, would provide an unfavorable environment for HPV colonization and a correspondingly lower oncogenic potential. Positive intervention on these factors is an innovative strategy for the prevention of precancerous lesions in HPV-positive women.

Papilocare® is a Class IIa medical device in the form of a vaginal gel. This gel contains a series of plant ingredients: *Coriolus versicolor,* Centella asiatica, Azadirachta indica (Neem) and Aloe vera, among others such as hyaluronic acid, Bioecolia, ß-glucan. Some of them are contained in niosomes and phytosomes, which improve penetration and increase the release time of the various ingredients. The components of Papilocare® have beneficial pharmacological effects, with antioxidant activity being the main one. It has a hydrating and regenerative effect on the vaginal mucosa, for reepithelialization of microlesions. In this way, it inhibits the integration of human papillomavirus and prevents potential infection[3].

CLINICAL HISTORY

A 30-year-old woman visited the gynecology office of the University hospital “St. Marina” - Pleven, Bulgaria in February 2023. The occasion was a routine examination, including a prophylactic Pap smear, colposcopy and vaginal ultrasound. The patient reported two miscarriages, two children born by cesarean sections in 2010 and 2012. In 2012, a right cystadnexectomy was also performed due to a benign cystic formation on the right ovary. Vaginal ultrasound revealed a normal uterus and left adnexa. Colposcopy showed a zone of transformation around the OECC measuring 12 mm in diameter, bleeding on touch. A leukoplakia area (L0-1), measuring 10x5 mm and located in the region of the anterior

FIGURE 1. Atypical colposcopic finding in PAP group IIIB and CIN 1.

lip of the PVCU, was also visualized (Fig. 1).

A PCR Real Time HPV test and a cervical smear were taken. The result of the prophylactic pap smear was PAP IIIB group. PCR Real Time-study showed positive three oncogenic types of HPV (16, 18, 31). The protocol for cytologically signaled patients with proven HPV infection requiring histological examination was discussed with the patient. Target biopsy of the suspected atypical area proved cervical precancer - cervical intraepithelial neoplasia - CIN 1. The woman was offered cervical conization with a separated sample abrasion. After informed consent, signed by the patient, the manipulation was performed on 15/03/2023. The histological result of the cervical cone was as follows: "Glandular ectropion with cervical intraepithelial neoplasia CIN 3 (high grade). Resection lines - intact". Postoperatively, the patient underwent therapy with Papilocare® according to the scheme. Treatment with Papilocare® is applied according to the following scheme and lasts six months: first month - three consecutive weeks of one vaginal application every night, before sleep and one week off (menstrual cycle). During each of the following five months - three consecutive weeks of one vaginal application every second night, before sleep and one week off (menstrual cycle). The scheme is easy and suitable for home treatment.

RESULTS

We established the following results: After completion of the six-month conservative treatment with Papilocare® of the patient with third-degree cervical intraepithelial neoplasia, a control Real Time PCR for HPV was performed. We found the following result: all three oncogenic HPV types were negative. A control smear was taken and a colposcopy was performed. The smear was group II, and the colposcopy showed absence of the boundary between the flat and cylindrical epithelium (Fig. 2 and Fig. 3).

At the sixth month after treatment, we found a 100% cure. In addition, we found that Papilocare® supports the postoperative healing of the cervix. The patient underwent control gynecological examinations every three months for one year after the HPV infection was cured. To date, no recurrence of the disease has been detected. Long-term results show a good trend.

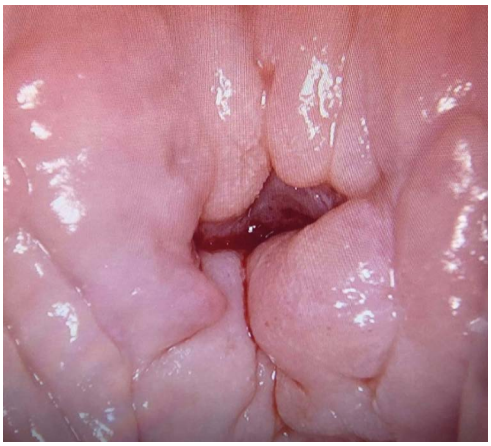

FIGURE 2. Colposcopic image of the cervix two months after conization.

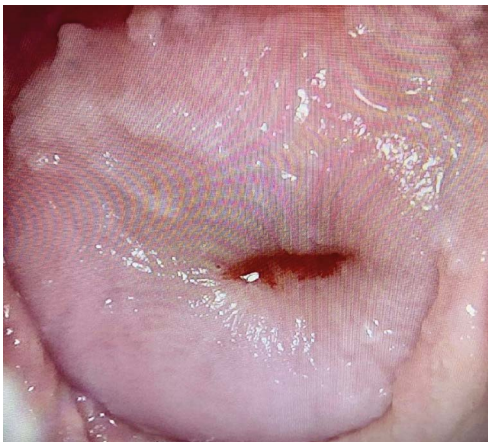

FIGURE 3. Absence of border between squamous and columnar epithelium six months after conization.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

In 2019, L. Serrano and co-authors presented the results of the PALOMA clinical trial. After a six-month treatment period, a non-hormonal vaginal gel based on *Coriolus versicolor* showed statistically significant efficacy in normalizing cervical lesions caused by HPV (ASCUS/LSIL on cytology and matching colposcopy result), especially in the subpopulation with high-risk HPV. There was also a trend toward increased HPV clearance in this subpopulation[4]. There is a lot of evidence that Papilocare® vaginal gel significantly improves the re-epithelialization of the cervix (95% of cases). If the cervix is well epithelialized, the possibility of incorporation of HPV with oncogenic potential decreases significantly.

Papilocare® offers a new preventive strategy: easy to use, without pronounced side effects for primary prevention of HPV-dependent lesions[5]. Similar results were presented in the study of Spanish doctors who investigated the effectiveness of therapy with a vaginal gel based on *Coriolus versicolor*.

Particular attention is paid to the concept of "vaginal health" as a condition that maintains the physiological conditions of the vaginal ecosystem. It has gained interest in recent years, including in clinically asymptomatic healthy women. It was found that even these women can have changes in the epithelialization of the cervix and the state of the vaginal microbiota.

The aim of their pilot prospective study was to evaluate the effect of vaginal application of Papilocare® on cervical mucosal epithelialization and vaginal microbiota in asymptomatic women[6-9]. The most popular treatment for cervical precancers is surgical excision (LLETZ) combined with im-

munomodulatory therapy for at least six months. Patients report some side effects after the surgical intervention such as pain, bleeding, hospital stay, absence from work and social difficulties.

Back in 1985, B.R. Duus et al. found that the cure rate of cervical precancers after surgical excision and histologically proven intact resection lines was 72%[10]. An additional advantage of surgical treatment is the possibility of histological examination. This provides information for subsequent adequate treatment of suspected malignant lesions. It is important to note that the treatment of HPV-associated cervical lesions should be complex.

Surgical excision removes the lesions. It is necessary to supplement the treatment with Papilocare® and with immunomodulating therapy. The goal of Papilocare® and immunomodulation is to eliminate the human papillomavirus. A number of world authors report on their experience and the benefits of HPV vaccines[11].

CONCLUSIONS

Based on our results, we reached the following conclusions: The treatment of HPV-associated cervical lesions should be complex. Definitive treatment of cervical precancers is surgical. The therapeutic regimen with Papilocare® is convenient and provides a high percentage of definitive cures with long-term effectiveness.

Treatment with Papilocare® is easy to administer, supports the elimination of HPV, prevents future malignancy and ensures a good quality of life for patients.

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CONSERVATIVE TREATMENT OF COEXISTING SQUAMOUS CELL CARCINOMA *IN SITU* AND ADENOCARCINOMA *IN SITU* OF THE CERVIX: CASE REPORT

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ABSTRACT

Adenocarcinoma-*in-situ* (AIS) of the uterine cervix is a precursor to cervical adenocarcinoma and may co-exist with high-grade squamous intraepithelial lesions of the uterine cervix. For fertility sparing reasons, conservative treatment is considered and the patient is well informed about the follow-up.We present a case report of patients with coexisting Squamous cell carcinoma *in situ* and Adenocarcinoma *in situ* AIS. We wanted to evaluate the effect and safety of CC with additional Papilocare® vaginal suppositories in this women and to evaluate recurrence or progression of disease in 12 months follow up period. Conservative treatment of coexisting squamous cell and adenocarcinoma *in situ* cervical cancer is possible with intensive follow up after conservative treatment. Intensive monitoring should preferably be done by endocervical cytology, and human papillomavirus and deviations should be subjected to further histological examination. Papilocare® is an effective additional treatment for patient with high risk HPV infection and cervical lesion.

KEY WORDS

Adenocarcinoma of the uterine cervix. Squamous intraepithelial lesions. Conservative treatment.

INTRODUCTION

Cervical cancer is the second most common form of cancer among young women worldwide[1]. Adenocarcinoma-in-situ (AIS) of the uterine cervix is a precursor to cervical adenocarcinoma and may co-exist with high-grade squamous intraepithelial lesions of the uterine cervix[2]. Studies show that 55% of women with AIS had co-existing squamous intraepithelial neoplasia[3].

On screening cytology there is a lower likelihood of detecting glandular lesions compared to precancerous squamous lesions, due to the fact that

the glandular lesions are generally high in the cervix or deep within the glands. Particular attention is needed to obtain adequate endocervical samples. Many patients with AIS are asymptomatic with the diagnosis often being made on routine cervical screening[4]. However, up to 60% of AIS lesions are detected incidentally following clinical examination for cervical intraepithelial lesion 2/3 (CIN 2/3)[5].

Cervical conization (CC) is considered to be the safe and preferred treatment for high-grade squamous intraepithelial lesions, while as hysterectomy is the preferred treatment for AIS due to the higher risk of residual AIS after CC and foci of adenocarcinoma cells that are not contiguous, also known as "skip lesions"[6]. However, studies show that in patients with AIS, achieving a negative margin after surgical excision was associated with a significantly lower risk of residual disease and recurrent disease compared with that for patients with a positive margin[7]. In a study by Munro et al, pure AIS lesions detected incidentally on an excision specimen had an increased risk of disease persistence/recurrence when compared to mixed lesions (AIS with co-existent cervical intraepithelial neoplasia grade 2/3)[8]. For fertility sparing reasons, conservative treatment is considered if AIS is completely resected by CC i.e. with negative margins, and the patient is well informed about the follow-up.

Follow-up after conservative treatment should preferably be done by endocervical cytology, and human papillomavirus testing. Abnormal results should be subjected to further histological examination[7].

We present a case report of patients with coexisting Squamous cell carcinoma *in situ* and Adenocarcinoma *in situ* (AIS) . We wanted to evaluate the effect and safety of CC with additional Papilocare® vaginal suppositories in this women and to evaluate recurrence or progression of disease in 12 months follow up period.

CLINICAL HISTORY

A 31-year-old patient (G3, P1) was referred to the University Clinic of Gynecology and Obstetrics – Skopje in June 2022 because of a repeated abnormal cervical cytology which showed persistent cervical intraepithelial lesion grade.

- Ethnicity: Albaninan.
- The patient's medical history was unremarkable.
- Personal disease history: no chronic diseases of interest.
- Smoker. Yes (4-5 cigarettes a day).
- First sexual relations: 16 years old.
- Married.
- Pregnancies: one, spontaneous delivery of a child.
- Abortion: No.
- Contraceptive method: No
- Family disease history: none of interest.
- Cytology provided; yes abnormal cervical cytology which showed persistent cervical intraepithelial lesion grade,
- HPV vaccination. No

PHYSICAL EXAMINATION

In a lithotomy position speculum examination showed a regular mucosa of the cervix and vagina. Transvaginal ultrasound examination was made at the patient with empty bladder and revealed an anteverted uterus with anteroposterior diameter of 40mm and endometrium with a diameter of 1 mm. Ovaries were normal. There was no free fluid in the pouch of Douglas. Laboratory tests were in referent ranges.

