SECOND EDITION
PRIZE DR.
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VILAPLANA

LESIONS CAUSED BY **HUMAN PAPILLOMAVIRUS**

SECOND EDITION

CERVICAL PATHOLOGY
EXPERTS COMMITTEE
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CLINICAL CASES

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SUMMARY

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SUMMARY

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Summary

CLINICAL CASES SUBMITTED AT THE SECOND EDITION OF THE DR. EDUARDO VILAPLANA PRIZE

High-Grade Cervical Lesion (HSIL) in a Nuligest Patient with Gestational Desire. Conservative Management using a Co-Adjuvant Treatment with a *Coriolus versicolor*-based Vaginal Gel

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Summary

Approach to HSIL in a young nulligravid woman, postponing a second excisional treatment until re-evaluation of the lesion after achieving gestation, with the use of adjuvant *Coriolus versicolor*.

Keywords: Cervical cancer; HPV, conization; Conservative management; *Coriolus versicolor*.

INTRODUCTION

Cervical cancer (CC) is the fourth most common cancer in women worldwide. The risk of progression to cervical cancer in high-grade intraepithelial neoplasia is 30-50%[1].

Approximately 1.5 in 1,000 women are diagnosed with HSIL (high grade intraepithelial neoplasia) annually in developed countries, and the incidence is highest among women aged 25-29 years of age, i.e. 8.1 per 1000 women[2], therefore most women treated for HSIL are in reproductive age, so although effectiveness is a key factor when choosing a treatment, it is also important to consider which impact this treatment may have on future fertility and pregnancy outcomes[3]. Different studies report between 24 and 70% spontaneous regression rates for HSIL after a follow-up of at least 12 months[4].

LLETZ conization (large loop excision of the transformation zone) is by far the most popular procedure, combining all the advantages of excisional techniques, together with relatively short duration, low cost, simplicity, and an easy learning curve. In addition to low morbidity and effectiveness eradicating and preventing intraepithelial lesions and cervical cancer[5]. However, existing data on its impact on fertility and pregnancy are contradictory[3]. A meta-analysis of 20 studies indicates that in the treatment of cervical intraepithelial neoplasia, diathermy loop conisation is associated with increased risk of subsequent perinatal mortality and other adverse pregnancy outcomes[6].

Molecular techniques for the detection of residual persistence of the human papillomavirus (HPV), improved[7,8], and the possible impact of disease on reproductive desire have led us to

FIGURE 1. Colposcopy image showing type 2 TZ. Acetowhite epithelial staining in 4 quadrants, the lesions are introduced in the cervical channel, compatible with major changes, high grade lesion.

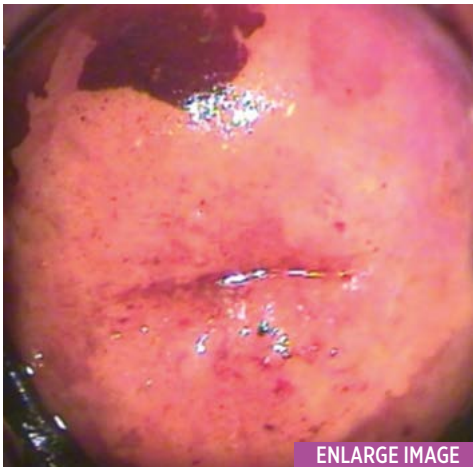

FIGURE 2. Lugol staining shows a wide iodine negative lesion, affecting 4 quadrants compatible with major changes, suggesting high grade lesion.

consider, before indicating an excisional treatment, if we should consider a wait-and-see attitude or conservative management with topical treatment such as imiquimod.

Papilocare® Vaginal Gel is the first treatment indicated to prevent and treat cervical lesions caused by high-risk HPV genotypes. In addition, its use has clinically demonstrated effectiveness eliminating high-risk HPV, with ranges between 50% to 70% in 7 different studies. These results reinforce the evidence of its beneficial effect for patients with high-risk HPV[9].

MEDICAL HISTORY

Here we present the case of a 33-year-old patient, nulligestive, referred to the Cervical Pathology Unit for HSIL.

She had no family or personal history of interest, except for of sterility, and no risk factors for HPV infection. Stable couple during the last years, under study for sterility of 2 years of evolution, being in the first visit of the Human Reproduction Unit (HRU).

At the Cervical Pathology Unit, a cytology study shows a high-grade lesion, the patient refers that she had been already screened 4 years ago. Asymptomatic.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Following the recommendations of the of the Spanish Association of Cervical of Cervical Pathology and Colposcopy (AEPCC) for the management of cervical lesions, based on the cytological findings, the following tests are performed:

- COBAS HPV test: siendo positivo para 16 y positivo para otros virus de alto riesgo (VAR). COBAS HPV test: being positive for 16 other high-risk HPV (HR-HPV).
- Colposcopy examination [Figures 1 & 2]: a type 3 TZ with an acral lesion with a rapidly appearing acetowhite lesion occupying all 4 quadrants more intense in the anterior lip and iodine negative, suggestive of a high-grade lesion.