The patient underwent a cervical biopsy, endocervical sampling and HPV testing. The histopathology result showed high grade squamous intraepithelial lesion and high risk HPV 18 positive.

DIFFERENTIAL DIAGNOSIS

HPV persisten infection.

Low or high grade squamous Intraepithelial lesion.

Adenocarcinoma *in situ* in extremely rare care.

TREATMENT

The patient was then treated with a cold knife conization. The surgery was uneventful. The histopathology report showed that it was a case of cervical squamous cell carcinoma *in situ* and adenocarcinoma *in situ*- HPV related.

The lesions of the highest risk on the histopathology report were the following:

- Squamous cell carcinoma *in situ* (HSIL) in the transformation zone and partially in the endocervix at the position around 1 o'clock and around 5 o'clock.
- Adenocarcinoma *in situ* (HCGIN): a small focus (0.7-1 mm) of several localized glands. In the endocervix at about 7 o'clock position.

The exocervical squamous epithelium is acanthotic with areas of koilocytosis (in addition to HPV infection). Exocervical and/or in the transformation zone are also foci with mild dysplasia. HSIL - moderate to severe dysplasia was found in the transformation zone at positions around 11-1 o'clock and 6 o'clock. In the transformation zone and partially in the endocervix, squamous metaplasia of the cylindrical mucin-producing epithelium can be seen, and a regular cylindrical mucin-secreting epithelium is also found deeper in the endocervix. Eroded zones with underlying granulation tissue and surrounding regenerative epithelial atypia are also present. Mucin-secreting glands are embedded in the stroma, some of which show squamous metaplasia of the glandular epithelium. In the stroma, especially subepithelially around the transformation zone, a moderate mononuclear inflammatory infiltrate can be seen, which propagates intraepithelially at some points. At the position around 4 o'clock and after deeper cuts, denuded cervical stroma is found.

The circumferential epithelial resection margin showed mild grade dysplasia (LSIL) at position 3 o'clock. No dysplastic changes were found in the cone apex.

The patient didn't accept hysterectomy and after consiliar examination of gynecologist and pathologist, was asked to be follow up by endocervical cytology, endocervical biopsy for histological evaluation and human papillomavirus testing every 4 months. The first month after the conization, patients received a 21 day Papilocare® vaginal suppository, and in the next five months she received Papilocare® vaginal suppository every second day. At the first in October 2022 controlled HPV typisatio was still HPV 18 positive, but at the second examination 8 months after conization in January 2023, HPV was negative. All controlled cytological and hystopatological findings were normal.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

This case presented an invasive double primary carcinoma of the uterine cervix composed of a squamous cell carcinoma *in situ* and adenocarcinoma *in situ*.

A double primary carcinoma of one organ is defined as a condition when the two carcinomas are histologically distinct and separated from each other by stroma or basal lamina. In the literature, simultaneous occurrence of cervical intraepithelial neoplasia and primary adenocarcinoma has been reported[9] Maiyer et al. analyzed the coexistence of squamous cell neoplasm in 230 cases of primary adenocarcinoma of the cervix [10]. They found that cervical intraepithelial neoplasia was present in 43% (99/230) cases, but only six cases (2%) exhibited concurrent invasive squamous cell carcinoma.

In our case we detected only squamous cell carcinoma at histopathological analysis of the endocervical biopsy, and we failed to detect adenocarcinoma. The reason of that is probably because more than half of cervical adenocarcinomas grow endophytically, and this may result in later detection of the disease than the typically exophytic squamous cell carcinomas. It is reported that clear cell adenocarcinomas of the cervix showed predominantly endophytic growth (80%) and extended to the uterine corpus, creating a barrel-shaped cervix[9].

The etiology of synchronous occurrence of squamous cell carcinoma and adenocarcinoma of the cervix is not clear, but infection with the high – risk HPV (especially with HPA 16 or 18) is one of the most significant oncogenic factor detected in >90% of squamous cell carcinomas of the cervix and approximately one half of squamous cell carcinomas[11]. Treatment of HPV infection could prevent development of cervical intraepithelial lesions. Papilocare® could help HPV clearens in the patients.

According the prognosis of the adenocarcinoma, in the literature results shows that mixed squamous and adenocarcinoma had more favorable prognosis than patients with AIS alone, probably because of the early detection of squamous cell abnormalities on PAP smear of punch biopsy which lead to further treatment and accidently made

early detection of AIS and this early detection of AIS might result in a favorable prognosis.

After the hystopatological finding of the coexisting Squamous cell carcinoma *in situ* (HSIL) and Adenocarcinoma *in situ* AIS we explained the two options of further treatment to the patients operative or conservative. Hysterectomy is recommended for AIS of the cervix, but for young women who wish to maintain fertility, cervical conization (CC) is feasible, but total hysterectomy is preferred after completion of childbearing[12,13]. The patient refuse hysterectomy and she wanted to have conservative treatment with intensive monitoring and follow up. She got Papilocare® vaginal suppositories for 6 months after the cold conization, and at the second control she had negative HPV result, and all cytology and histopathology findings which were repeated every 4 months after the conization were normal.

CONCLUSION

Conservative treatment of coexisting squamous cell and adenocarcinoma *in situ* cervical cancer is possible with intensive follow up after conservative treatment. Intensive monitoring should preferably be done by endocervical cytology, and human papillomavirus and deviations should be subjected to further histological examination.

Papilocare® is an effective additional treatment for patient with high risk HPV infection and cervical lesion.

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USEFULNESS OF PAPILOCARE® IN YOUNG PATIENTS WITH LOW-GRADE LESIONS (CIN 1)

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ABSTRACT

Human papillomavirus infection is becoming increasingly common. Earlier sexual debut, a lack of barrier planning methods and timely screening by pap smear and/or colposcopy have allowed early detection of dysplasia (low-grade cervical intraepithelial or CIN 1 lesions). It is reported that spontaneous regression can be achieved in young patients within one to two years if they undergo lifestyle changes that allow the immune system to help ensure an adequate cell turnover. The use of antioxidants as well as vitamins, minerals and trace elements and substances that stimulate re-epithelialisation and/or healing could increase the rate of spontaneous regression and prevent progression to a high-grade lesion. Our study is based on the use of Papilocare® for three months as part of the management to reduce the low-grade lesion and assess its effects.

KEY WORDS

Human papillomavirus (HPV). Low-grade cervical intraepithelial lesion (CIN 1). Spontaneous regression. Papilocare®.

CLINICAL HISTORY

28-year-old female paramedic whose family history includes a maternal great-grandmother with a history of cervical cancer, unbalanced diet due to work schedules and eating out, no history of chronic disease, no surgical history, no history of allergies, gynaecological history: start of sexual activity at age 18, five sexual partners, no family planning method, having previously used pills and occasionally condoms, no cervical cancer screening with Pap smear or colposcopy, no pregnancies.

Clinical picture: She came for a check-up due to persistent asymptomatic leucorrhoea despite the use of over-the-counter antifungal ovules. She reported that she had not undergone any cervical cancer screening, which is another reason for consultation.

PHYSICAL EXAMINATION

A complete physical examination was carried out by organ system. The female genital system was examined by means of a vaginal mirror and a small amount of whitish leucorrhoea was found. A Pap smear and colposcopy were performed with the colposcopic results revealing a minor lesion within the transformation zone in a radius between 7 and 9 o'clock of the lower right

FIGURE 1. Image of the lesions identified by colposcopy and delimited after application of Lugol's iodine during her first consultation.

quadrant as well as part of the endocervical canal. Given the colposcopic suspicion, a biopsy of the lesion was taken and sent to pathology together with a Pap smear slide, for which both results corroborated CIN 1.

DIFFERENTIAL DIAGNOSIS

Low-grade intraepithelial lesion versus high-grade intraepithelial lesion.

TREATMENT AND PROGRESS

The treatment used was Papilocare® gel applied vaginally after the end of her menstrual bleeding for 21 days for three months, as well as reducing activities that could reduce the effectiveness of

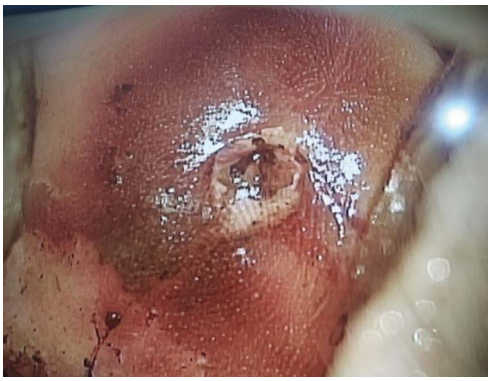

FIGURE 2. Image of follow-up cervical colposcopy following a history of having minor lesions seen on colposcopy (CIN 1 according to biopsy and Pap smear), treated for three months with Papilocare®. It can be seen how the lesions in the radius between 7 and 9 o'clock regressed to normal.

the immune system, such as excessive alcohol use and smoking and avoiding sleepless nights. A follow-up colposcopy at three months showed regression of the outermost lesions of the transformation zone to normal; however, part of the periorificial lesion still persisted.

FINAL DIAGNOSIS

Low-grade intraepithelial lesion with partial regression of minor lesions.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

According to the literature, 60 to 70% of young patients with low-grade lesions can regress to normal within one to two years with lifestyle changes that help their immune system control the HPV infection, re-epithelialising with healthy cells. In the case of our patient, there

was an evident improvement in a short period of three months, with the most external colposcopic lesions disappearing in the transformation zone. It is also worth studying whether the device for applying Papilocare® gel should have a longer tip to reach the areas closest to the endocervical canal. Comparative studies are needed to evaluate the superiority of using Papilocare® *versus* patients who do not use Papilocare®. It is worth mentioning that the leucorrhoea also decreased considerably in our patient, the main symptom for which she attended her first assessment.

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INTEGRATED MANAGEMENT OF ADOLESCENTS WITH MULTIFOCAL CONDYLOMATOUS LESIONS, A NOVEL THERAPEUTIC ALTERNATIVE IN PERU

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ABSTRACT

Combined novel alternative treatment (*Coriolus versicolor* + CO_2 laser) in adolescent with CIN 1 and multifocal condylomatosis.

KEY WORDS

Condylomatosis. HPV. Fractionated CO_2 laser. *Coriolus versicolor*.

INTRODUCTION

Condylomata acuminata, or genital warts, are the most prevalent sexually transmitted infection (STI) in the world[(1)], with approximately 5-10% of the population estimated to have at least one episode in their lifetime[(2)]. The genotypes most frequently isolated in condyloma acuminatum tissue lesions are 6, 11, 16 and 18[(3)]. HPV causes transient cellular changes (cervical intraepithelial neoplasia, CIN) in young women. Most cases of CIN 1/CIN 2 will regress spontaneously in less than 24 months. Conservative management should be considered, especially in women of childbearing capacity with high expected compliance[(4)].

Unlike the 2012 ASCCP (American Society for Colposcopy and Cervical Pathology) guidelines, which relied on algorithms based on test results, the new consensus guidelines follow a risk-based approach to determine the need for surveillance, colposcopy or treatment. Thus, in the new recommendations, observation is preferred to treating all patients with CIN 1[(5)] . We present the case of a late adolescent girl aged 19 years with multiple lesions due to HPV viral infection in whom new techniques were used in the conservative management of this condition, achieving promising results.

CLINICAL HISTORY

Reason for consultation: Appearance of strange lesions and itching in the genitals.

Current Illness: A 19-year-old female patient who consulted for irregular lesions in the genital area of three months duration (May 2023), which were initially

small and increased in size and quantity, with an irregular shape, concomitant moderate pruritus and no exacerbating factors, which is why she came to the clinic for evaluation, diagnosis and treatment.

Family History: Living father, mother and brother. No apparent disease history in any family members.

Personal and gynaecological/obstetric history: Carbohydrate-rich, starchy, protein- and lipid-poor diet. No significant pathological findings were reported. Menarche: 12 years. Sexarche: 19 years. Sexual partners: 01. 0 pregnancies. No use of oral contraceptives and barrier methods.

Physical examination: Weight: 44 kg, Height: 1.56 m, BMI: 18.10.

Good general condition, afebrile, hydrated, active. Asthenic body type. Skin: phototype III.

Oral cavity: No apparent lesions on oral mucosa. External genitalia: Two warty lesions at the posterior junction of the labia majora and labia minora with an irregular surface, raised, pale pink and pearly, mirror image. The right lesion measured 2.5 x 1.5 cm and the left lesion measured 3 x 2 cm, converging centrally, and there was another fusiform lesion of the same size above the right lesion, measuring 1.5 x 0.5 cm. On the edges of both labia minora and the vaginal introitus there are multiple lesions with a digitiform appearance, others are rounded with a smooth surface and others are acuminate and irregular. Those of the labia minora are the same colour as the vulvar tattoo and those of the vaginal introitus and hymenal caruncles are pearly white.

Speculoscopy: presence of multifocal, pearly white lesions on the vaginal mucosa, some rough and flat, others raised. Cervix central, external cervical os (ECO) rounded, erythematous. A generalised whitish periorificial lesion with a rough, flattened surface is visible to the naked eye.

On palpation: cervix central, posterior, mobile, non-painful, no visceromegaly. Central uterus in anteversion and anteflexion, intrapelvic. No palpable adnexal masses. No perineal or perianal lesions are observed. Rest of the physical examination within normal limits.

DIFFERENTIAL DIAGNOSIS

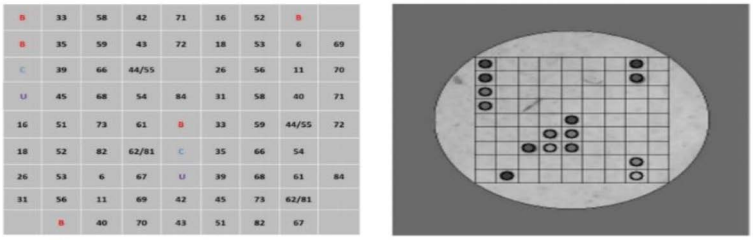
Vestibular papillomatosis: A benign condition, unrelated to HPV infection, presenting as digitiform mucosal lesions located on the inner surface of the labia minora and occasionally projecting to the vestibular region. These lesions have a connective and vascular tissue axis.

DIAGNOSIS

1. Multifocal condylomatosis (Vulvar, Vestibular, Vaginal and Cervical).
2. CIN 1 - HPV.
3. Low weight.

Additional tests: In view of the findings on physical examination and the aggressive evolution of the lesions, it was decided that the recommended primary HPV screening algorithm should be applied[6].

Molecular test for detection of HPV viral DNA and genotyping test for 35 HPV types by Direct Flow CHIP system



B	33	58	42	71	16	52	B	
B	35	59	43	72	18	53	6	69
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U	45	68	54	84	31	58	40	71
16	51	73	61	B	33	59	44/55	72
18	52	82	62/81	C	35	66	54	
26	53	6	67	U	39	68	61	84
31	56	11	69	42	45	73	62/81	
	B	40	70	43	51	82	67	

FIGURE 1. HPV Viral Genotyping Result. Methodology: PCR-Hybridisation.

by PCR (polymerase chain reaction) followed by reverse hybridisation: Positive. Genotypes: low risk 6, 62/82 and 67, respectively (Fig. 1).

Cytology: Satisfactory for evaluation. Negative for squamous intraepithelial lesion and malignancy. Severe non-specific inflammation.

Vulvoscopy and Colposcopy: Vulvoscopy: Acetowhite lesions on the introitus, vulvar fourchette, labia minora and hymenal caruncles extending into the vaginal mucosa. Colposcopy: Adequate overall assessment. Vaginal walls with multifocal lesions, some raised and some flat, on the vaginal mucosa, acetowhite epithelium: positive (+). Transformation Zone: Type 1. Squamocolumnar junction: fully visible. Abnormal colposcopic findings: Acetowhite epithelium positive (+), time reference 12-3 and 6-10. Non-specific: Lugol's stain (Schiller's test): positive (+), same time references as with acetic acid. Miscellaneous findings: open glandular orifices and diffuse colpitis (Fig. 2).

Colposcopy-guided biopsy: Low-grade intraepithelial lesion: CIN 1. Moderate chronic cervicitis.

TREATMENT

After informed consent and administration of local anaesthetic formula with 5% prilocaine, 5% lidocaine and 7% tetracaine for ten minutes, as well as local cold application, fractionated CO_2 laser photovaporisation was performed with Edge One® equipment, Model Jeisys, Wavelength: 10,600 nm. Parameters used: Surgical mode. 50 handpiece, Pulse duration: 200 µs, Frequency: 200 Hz, Laser mode: Ultra. Spectral absorption, Chromophore: water.

In parallel, *Coriolus versicolor*-based gel (Papilocare®) containing hyaluronic acid niosomes, beta-glucan niosomes, Centella asiatica phytosomes, Bioecolia, aloe vera and neem extract was indicated, prescribing the administration of the contents of one vaginal cannula daily for three consecutive weeks and then every other day for three months. Its use should be omitted during menstrual bleeding.

Additionally, the use of a nutritional supplement containing vitamin C, zinc, glucosamine, arginine, glycine, calcium pantothenate, pyridoxal, folic acid, cyanocobalamin and malic acid (Viusid®)

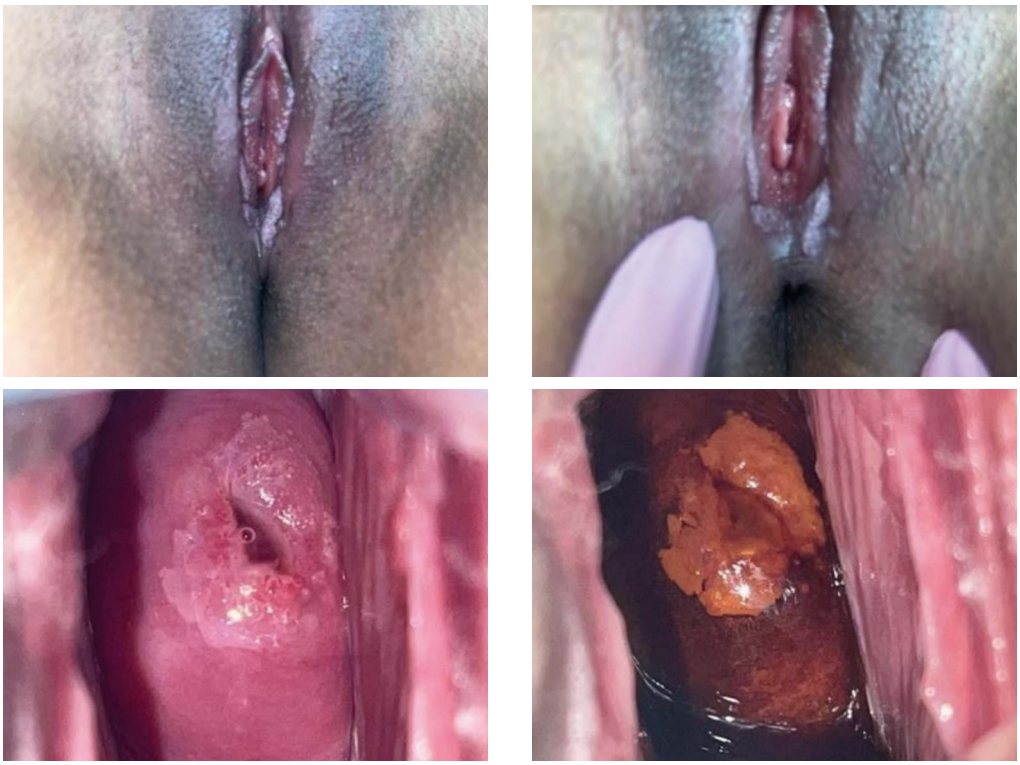

FIGURE 2. Images of condylomatous lesions before and during vulvoscopy and colposcopy.

was indicated: take the contents of one sachet in half a glass of water and take daily for three months.

Vaccination with Gardasil® 9 was started. Treatment was discussed and urological evaluation of the sexual partner, use of barrier methods during sexual intercourse and hygiene and dietary recommendations were suggested. 21-day follow-up visit for re-evaluation of external condylomatous lesions. Cervical screening appointment in 90 days.

Progress. Satisfactory, 21 days post photovaporisation: external acuminate condylomatous lesions absent, skin undergoing a normal process of healing and re-epithelialisation.

Gynaecological evaluation after 90 days of treatment with *Coriolus versicolor,* post HPV vaccination, use of nutritional supplement, lifestyle modification, follow-up of hygiene and dietary recommendations: favourable. There was no evidence of lesions on the vaginal mucosa or cervix (Fig. 3). Satisfactory re-epithelialisation process. Positive impact on the patient's psychological, sexual and aesthetic sphere.

Liquid-based cytology (follow-up at 3 months): Satisfactory sample for oncological evaluation. Trophism: trophic. Micro-organisms: Döderlein's bacilli, normal squamous cells. Leukocytes: 2+, Endocervical cells: normal. Conclusion:

FIGURE 3. Evolution three months post-treatment.

negative for neoplastic cells. Mild inflammation.

Hygiene and dietary recommendations, modification of risk factors and use of condoms are maintained. Complete the vaccination schedule. Maintain treatment with *Coriolus versicolor* for an additional three months and gynaecological check-up in three months. Insist on assessment of her sexual partner by a specialist.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Early sexual debut leads to social, economic and public health problems, with increased sexual exchange with a variety of partners, promiscuity and low awareness of the risks of pregnancy and STIs. . Immaturity of the epithelium of the cervix and vaginal mucosa is an additional factor in HPV viral infection. Conservative management of HPV viral infection as well as cervical lesions has a negative psychological impact on patients. HPV diagnosis in women is typically associated with symptoms of anxiety, increased emotional suppression, shame and internalised emotions, sexual dissatisfaction and a negative impact on quality of life[8].

A combined treatment alternative is proposed with: a) the benefits of CO_2 laser and b) *Coriolus versicolor*-based therapy for the treatment of condylomata. In the former, its action on the coagulation of blood vessels and the necrosis of warts without producing thermal damage to neighbouring healthy tissue is noteworthy, reducing the risk of infection and achieving aesthetic, regenerative and functional results. In primary and sensitivity analysis, CO_2 laser therapy was the treatment that ranked first in achieving complete viral clearance at the end of treatment[9]. In the second, according to the findings of the PALOMA study, the power of repair of low-grade lesions has been shown to significantly outperform those obtained with the expectant management approach (eight out of ten women achieved normalisation of their lesions), higher HPV clearance rates, more than double (63%) the established value at six months, achieving negative cytology and/or HPV

clearance/reduced viral load)[7], which is consistent with the clinical and cytological findings in the case presented. Further studies are required in this area in Peru in order to generate statistically sustainable data; however, in light of the patient's rapid and effective clinical evolution, it is suggested that this treatment alternative should be considered. In conjunction with compliance with the vaccination schedule, lifestyle changes, primary screening with high sensitivity and specificity tests, the use of barrier methods and adherence to HPV intervention strategies, interesting clinical experience in this respect is raising the interest of the scientific community in this line of research.