- Targeted biopsy of the different areas showing abnormal changes by colposcopy, according to the anatomical pathology report, and the histological confirmation of the lesion: non-gradable dysplasia with suspicion of high-grade lesion.

TREATMENT AND EVOLUTION

Given the characteristics of the lesion, a LLETZ conization and vaccination for HPV are performed. In the conization specimen, the histology report shows a high-grade lesion (HSIL), with positive exocervical margins for HSIL. Biopsy of the endocervical canal negative for malignancy.

At the first postconisation check-up at four months, the following results were obtained:

- Cytology of LSIL (low grade squamous intraepithelial lesion).
- COBAS HPV test: positive for type 16 and others.
- Biopsy of exocervix with non-gradable dysplasia suggestive of high-grade lesion (ASC-H).
- Negative endocervical biopsy.

Despite the anatomopathological findings, it was decided to maintain a watchful waiting approach, with close follow up visits and complete HPV vaccination with 3 doses, so that the patient could continue with the follow-up at the URH and achieve pregnancy before a new excisional treatment was indicated.

During the conservative management, adjuvant treatment with Papilocare® Vaginal Gel was indicated and a new check-up in 4 months' time. During this 4 months' time, the patient became pregnant by artificial insemination and during the consultation the patient informed of being at 8 weeks gestation. The following was performed:

- Cytology reporting non-grading dysplasia suggestive of high grade.
- COBAS HPV test: positive for HPV 16 and others.

The conservative management was continued during pregnancy, treatment with Papilocare® Vaginal Gel was temporarily suspended, and quarterly check-ups were carried out according to the unit's protocol and the AEPCC recommendation for pregnant women with high-grade HPV lesions:

- Cytologies ranged from negative, ASCUS and LSIL.
- COBAS was positive in all controls for HPV 16 and others.

Finally, she achieved a normal pregnancy course with a eutocic delivery at 40+2 weeks, with a healthy newborn of 3,650 g.

A postpartum check-up was performed, with co-test at 6 weeks, in which she presented:

- Negative cytology.
- COBAS positive for HPV 16 and others.

Given the history of high-grade lesion, a colposcopy was also performed and was normal.

With these results, given the persistence of HPV, treatment with Papilocare® Vaginal Gel was prescribed again, together with a new check-up in 6 months. In this control COBAS tested negative as well as cytology. Therefore, after completing the treatment with the *Coriolus versicolor*-based vaginal gel, the HPV infection was finally cleared. The patient was discharged from the Cervical Pathology Unit and referred for population-based screening.

FINAL DIAGNOSIS

Diagnosis of persistent HSIL and high-risk HPV after conization in a young nuligestive woman with gestational desire, postponing the re-conisation until full-term pregnancy is achieved. Clearance of HR-HPV and elimination of cervical lesion is also achieved by combining excisional treatment with the co-adjuvant use of *Coriolus versicolor*-based gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

According to the guidelines for the management of cervical lesions, specifically: "Secondary prevention of cervical cancer, 2022. Clinical management of abnormal cervical screening test results" of the AEPCC, excisional treatment for high-grade cervical lesions is recommended (moderate

level of evidence, strong recommendation in favour). However, observation without treatment, for up to 2 years, is an acceptable option in case of HSIL/CIN 2 in a woman with gestational desire[1], so in this case we opted for follow-up and a watchful waiting approach/expectant attitude after a first conization, so that the patient could continue with the follow-up in the HRU and be able to achieve gestation before indicating a new excisional treatment.

Following this conservative management after conization, the patient, diagnosed with persistent HSIL and HPV, fulfilled her gestational desire and had a good evolution with the expectant attitude and adjuvant treatment with Papilocare® Vaginal Gel leading to the disappearance of the lesion and clearance of HPV.

Some studies show that viral clearance is higher in women treated with Papilocare® Vaginal Gel[10] a *Coriolus versicolor*-based vaginal gel. Through its action on the re-epithelialization of the cervix, restauration of microbiota and improvement of local immunity, it can favour the regression of high-grade cervical intraepithelial lesions/CIN 2 and/or HPV clearance.

Although more experience needs to be gained with the use of Papilocare® Vaginal Gel in the treatment of HPV lesions that meet conservative management criteria, in the clinical case we exposed here, the evolution was satisfactory.