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HPV, PAPILOCARE®, NILM, COLPOSCOPY, *CORIOLUS VERSICOLOR*

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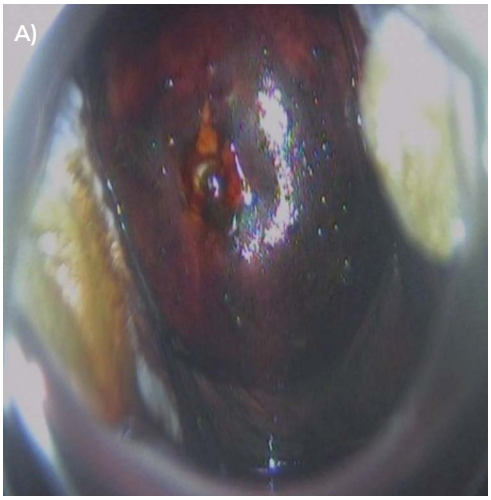
CLINICAL CASES

1. Patient 40 years of age, LSIL lesion present, HPV strain 18, 56, 53, tec negative CIN, Biopsy-CIN 1 (BGC-colposcopically guided biopsy). The patient was prescribed treatment with Isoprinosine and Papillocare® for 6 months. (In the first month 21 days with 7 days break the period of menstruation and from the 2nd month to the 6th month an application every two days with 7 days break the period of menstruation). Following treatment with Papilocare®, cytological negativity was observed at 6 months and HPV Test 53 present. The patient received another 3 months of treatment with *Coriolus Versicolor* and Papilocare®. NILM was observed, HPV negative after (Fig. 1 A and B).
2. Patient 39 years of age, ASCUS lesion and HPV 6 present. Cervico-vaginal condylomatosis. Treatment: 6 months Isoprinosine + Papillocare® 6 months, Gardasil® monavalent vaccination Colposcopy reevaluation after 3 months of treatment. After treatment 6 months: Cytological negativity but persistence HPV→ *Coriolus* and Papillocare® 3 months. Reassessment after 6 months: NILM, HPV negative (Fig. 2).
3. Patient 30 years of age, ASCUS lesion present, HPV strain 33, 30, CIN Tec negative. Treatment: Isoprinosine + Papillocare® 6 months. Cytological reassessment at 6 months: NILM HPV testing 2 months after completion of treatment: HPV negative (Fig. 3 A and B).
4. Patient aged 33 years, ASCUS lesion, HPV 45, CIN Tec negative. Treatment: *Coriolus Versicolor* and Papillocare® for 6 months. Cytological negative and negative HPV test after treatment (Fig. 4 A and B).
5. Patient aged 31 years, ASCUS lesion also had HPV strain 31. Treatment: *Coriolus Versicolor* and Papillocare® for 6 months. The patient was cytologically reassessed at 6 months: NILM. HPV testing 2 months after completion of treatment: HPV negative (Fig. 5 A-C).
6. Post-conization adjuvant therapy. Patient 45 years of age, HSIL lesion also had HPV present, strain 59. The patient was conized. CIN Tec test result: CIN 2/3. She was prescribed adjuvant treatment *Coriolus Versi-*



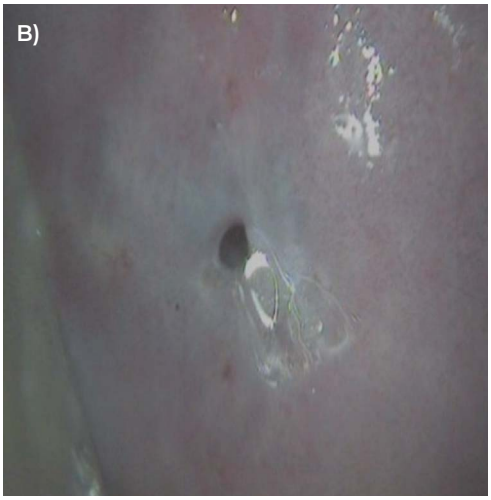


FIGURE 1 A Y B.

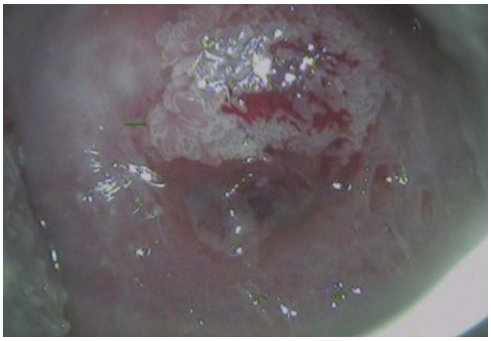


FIGURE 2.

color and Papillocare® for 6 months. Result: Col N, NILM, HPV negative 6 months after electroconization (Fig. 6 A-D).

7. Patient 30 years of age, HSIL lesion present, HPV strain 16 present and CIN 3 present. The patient was electroconized: CIN 3. Treatment: Isoprinosine concomitantly with Papillocare® for 6 months. NILM was reassessed at 6 months and HPV genotyping was negative (Fig. 7 A-D).

FIGURE 3 A Y B.

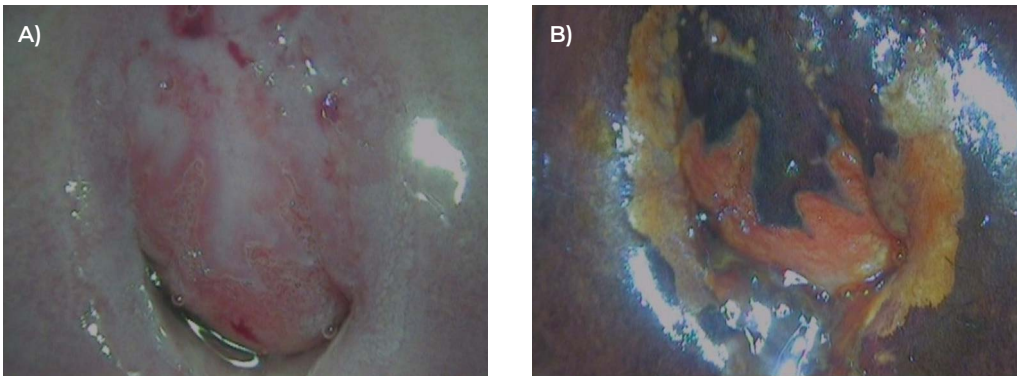


FIGURE 4 A Y B.

FIGURE 5 A, B Y C.

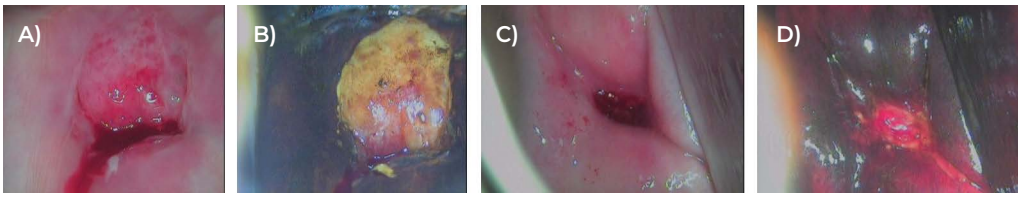


FIGURE 6 A, B, C Y D.

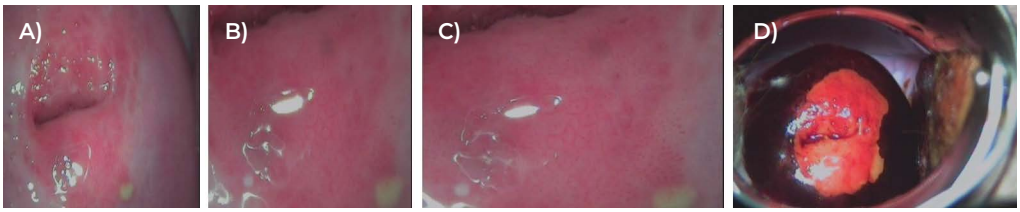


FIGURE 7 A, B, C Y D.

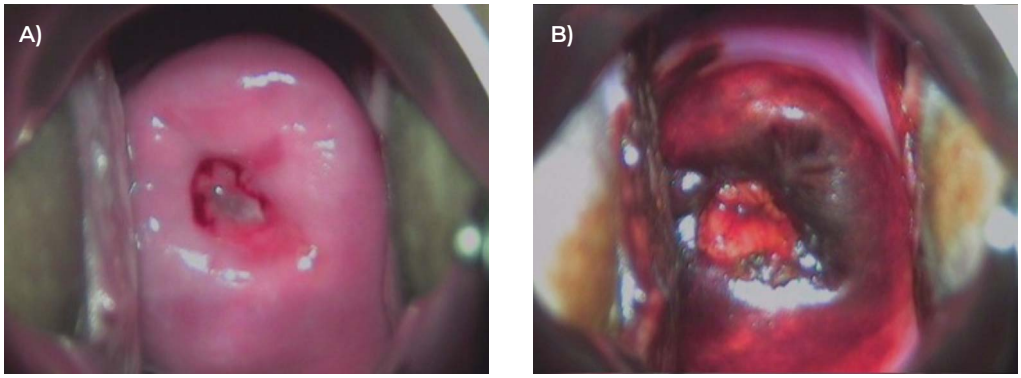


FIGURE 8 A Y B.

FIGURE 9. A, B Y C.

8. Patient aged 30 years, HSIL lesion present, strain HPV 16 and CIN 3. The patient was electroconized: CIN 3. Treatment: Isoprinosine and Papillocare® for 6 months. 6-month NILM reassessment, HPV negative (Fig. 8 A and B).

9. Patient 40 years of age, HSIL lesion present, HPV strain 16 and CIN 3. The patient was electroconized: CIN 3. Treatment: Isoprinosine and Papillocare® for 6 months: NILM and negative HPV test after treatment (Fig. 9 A-C).

TREATMENT OF CERVICAL LESIONS ± HPV WITH PAPILOCARE®

Dr. Maria Ramona Neamu

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CLINICAL HISTORY

Case 1. aged 40 years with LSIL, HPV negative, Positive colposcopy.

Case 2. aged 24 years, ASCUS, HPV poz (X), positive colposcopy.

Case 3. Aged 32, NILM, HPV pozitive (16,53,6), positive colposcopy.

PHYSICAL EXAMINATION

All cases had positive colposcopy for cervical lesions. Differential diagnosis:Ectopia of endocervical tissue. Treatment and evolution: All cases have had treated with Papilocare, at least 4 month. Final diagnosis: Cervical dysplasia.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

They all had low grade scoamos epitelium lesions.

CASES

Patient aged 40 years. He underwent colposcopic examination. Result: cervix with red area on anterior lip, external cervical point orifice, rosacea exocervical epithelium, with vascular drawing at green filter plication. Application of acetic acid: fully visible scalylindrical junction on the anterior lip, white aceto epithelium with mosaic present, as well as at 5 o'clock where an area of fine EAA is present. Application of Lugol: iodine negative zone with smooth edges at the level of previously determined areas of aceto-white epithelium; otherwise uniform uptake of iodine. Conclusions: colposcopic aspect suggestive of moderate grade lesion.

- LMP: 02.09.2023.
- CM: regular, 31 days, 7 days, moderate flow, painless.
- Births: 2 by caesarean section.
- Abortions: 1 on demand.
- FP at 14.
- Mother's age at MP: 55 years.
- BMI = 1.67 cm / 58 kg.
- Nonsmoking PPA: no.
- HCA: mother- cervical cancer.
- Father: IC.
- Blood group: AB IV, RH positive.
- Analyzes: LSIL, HPV negative.
- Treatment: 6 months Papillocare® (in the first month 21 days with break during menstruation; month 2 -6 an application with one application every two days with 7 days break

menstruation period). Colposcopy result after treatment: negative and repeat the Pap test in 6 months.

Patient aged 24 years. He underwent colposcopic examination. Result: Ex. native: cervix with OC in the transverse slit, rosacea exocervical epithelium, without vascular drawing when applying the green filter. Application of acetic acid: junction fully visible, on the anterior lip white aceto epithelium extended on the posterior lip shows the insular area of EAA fine. Application by Lugol: ZIN with net margins at the level of EAA areas described above. Conclusions: colposcopic aspect suggestive of minor grade lesion.

- LMP: 05.08.23.
- CM: regular, 28 days, 4 days, moderate flow, painless.
- Births: 0.
- Abortions: 0.
- CO: No.
- FP: 14 years.
- Sex life: 20 years.
- BMI= 1.70 cm/70 kg.
- PPA smokers: folliculitis, vitamin D deficiency – treatment with Detrical.\ HCA: mother PCOS.
- Blood group: IBII, RH negative.
- May 2023, ASCUS. Dysplasia of the cervix, unspecified, N87.9. Treatment: HPV positive for genotype X. She took Papilocare®, 21 days in succession. Then 4 months, 1 app/2 days. Pap smear in December negative, with indication of reevaluation after 6 months.

Patient aged 32 years. He underwent colposcopic examination. Result: Ex. native: cervix with OC in the transverse slit, rosacea exocervical epithelium, without vascular drawing when applying the green filter. Application of acetic acid: junction fully visible, on the anterior lip white aceto epithelium extended on the posterior lip shows the insular area of EAA fine. Application by Lugol: ZIN with net margins at the level of EAA areas described above. Conclusions: colposcopic aspect suggestive of minor grade lesion.

- LMP: 17.06.2023.
- CM: regular, at 25-26 days, with moderate flow 3-4 days, painless.
- Births: 0.
- Abortions: 0. PM: 13 years.
- BMI: N Non-smoking PPA: no.
- AHC: denial.
- Blood group: BIII, RH positive. NILM performed. Treatment: 4 months' treatment with Papillocare® 21 days per month. Result: negative colposcopy.

TREATMENT OF PERSISTANT LSIL LESIONS WITH HR-HPV PERSISTANT INFECTION IN A 46-YEAR-OLD WOMAN

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ABSTRACT

LSIL is still the most frequently encountered anomaly in smear examinations, seen in 1.5% to 1.8% of total smears. Nowadays recommendation for adolescents for biopsy proven cervical intraepithelial neoplasia (CIN 1), management is similar with yearly cytology indefinitely or until high HSIL or CIN 2/3 develops. Still, we have contraversa in patients over 45 with hystological LSIL and positive HPV infections.

KEY WORDS

LSIL. HPV infection. Treatment over 45 years old.

INTRODUCTION

Patient was 46 year old women who came at the Institute with PAP smear HSIL. Cytology was reported according to the Bethesda system. Histopathological diagnosis was regarded as negative for intraepithelial lesion or malignancy (NILM) when no abnormalities with evidence of HPV were detected. Histopathological low-grade squamous intraepithelial lesion (LSIL) was defined as either HPV atypia/atypia condylomatosa or cervical intraepithelial neoplasia grade 1 (CIN 1).

CLINICAL HISTORY

Family history was negative on malignancy, one vaginal delivery, no clinical symptoms, previous PAP smear one year ago was NILM, menstrual cycles regular.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Gynecological exam was without clinical pathological findings. Exam under the speculum: Cervix was epithelialized no macroscopically suspicious. Colposcopy was unsatisfactory ‘couse ZT type 3. Detection of HPV was performed and it was positive on HR-HPV type 39, and 68.

As we get positive HR-HPV, ZT type 3 in 46 year old women the biopsy and endocervical curettage was performed.

Final histopathological findings were ectocervical LSIL and endocervical LSIL.

TREATMENT AND EVOLUTION

Loop excision with endocervical curettague (ECC) was performed, 17.02.2022.

Final histopathological findings was LSIL with negative margins, ECC was negative on displasia.

Because positive HR-HPV, we continued the treatment with Papilocare® gel every evening for 21 days, pause during menstruation and repeated for next two menstrual cycles 1x1, 21 days, overall three months.

Five months after the treatment control PAP smear was NILM.

Control of the HPV infections was performed 12 months after treatment and it was negative such as second controled PAP smear.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

In ALTS, 83% of the women of the LSIL group were positive for high-risk type HPVs[1]. Overall approximately 95% of HSIL lesions were positive for HR-HPV types included in most HPV tests approved for screening: up to 96% in women under 30 and 90% in women over 45. In women under the age of 30 nearly 90% of CIN 3+ and all cases AIS+ were associated with HPV16/18 in comparison to only approximately half of CIN 2 cases and a fourth of HSIL cases. HPV16/18 positivity in this age group can be considered to be strongly associated with true high-grade disease[2]. In Aro K et al study results showed that HPV type distribution in high grade cervical lesions is distinctly polarised according to age in a highly screened population with HPV16/18 attributed disease most prevalent in younger women. In women over 45, only a third of the HSIL+ findings were attributable to HPV16/18, while other hrHPV types and hrHPV negativity were more prevalent[3]. The life of LSIL in 90% of adolescent will spontaneously regress (< 21 years of age). 90% of high risk HPV positive cytological LSIL patients spontaneously regress within 24 months. 70% of LSIL with high risk HPV infected patients were spontaneously cleared of their infections. Therefore, surgical treatment of LSIL is usually not preferred[4-6]. Still for pathological LSIL patients whose history was preceded by cytological HSIL or atypical glandular cells have to consider diagnostic excision biopsies or 6 month interval follow-ups of colposcopy and cytology[7]. Even we have good results in spontaneous regression of LSIL and HPV infections in younger populations have to be careful in patients over 40 year old with positive HR-HPV and suspicious PAP smear.

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TREATMENT WITH PAPILOCARE® IN A PATIENT AFTER LOOP EXCISION PROCEDURE AND A MULTIPLE HPV INFECTION

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ABSTRACT

Many women diagnosed with premalignant diseases are treated by local therapy including laser ablation, the loop electrosurgical excision procedure (LEEP) and cone biopsies, and 5% to 15% of these women are diagnosed with CIN 2 or CIN 3 or cervical cáncer (CIN 2+) again after treatment[1]. Post-treatment HPV persistence estimates varied widely and were influenced by patient age,HPV-type, detection method, treatment method, and minimum HPV post-treatment testing interval. HPV persistence to be relatively shorter in duration: nearly 25% of women had a "persistent" HPV infection at 6 months after treatment, and approximately 15% at 12 months post-treatment. Routine HPV testing after treatment of CIN 2–3 is recommended for early detection of disease recurrence or progression[2,3].

KEY WORDS

HPV test. Cervical dysplasia.

INTRODUCTION

Patient was treated with loop exscision after confirmed HSIL by biopsy. She was 32 years old. Cytology was reported according to the Bethesda system and it was ASCH. HPV test was performed and test was positive on HPV type 16, 51,52.

CLINICAL HISTORY

Family history was negative on malignancy, nullipara, no clinical symptoms, menstrual cycles regular for both patients.

PHYSICAL EXAMINATION

Gynecological exam was without clinical pathological findings. Exam under the speculum: Cervix was epithelialized after procedure no macroscopically suspicious. Colposcopy was with minor colposcopy picture of fine mosaic on 1 o'clock. Detection of HPV was performed before the initial

treatment and HPV 16, 51 and 52 were confirmed. Final histopathological findings was HSIL (CIN 3) on ectocervix and endocervix.

TREATMENT AND EVOLUTION

Loop excision with endocervical curettague (ECC) was performed, 14.11.2022.

Final histopathological findings was HSIL (CIN 3) with negative surgical margins and ECC was negative on displasia.

Because of nulliparity and multiple HPV infections we suggest patients approach with Papilocare® gel every evening for 21 days, pause during menstruation and repeated for next two menstrual cycles 1x1, 21 days, overall three months.

Six months after the treatment control PAP smear was NILM such as HPV was negative.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

After surgery therapy, the strategy and procedures of follow-up represent a critical point for risk stratification, because HG-CIN recurrence is a major marker for progression to invasive cancer. HPV detection, and particularly genotyping, has an adequate high rate of sensitivity and specificity (along with an optimal reproducibility), for accurately predicting treatment failure, allowing for an intensified monitoring activity. Women with a negative HPV-test, 6 months after therapy, have a very low risk for residual/recurrent disease, leading to individualized follow up schedule, which allows gradual return to the normal screening scheme. In post-treatment follow-up of CIN 2+ patients for early detection HPV testing should be routinely included[4]. Papilocare® has shown significant and consistent rates of HR-HPV clearance ranging from 50% to 70% in the 6 different studies[5-7]. Also have to point that treatment of CIN lesions is associated with labor dystocia as well as a higher rate of spontaneous abortions in the first and second trimesters. Studies show that there is a direct positive correlation between the depth and volume of conus and the incidence of adverse pregnancy outcomes[8,9].

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TREATMENT WITH PAPILOCARE® IN A 40-YEAR-OLD PATIENT WITH LSIL AND POSITIVE HPV TYPE 16

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ABSTRACT

Many women diagnosed with premalignant diseases are treated by local therapy including laser ablation, the loop electrosurgical excision procedure (LEEP) and cone biopsies, and 5% to 15% of these women are diagnosed with CIN 2 or CIN 3 or cervical cancer (CIN 2+) again after treatment. There are situations where clearence of HPV can be difficult. This is often the case when the infection is caused by a high-risk type of HPV, especially in patients over the age of 40, whose immune systems tend to be a little weaker[1].

KEY WORDS

HPV infection. Cervical dysplasia.

INTRODUCTION

Patient was diagnosed LSIL by biopsy. She was 40 years old, nullipara, Cytology was reported according to the Bethesda system and it was ASCUS. HPV test was performed and test was positive on HPV type 16.

CLINICAL HISTORY

Family history was negative on malignancy, nullipara, no clinical symptoms, menstrual cycles regular for both patients.

PHYSICAL EXAMINATION

Gynecological exam was without clinical pathological findings. Exam under the speculum: Cervix was epithelialized after procedure no macroscopically suspicious. Colposcopy was ZT type 3. Detection of HPV was performed before the initial treatment and HPV 16 was confirmed. Histopathological findings of biopsy was LSIL and ECC was negative on displasia.

TREATMENT AND EVOLUTION

Because of nulliparity, LSIL, HPV infections we suggest patients approach with Papilocare® gel every evening for 21 days, pause during menstruation and repeated for next two menstrual cycles 1x1, 21 days, overall three months.

Four months after the treatment control PAP smear was NILM, but HPV was persistan positive on type 16.

We repeated treatment with Papilocare® with the same scheme

After three continuous months of treatment, the follow-up PAP smear was NILM, and HPV was negative for type 16, but low-risk HPV type 6 was confirmed.

No adverse events were recorded during follow-up.

Patient is on routine follow up, six months.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Eliminating high-risk types of HPV is one of the most important goals of treating this infection.

After treatment with Papilocare® vaginal gel for 6 months, 63% of patients were cured of high-risk HPV, compared to 40% in the control group[2]. In PALOMA study a specific subanalysis was performed for this subpopulation of patients.

It was observed that Papilocare® vaginal gel led to regression of low-grade lesions in 92% of patients compared to 50% in the control group and 90% of patients with high-risk HPV compared to 33% of those who were not treated. The mean age of this subgroup was 47.7 (±5.56)[2]. In patients over the age of 40 clearence of HPV can be difficult. This is often the case when the infection is caused by a high-risk type of HPV.

In our case even after three months of treatment the HPV type 16 was persistan but in continued treatment after next three months we got negative test on HPV type 16. In PAPILOBS study after the first six months of treatment, 128 of the 191 patients enrolled in the study had regression of the low-grade cervical lesion.

At 12 months of treatment, only 14 women still had abnormal cytology. Lesion regression was verified in 77% of women from the start of treatment. In study by Criscuolo AA et al. multivariate analyzes adjusted for age, smoking, and estro-progestin pill use, compared with controls, gel-treated women were significantly more likely to experience HPV DNA clearance (OR 4.81; 95% 2.43–9.53) and remission on colposcopy (OR 2.30; 95% 1.00–5.31) and cytology (OR 5.13; 95% 2.40–10.96) at 6 months[4].

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HPV INFECTION IN PREGNANCY

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CLINICAL HISTORY

22-year-old primigravida patient married since 1 year with LMP 2-10- 22, EDD 9-07-23.

PHYSICAL EXAMINATION

Came to OPD - June 2023 at 30+ weeks pregnancy with no previous medical history, no previous surgical history and Family Hx father had diabetes.

History of contraception use for 6 months.

She came with only a fleshy mass protruding from labia minora close to introitus since 1 month, there was no pain or itching associated with the mass.

- PA hof 30 weeks.
- Uss in clinic SAF corressponding to GA 30 weeks.
- FHS+ lie longitudinal.
- pp cephalic.
- PV small cervical erosion.
- HVS taken showed candida only.
- Fleshy irregular mass/growth protruding from introitus.
- It was not painful and did not bleed on touch so was planned for excision of the growth on 7-05-23.

Solitary Vulval growth excision of lesion was done under LA after aseptic measures, patient scrubbed and draped, EUA done, growth seen localized in rt side of introitus, xylocaine used as spray then local infiltration, growth excised sent for H/P with haemostasis secured, wound stitched with 3/0 no bleeding at the end.

DIFFERENTIAL DIAGNOSIS

Reported by “Vulval mass” consists of single, pale gray brown, soft piece of tissue, measuring 2.2 x 1.5 cm in size. Bisected and submitted entirely in single.

Biopsies from vulval mass lesion: -

Histological features consistent with an inflamed and exophytic condyloma acuminatum of the vulva.

The lesion is markedly inflamed and shows evidence of keratosis and parakeratosis with evidence of koilocytotic atypia compatible with human papilloma virus infection (HPV).

Foci of low-grade dysplasia are also

FIGURE 1.

FIGURE 2.

noted with increased mitoses and basal cells hyperplasia.

Negative for high grade dysplasia and malignancy. Complete excision and follow up with cytologic surveillance are suggested.

FINAL DIAGNOSIS

HPV infection in pregnancy.

TREATMENT AND EVOLUTION

Patient was prescribed Papilocare® vaginal gel intravaginally, 1st Month one canula daily for 21 days, then every other day for 5 months.

In November 2023 (5-11-23), she had no complaints, no new growths or abnormal discharge. We conducted a repeat HVS and Pap smear which showed:

- Satisfactory for evaluation.
- Endocervical and metaplastic cells are not seen.
- Negative for squamous intraepithelial lesion and malignancy.
- HVS showed normal growth.
- Patient was advised to continue same treatment and next follow up advised after 3 months.

CONCLUSION

This young primigravida at 30 weeks came with atypical presentation and candida infection only, but the growth histopathology showed HPV, so after growth excision and Papilocare® use patient responded satisfactorily.

COMMENTS

Pregnancy then progressed smoothly.

Date: 13-7-2023.

Primigravida 40 weeks+3 days.

Came to emergency in labor with vaginal examination: 6cm, 80% effaced, -2 stat, MI.

Normal Vaginal Delivery with episiotomy on 13-07-2023.

Outcome was a single, cephalic, baby girl, alive and well, APGAR score 9/10, weight 2.8 kg.

HISTORY OF EXTERNAL GENITAL WARTS

Dr. Afaf Khaled

Al Raed Hospital, Riyadh, KSA

RESUMEN

History of external genital warts transmitted after her husband diagnosis with HPV.

PALABRAS CLAVE

Genital warts. HPV. Papilocare®.

CLINICAL HISTORY

36-year-old lady with 3 normal deliveries, history of external genital warts transmitted after her husband diagnosis with HPV.

Her pap smear negative other than inflammatory changes.

PHYSICAL EXAMINATION

Multiple external genital warts already cauterized in dermatology clinic.

DIFFERENTIAL DIAGNOSIS

3-4 vaginal warts, with cervical erosion bleeding on touch.

TREATMENT AND EVOLUTION

Started on Papilocare® treatment to be taken daily for 3 weeks then for re-assessment.

She presented after 10 days, and re-examined.

Vaginal warts almost disappeared and cervial erosion started to faint.

Planned to continue on the treatment for full recovery.

FINAL DIAGNOSIS

Verrugas genitales externas múltiples.

COMMENTS

Her pap smear mentioned that vaginal warts almost disappeared and cervical erosion started to faint.

A CASE STUDY OF USING A NEW LOCAL SYNERGISTIC TREATMENT FOR CERVICAL RE-EPITHELIALIZATION AFTER LLETZ PROCEDURE

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KEY WORDS

LETZ. Re-epithelialization. HPV.

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is a premalignant squamous lesion of the uterine cervix diagnosed by cervical biopsy and histologic examination[1].

Screening for cervical cancer includes cervical cytology and testing for oncogenic subtypes of human papillomavirus (HPV). Follow-up of abnormalities in screening tests with colposcopy and cervical biopsy may result in a diagnosis of CIN or cervical cancer[2].

CIN may be low-grade or high-grade. Patients with low-grade CIN have minimal potential for developing cervical malignancy, while those with high-grade lesions are at high risk of progression to malignancy[2].

Human papillomavirus (HPV) is a sexually transmitted pathogen that causes anogenital and oropharyngeal disease in males and females. Persistent viral infection with high-risk HPV genotypes causes virtually all cancers of the cervix. The high-risk HPV genotypes 16 and 18 cause approximately 70 percent of all cervical cancers worldwide, and types 31, 33, 45, 52, and 58 cause an additional 20 percent. HPV types 16 and 18 also cause nearly 90 percent of anal cancers and a significant proportion of oropharyngeal cancer, vulvar and vaginal cancer, and penile cancer.

HPV types 6 and 11 cause approximately 90 percent of anogenital warts[3].

CLINICAL HISTORY

A 48-year-old lady presented to my clinic in Kuwait in November 2022. She

was referred from a dermatology clinic after being evaluated and treated for multiple vulvar condyloma using local cryotherapy 1 month back, she was referred for pap smear.

Ethnicity: Bosnian.

Parity: P2+0 both normal deliveries.

Personal disease history: no chronic disease of interest.

Smoker: yes (2-4 cigarettes per day).

First sexual relation: 18 years old. Number of sexual partners stated: 2. Long term sexual partner: 1. Contraceptive method: No.

Family disease history: None of interest.

FIGURE 1. Shows the cervix examined by colposcopy with the apparent ulceration.

PHYSICAL EXAMINATION

Examination was done in the lithotomy position, a thorough examination was performed, no perianal lesions noticed, no vulvar condyloma was observed. Using vaginal speculum, examination of the vaginal wall was done followed by examination of the cervix. No lesions were detected either in the vaginal wall or cervix but the cervix had an ulcerative lesion at 1, 2, 6 and 9 o'clock.

Pap smear and HPV DNA test were taken and sent for the lab for diagnosis of abnormal cervical cells and presence of HPV infection.

Cytology result revealed: Atypical squamous cells of undetermined significance (ASC-US) while HPV test revealed infection with HPV number 45 which is categorized as one of the high- risk HPV genotypes.

In the next visit, explanation for the results and highlighting the importance of the next step which is colposcopy guided cervical biopsy, written consent was obtained from the patient.

The procedure was done while patient was in lithotomy position. Thorough examination of vulva, vaginal wall, then cervix. Identification of the transformation zone. Application of 3% diluted glacial acetic acid to the cervix. A dense aceto-white area was apparent on cervical mucosa at 1, 2, 6 and 9 o'clock which turned light brown after application of Lugo's iodine solution. Cervical biopsies were taken from suspicious areas and sent for histopathology lab.

Histopathology report revealed: A focal area suspicious for low-grade squamous intraepithelial neoplasia (LSIL).

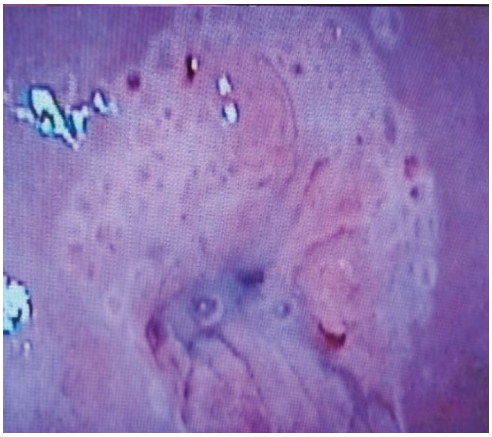

FIGURE 2. Shows the cervix after addition of diluted glacial acetic acid.

FIGURE 3. Shows the cervical lesion after addition of Lugo's iodine solution.

DIFFERENTIAL DIAGNOSIS

Molluscum contagiosum: A skin infection, caused by pox virus that results in raised, rounded, skin-colored bumps with a dent or dot at the top. Lesions are itchy, can take on a pink color. Bumps appear in genitalia and other areas like face, trunk, arms or legs.

Condylomata lata: Represent one of the manifestations of secondary syphilis. These lesions are as 1–2-cm, flat-topped, smooth-surfaced papules and small plaques. They may be skin-colored, pink, white, or brown.

Seborrheic keratosis: Usually brown, black or light tan. The lesions look waxy or scaly and slightly raised. It commonly present in adult and elderly patients. They are benign skin lesions and often do not require treatment.

Skin tag: A common soft harmless lesion that appears to hang off the skin. It develops in both men and women. Skin tags (fibroepithelial polyps) are pedunculated benign lesions that vary in size and color.

They are frequently multiple and often seen together with seborrheic keratosis.

Malignant tumors: The lesions are exophytic, hard, ulcerative with bleeding surface.

Fordyce spots: They are enlarged oil glands. They are whitish-yellow bumps that can occur on the edge of the lips or inside cheeks. Less often, they can appear on labia.

TREATMENT

Suitable explanation was provided to the patient regarding the evolution of the process, the purpose of treatment, the potential adverse effects that may appear, and the healing and relapse percentage.

LLETZ (large loop excision of the transformation zone) procedure was

done for the patient after taking written consent. The affected area was removed using a thin wire loop with an electrical current running through it. The electrical current heats the wire, allowing us to cut the tissue and seal the wound at the same time.

My patient was very irritable and preferred to opt for general anesthesia. Advices were to the patient to avoid using tampons, swimming, or having sexual intercourse for four weeks. Also, avoid any heavy lifting or strenuous exercise for one week.

I recommended the use of a co-adjuvant home medication, Papilocare® vaginal gel, a *Coriolus versicolor*–based vaginal gel that combines ingredients boasting known properties, such as moisturizing, tissue regeneration, and balancing of the vaginal microbiota (hyaluronic acid, Asian centella, Aloe vera, and α-glucan oligosaccharide)[4], with other ingredients with demonstrated positive effects on both HPV-dependent cervical lesions and HPV clearance (C. versicolor, Azadirachta indica, and carboxymethyl-α-glucan)[5].

It is recommended to be used for 6 months. For the first month: it should be Applied once daily before bed time for 21 consecutive days and to skip the treatment during menstruation. For the following months: it should be applied once every other day for 21 days with a break during menstruation.

She was evaluated after 2 weeks of LLETZ procedure, good healing process with small raw areas, little brownish discharge. Re-evaluation was done after 2 more weeks, complete healing of cervix with no residual ulceration or abnormal discharge.

Follow up by pap smear 6 month after the procedure, the result was satisfactory and negative for intraepithelial lesion or malignancy.

She was advised to:

- Stop smoking.
- Always use a barrier method.
- Visit for check- up every 12 months.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Human papillomavirus (HPV) is one of the most common sexually transmitted infections and the most important etiological agent in cervical cancer. [6] Most HPV infections are asymptomatic and clear within 2 years without treatment[7].

Despite its low risk of progression to cervical cancer, many women experience negative emotional responses and even long-term psychological distress associated with an HPV-positive diagnosis and an abnormal cytology[8].

Clearance of LSILs after a conservative approach is of approximately 59% within 2 years of the diagnosis. Nevertheless, the likelihood of progression of these lesions to a high-grade squamous intraepithelial lesion within 5 years is 12.7%[9].

The initial approach to management of CIN is primarily based on the patient's risk for progression to cancer, but also considers treatment-related morbidity and the likelihood of compliance with a management plan. There are two general approaches:

- Close observation with human papillomavirus (HPV) testing, cervical cytology, and/or colposcopy.
- Treatment with excision or ablation of the cervical transformation zone[2].

Although age and CIN grade are predictive of risk for progression to cancer, other factors also affect this risk. These factors include the patient's HPV and cytology results preceding the diagnosis of CIN[10].

Treatment with Papilocare® has demonstrated a better clinical benefit than the conventional watchful waiting approach in clinical practice for total and high-risk HPV patients in terms of its efficacy to treat HPV-related cervical lesions and to clear all HPV strains after a single 6-month period. It has demonstrated an adequate safety and tolerability and confers additional benefits such as higher re-epithelization, stress reduction, and high treatment adherence[11].

For my clinical case, combination of surgical excision with LLETZ plus the locally administered vaginal Papilocare® were suitable for this patient with satisfactory results, normal pap smear and no relapse after 9 months of treatment.

HPV vaccination provides safe, effective, and lasting protection against the HPV infections that most commonly cause cancer. CDC recommends HPV vaccination for all boys and girls at ages 11-12 to protect against HPV-related infections and cancers, also recommends vaccination for everyone through the age of 26 years, if not already vaccinated[12].

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TREATMENT OF VAGINAL INTRAEPITHELIAL NEOPLASIA (VaIN) WITH PAPILOCARE®

Dr. Pham Ho Thuy Ai

Tu Du Hospital, Vietnam

ABSTRACT

VaIN is considered the precursor lesion of vaginal cancers. Monitoring low-grade VaIN lesions can help limit unnecessary treatment interventions.

KEY WORDS

VaIN. HPV. Papilocare®. Colposcopy.

INTRODUCTION

Vaginal intraepithelial neoplasia (VaIN) means that there are abnormal cells in the inner lining of the vagina. It's an exceedingly uncommon disease, making up less than 1% of all intraepithelial neoplasia cases in the female genital tract. Similar to cervical intraepithelial neoplasia, there are three different grades of VaIN: grades 1, 2 or 3. There still is little understanding about the natural course of VaIN and its capacity for pro-or regression. Around 3,170 women receive a diagnosis of vaginal cancer annually in the United States, resulting in roughly 880 deaths attributed to this condition[1]. Examining the role of potential dysplasia in the lower genital tract and its connection to the risk of malignancies in women diagnosed with high-grade VaIN becomes a pivotal focus, needed to inform optimal treatment and surveillance for patients with high-grade VaIN.

Many studies have shown a strong correlation between high-risk HPV infection and VaIN. Zhang study reported that the prevalence of HPV was 91.2% in VaIN (97.5% in VaIN1; 100% in VaIN2 and VaIN3 and 87.5% in cancer)[2]. The prevalence of HPV 16 showed a direct relationship with the grade of VaIN and was found in the majority of VaIN 3 patients (76.0%)[3]. In women, HPV can lead to cellular changes in the vaginal area, increasing the risk of developing VaIN. However, not all cases of HPV infection lead to VaIN, and not all instances of VaIN originate from HPV. The development of VaIN can depend on various factors, including immune system health and environmental factors.

FIGURE 1.

FIGURE 2.

Treatments for VaIN were categorized as observation, laser ablation with/without topical agent, topical management, surgical excision, and radiotherapy. The regression rate of VaIN lesions is relatively high, especially for VaIN 1, where the regression rate accounts for over 50%. Therefore, it can be expectantly managed[4].

Papilocare® vaginal gel is a *Coriolus versicolor*–based vaginal gel that combines ingredients boasting known properties, such as moisturizing, tissue regeneration, and balancing of the vaginal microbiota with demonstrated positive effects on both HPV-dependent cervical lesions and HPV clearance. There's a suggestion that minimizing HPV integration could be achieved by reducing the available mitotic surface through re-epithelization. On the other hand, the vaginal microbiota status plays a decisive role in the persistence or clearance of local infections. Study reported about vaginal health that the percentual change in the vaginal health index after 3 and 6 months of follow-up was numerically higher in the treatment group[5].

CLINICAL HISTORY

35-year-old women presenting for the abnormal cytology – ASCUS and negative results HPV high-risk on May 2022 from a private gynecologist. Afterward, the patient visited our hospital's diagnostic unit for examination.

Family history: negative for breast, ovarian and/or endometrial cancer. No hereditary diseases.

Personal history:

- No known allergies.
- No toxic habits.

Obstetric and Gynecology history:

- Nulliparous.
- Ectopic pregnancy was surgical (May, 2022).
- First intercourse: 16.
- Menarche at age 18.
- Menstrual type: regular 4/30.
- Number of sexual partners : 2.
- Contraceptive method: No.
- Not vaccinated against HPV.

PHYSICAL EXAMINATION

When performing a vaginal examination, we noticed scattered small clusters of bumps on the vaginal walls. Consequently, the patient underwent a colposcopy to further assess the lesions.

Colposcopy: Unsatisfactory, Type 3 TZ, normal vascularization.

Abnormal findings: Vaginoscopy observed a fine mosaic area in the right corner of the vaginal vault.

Biopsies: 10 o'clock vaginal vault and endocervical curettage. The result of the biopsy informs us of a low-grade VaIN 1 and negative ECC.

TREATMENT AND EVOLUTION

In the view of these results, it is proposed to observation (cytologic and colposcopic follow-up) and treat with Papilocare® Vaginal Gel. The patient used Papilocare® vaginal gel daily for one month and then every 48 hours for next 5 months, resting on the days of menstruation.

After this time of treatment, the patient attends to the clinic for check-up.

- Pap's test: normal.
- Vaginoscopy was performed in which the previously observed weak lugol area in the angle of the vagina was no longer evident. Unsatisfactory, type 3 TZ. Using acetic acid, there's no acetowhite in cervical and vaginal.

FINAL DIAGNOSIS

VaIN1 with low-grade cytology abnormalities and a high-risk HPV-negative status. The healing of vaginal lesions might be attributed to the re-epithelialization effects on vaginal epithelial tissue provided by Papilocare® vaginal gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

VaIN is strongly associated with HPV infection[6]. However, not every case of HPV infection progresses to VaIN. There are various factors influencing the development of VaIN have been described for vaginal cancer like smoking, immunosuppression, high number of sexual partners, and also history of cervical precancerous and cancerous lesions. The goal of treatment of VaIN is to prevent its progression to invasive vaginal cancer[7]. VaIN 1 has a spontaneous regression rate of over 50% and therefore it can be expectantly managed. In cases of patients with LSIL (VaIN), observation without treatment is recommended, justified because most of these low-grade lesions regress spontaneously[8]. Therefore, in this case, we decided to opt for monitoring and treatment using Papilocare® with the aim of awaiting lesion regression and limiting unnecessary treatment interventions.

Improved re-epithelization and vaginal microbiota restoration have been observed in previous pilot studies involving the use of Papilocare® in both asymptomatic, healthy women and HPV-positive patients with no cervical lesions. Nowadays, there are few reports available on the effect of this vaginal gel on VaIN and will be hard to find more in future. Given the low frequency of these lesions and the paucity of studies with

sufficient evidence, the different therapeutic modalities available are not well protocolized at the moment[8]. However, due to the available literature Papilocare® is a sanitary product in the form of a gel for vaginal application with known immunostimulant properties, anti-microbial and anti-tumor activity. This gel acts as an immunomodulator, and its β-glucans can cause selective apoptosis on cancer cells without affecting healthy cells. A cellular immunity-enhancing effect has been demonstrated in humans. With the published benefits of Papilocare® and the observed improvement in abnormalities in this patient, there's hope that this could be an effective treatment approach for low-grade VaIN lesions.

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PAPILOCARE® VAGINAL GEL IN PERSISTANT ASCUS CYTOLOGY POST-CONIZATION FOR CIN 2

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ABSTRACT

After undergoing conization for CIN 2, individuals may still be at risk of experiencing a recurrence of CIN 2+ within two years, as suggested by cytology and colposcopy.

KEY WORDS

CIN 2+. Cytology. Conization. Papilocare®.

INTRODUCTION

Cervical cancer poses a significant public health challenge worldwide, especially burdening numerous low-income and middle-income nations.

In 2020, there were approximately 604,127 reported cases of cervical cancer worldwide, leading to 341,831 deaths. The standardized incidence rate was 13.3 cases per 100,000 women-years, and the mortality rate stood at 7.2 deaths per 100,000 women-years[1]. Margaretha's report highlighted a 1.6% progression to cancer within 10 years after the onset of CIN 2/3, while specifically noting a 2.4% risk of progression in HPV-16-positive CIN 2/3 cases over the same timeframe[2]. Screening for cervical cancer identifies precancerous lesions, enabling their treatment and ultimately preventing cancer. High screening coverage within a population typically leads to reduced cervical cancer incidence and mortality rates.

There are three principal treatments accessible in low- and middle-income countries to treat CIN: cryotherapy, large loop excision of the transformation zone (LLETZ, or LEEP), and cold knife conization (CKC). The expert panel recommends LEEP over no treatment for women who have histologically confirmed CIN 2+ disease with strong recommendation despite low-quality evidence. However, excisional procedures carry the risk of complications, especially during pregnancy, such as cervical insufficiency, premature rupture of the membranes, and premature delivery. The impact of LEEP on spontaneous abortion and infertility remains uncertain and hasn't been definitively established thus far[3]. Even after undergoing cervical conization for CIN 2+,

FIGURE 1.

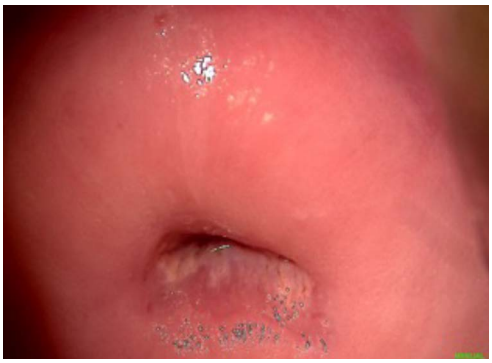

FIGURE 2.

women remain susceptible to the recurrence of CIN 2+ or the potential development of invasive carcinoma within two years post-treatment[4]. Based on ACOG guidelines for early detection of recurrence, long-term follow-up by repeated cervical cytology and colposcopy of the cervix after cervical conization has been recommend[5]. Although ASC-US comprises a wide variety of cervical cells, including benign and malignant cells, a substantial proportion of cases displaying ASC-US have underlying high-grade CIN (2 or 3) and, thus, are at an increased risk of developing cervical cancer. Based on these facts, patients treated for CIN previously are reported to be at 2-fold risk of CIN 2 at subsequent colposcopic referral for ASCUS or low-grade squamous intraepithelial lesion cervical cytology[6].

Papilocare® vaginal gel is specifically designed to activate the two modifiable factors that can influence the persistence or clearance of HPV. The effectiveness of Papilocare® vaginal gel has been studied and demonstrated in several international clinical trials in which more than 600 patients have participated. Normalization of low-grade cervical lesions in 88% of patients infected with high-risk HPV after six months of treatment, compared to 56% of patients who were not treated[7].

MEDICAL HISTORY

A 46-year-old female was performed a Loop Electrosurgical Excision Procedure for CIN 2 with margin-negative.

Personal history: No known allergies. No toxic habits.

Obstetric and Gynecology history:

- Multiparous: two cearean sections.
- Menarche at age 15.
- Menstrual type: regular 5/30.
- Contraceptive method: fertility awareness-based methods.
- Not vaccinated against HPV.

PHYSICAL EXAMINATION

The result of the negative cervical cone biopsy leads us to decide on monitoring through cytology and repeated cervical examinations every 6 months.

After following by cytology and colposcopy every 6 months. Three- repeat ASCUS cytology are observed and negative HPV test.

- Colposcopy examination: Unsatisfactory, type 3 TZ. Using acetic acid, there's no acetowhite in cervical and vaginal.
- Endocervical curettage: Negative.

It is proposed to observation (cytologic and colposcopic follow-up) and treat with Papilocare® Vaginal Gel.

After using Papilocare® 6 months. First month: daily application for 21 consecutive days or until the first day of menstruation and rest during bleeding. Subsequent months: One application every other day for 21 days or until the first day of menstruation and rest during bleeding. Then patient attends the clinic for check-up.

- Pap's: normal.
- Colposcopy: There's no acetowhite in cervical and vaginal.

FINAL DIAGNOSIS

Diagnosis of persistant ASCUS cytology after conization for CIN 2 with negative high-risk HPV infection and normalized colposcopy. The normalization of cytology might be attributed to the effectiveness of *Coriolus versicolor*-based gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Cervical conization is the recommended treatment for cervical intraepithelial neoplasia (CIN) grade 2+. The margin-negative recurrence rate after conization for CIN 2+ is 2–4%. After treatment, HPV test, cytology and colposcopy are preffered the first post-treatment control. So, in this case we deciced for follow-up every 6 months. ASC-US was the most common abnormal cytological finding after treatment for CIN 3. It has been reported that, with cervical cytology alone, ASC-US accounts for 6.9% of CIN 2, 2.6% of CIN 3, and 0.18% of cervical cancer cases[8]. As regards risk stratification for women following treatment for CIN, an appropriate triage method used to identify women with ASC-US who have or will develop a cervical cancer precursor is crucial. Although ASC-US comprise a wide variety of cervical cells, including benign and malignant cells, the presence of ASC-US has been considered as a low-risk abnormal cervical cytological characteristic. However, a substantial proportion of cases displaying ASC-US have underlying high-grade CIN (2+) and, thus, are at an increased risk of developing cervical cancer[9]. Although this patient has had three consecutive ASCUS cytology results, they tested negative for HPV and haven't shown any abnormalities on cervical colposcopy. Therefore, we chose to treat with Papilocare® to limit the necessity of a second cervical conization.

Thus, it is reasonable to consider women with ASC-US following post - conization for CIN to be at an increased risk of developing cervical cancer compared with women with ASC-US after no treatment. Papilocare®, a *Coriolus versicolor*-based vaginal gel which has shown to improve the epithelialization

of cervical mucosa and the composition of vaginal microbiota emerges as a safe treatment option for helping to repair low-grade lesions and it may help lower stress levels in women by making them active participants in their own treatment[10].

Hence, there's a necessity for enhanced monitoring of CIN to reduce the risk of cervical cancer. Careful consideration should be given when deciding on treatment options.

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TREATMENT OF A 35-YEAR-OLD WOMAN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 (CIN 2) ASSOCIATED WITH HUMAN PAPILLOMAVIRUS TYPE 16 (HPV 16)

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ABSTRACT

This case report describes the sucessful management of a 35-year-old female with cervical intraepithelial neoplasia grade 2 (CIN 2) associated with human papillomavirus type 16 (HPV 16). The patient underwent treatment using Loop Electrosurgical Excision Procedure (LEEP) followed by adjuvant therapy with Papilocare® Vaginal Gel. The outcome demonstrated effective lesion removal and highlighted the potential benefits of Papilocare® Vaginal Gel in post-treatment care.

KEY WORDS

CIN 2. HPV. Papilocare®.

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is a premalignant squamous lesion of the uterine cervix diagnosed by cervical biopsy and histologic examination[1]. It is typically divided into three grades or levels of severity: CIN 1, CIN 2, and CIN 3. CIN 1 is a low-grade lesion that has a low potential for progression to malignancy and a high potential for regression, while CIN 2,3 is a high grade lesion that has a higher potential for progression and a lower potential for regression[1]. Human Papillomavirus (HPV) infection is the main cause of cervical carcinoma. There are at least 15 high-risk HPV types that are significantly connected with progression of CIN into cervical carcinoma[2]. The standard treatment for CIN involves excisional procedures like LEEP, aimed at removing abnormal cervical tissue.

CLINICAL HISTORY

A 35-year-old woman, gravida 2, para 2, presented to the gynecology clinic after receiving HSIL cytology result during a routine screening. She reported a history of regular Pap smears with no abnormalities and no significant medical or gynecological history. She was asymptomatic, with no complaints of abnormal bleeding, pelvic pain, or unusual discharge.

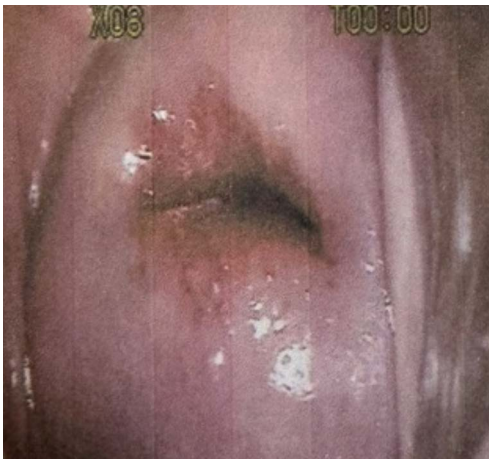

FIGURE 1. Initial colposcopy.

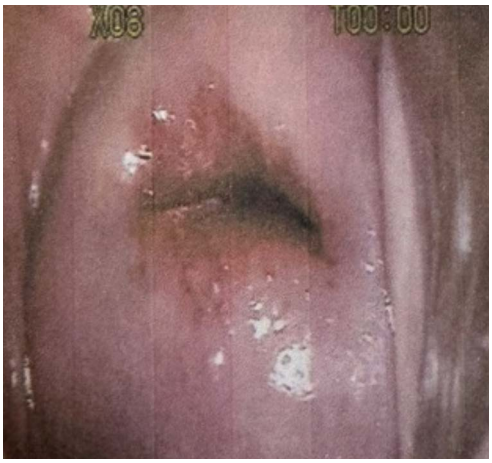

FIGURE 2. After applied acetic acid.

PHYSICAL EXAMINATION

Given the diagnosis of CIN 2 and the association with high-risk HPV 16, we have discussed treatment options with the patient. Considering patient's age, fertility status, LEEP of the cervix was performed. The excised tissue was sent for histopathological examination, confirming the presence of CIN 2 and ensuring negative endocervical and exocervical margins. Post-LEEP, the patient was instructed to refrain from sexual activity, heavy physical activity for four weeks. She was prescribed a course of antibiotics to prevent infection. She has been scheduled for a follow-up examination in 3 months.

In the follow-up visit at 3 months, the cytology result is LSIL, and a cervical colposcopy was performed, but no abnormalities were observed. Because of recent positive HPV 16 and LSIL cytology result after LEEP, it was decided to initiate treatment with Papilocare® Vaginal Gel to help the regression of cytology and clearance of HPV, daily for 1 month and every other day for at least 3 months.

After six months of treatment, the patient underwent a co–testing and colposcopy. The follow-up Pap smear showed an improvement in cytology, with a regression from LSIL to normal, the HPV test was negative, indicating the clearance of the high-risk HPV infection and the colposcopic examination was normal. No adverse effects during the treatment period. One year later, a new co-testing was made with negative result. Therefore, the patient has been scheduled for a gynecological follow-up examination in another 3 years.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

In Vietnam, cervical cancer was the fourth most common cancer in women with 5146 new cases and 2423 cervical cancer deaths in 2012[3]. Guidelines for

cervical cancer screening in Vietnam have not yet been standardized. Cytology remains the most common test for cervical cancer screening, VIA is a technique utilized in regions where cytology test is not available. HPV test is a highly sensitive and specific screening method for detecting pre-cancerous cervical lesions. In many high-income countries, HPV test can be performed alone, without cervical cytology as a primary method to screen cervical cancer[4]. In Vietnam, HPV testing has been widely used in cervical cancer screening in recent years. This has yielded significant results in altering disease patterns and leading to an increased detection rate of CIN and early-stage cervical cancer.

The initial approach to management of CIN is primarily based on the patient's risk for progression to cancer. There are two general approaches, that are close observation with co – testing and treatment with excision or ablation of the cervical transformation zone. Hysterectomy is occasionally performed instead of excision or ablation but is unacceptable as a primary treatment for CIN in most instances. The choice of treatment depends on factors such as the grade of CIN, the extent of the abnormalities, the woman's age, desire for future fertility, and overall health. Patient with fulfilled gestational desire and a biopsy with CIN 2, should undergo excisional treatment. This case underscores the successful management of CIN 2 associated with HPV 16 through LEEP, with the additional use of Papilocare® Vaginal Gel as an adjunctive therapy in post-treatment care. The combined approach resulted in the complete removal of lesions and demonstrated the potential benefits of Papilocare® Vaginal Gel in supporting cervical tissue recovery and helping to enhance regression of cervical lesions and HPV clearance. In the PALOMA study, the percentage of patients with normal Pap Smear and colposcopy 3 and 6 months after treated with Papilocare® was significantly higher than without treatment (54.8% vs 64.5%), especially in high – risk HPV patients[5]. Another study, PAPILOBS study showed that 68% of patients (121/178) had negative Pap smear and concordant colposcopy. HR-HPV clearance was observed in 57.4% of patients (101/176) after 6 months treatment with Papilocare®[6]. However, further research is needed to demonstrate the treatment efficacy of Papilocare®.

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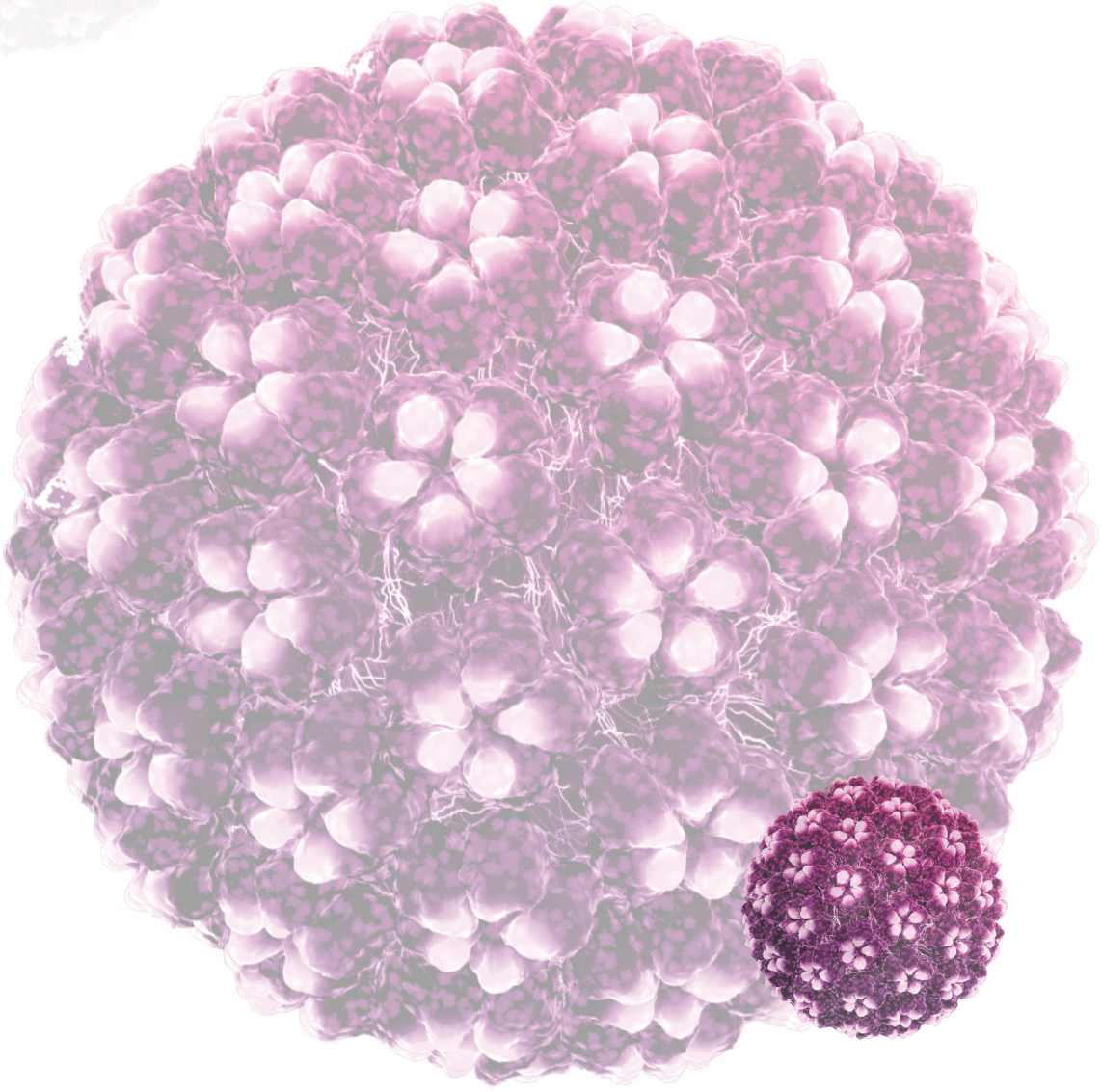

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