Prior to indicating a destructive treatment of a cervical lesion, it is important to individualise each patient and consider their needs, the characteristics of the lesions and the risk of developing a lesion with a high pre-malignant or malignant potential, deciding the clinical management based on these factors[1].

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FINALIST

Treatment with Papilocare® in an HIV-Positive Patient with Persistent HPV and Refractory Condylomas

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Summary

Immunosuppressed patients are highly susceptible to persistent HPV infection and are at increased risk of developing premalignant and malignant cervical lesions and condyloma acuminata. Here we describe a clinical case of an HIV-positive patient with vulvar, vaginal, and cervical condylomas resistant to medical and surgical treatment as well as severe cervical dysplasia that required two excisional treatments.

Keywords: Condyloma; HPV; Inmunosuppression.

CLINICAL CASE

A 23-year-old patient, nulligest, without any relevant medical or familial history. Smoker of 15-20 cigarettes a day. Contraceptive method: combined oral contraceptives.

The patient started cytological screening for cervical cancer prevention at the age of 20.

First cytology negative but the following year, vulvar condylomas appeared and were treated with podo-phyllotoxin [Figure 1].

The next cytology at the age of 24 detected a high-grade intraepithelial lesion (HSIL) with cervical biopsy compatible with severe squamous epithelial dysplasia (CIN 3). She was referred to the hospital and, despite the patient's age, a conisation was performed given the extent of the lesion. The surgical specimen confirmed the diagnosis of severe squamous epithelial dysplasia with lesion-free margins. The patient refuses to stop smoking and the use of combined oral contraceptives.

At the age of 25, the patient was diagnosed with human immunodeficiency virus (HIV) infection, for which the patient started treatment with Genvoya® (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) with good adherence and tolerance. Maintains undetectable viral load with CD4 cell count > 500/mm^3 over the years.

During follow-up visits, vulvar, perianal and vaginal condyloma acuminata recur with poor response to most treatments (podophyllotoxin, imiquimod, trichloroacetic acid, green tea leaf extract and multiple fulgurations). Control smears are negative but infection with HPV 16, 18 and other high risk genotypes persist. Administration of the HPV vaccine is recommended but the patient refuses it.

FIGURE 1. Vulvar and perianal condylomas before podophyllotoxin administration.

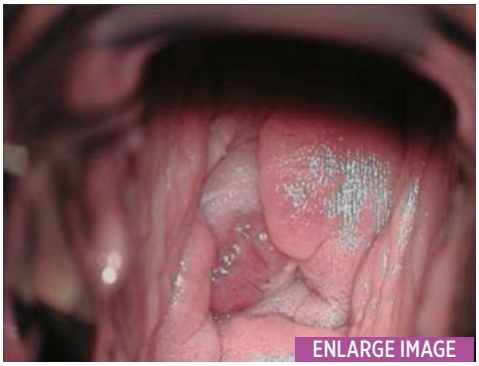

FIGURE 2. Normal cervical anatomy is lost after the second conization.

At the age of 30, the cytology result shows again a high-grade intraepithelial lesion (HSIL). A colposcopy was performed which detected major changes in the anterior cervical lip and the appearance of a cervical condyloma close to the lesion previously described. The result of the cervical biopsy was moderate/severe squamous epithelial dysplasia (CIN 2). A second conisation was performed, confirming the diagnosis of a high-grade squamous intraepithelial lesion with affected endocervical and exocervical margins. The patient is again advised to stop smoking and the use of combined oral contraceptives, which the patient continued to refuse.

During follow-up visit, vulvar, perianal, vaginal and cervical condylomas persist and are resistant to most medical and surgical treatments. Due to the two surgeries, the cervix is distorted and fused to vaginal fornixes with loss of normal anatomy [Figure 2].

During the first cytology control, a persistent high-grade intraepithelial lesion (HSIL) was found but the colposcopy showed only a condyloma lesion of about 3 cm in the anterior lip and minor changes in the anterior lip, which was biopsied with a result of mild dysplasia (CIN 1) and endocervical curettage without alterations. Therefore an exhaustive control was decided on [Figure 3]. In the following cytologies, the result was a low- grade lesion (LSIL) but large vaginal and cervical condylomas persisted.

Given the persistence of the LSIL in the cytology and positivity of other high-risk HPV genotypes for four consecutive years associated with the unsatisfactory colposcopy, a third conisation is currently being considered.

At the same time, a diagnosis of T1N0M0 right breast neoplasm was made with histology of non-special grade 1 infiltrating carcinoma, hormone receptor positive, Her2 negative and Ki-67 21%. She was treated with right breast lumpectomy and selective sentinel lymph node biopsy, radiotherapy and hormone therapy (tamoxifen). The patient finally stops taking combined oral contraceptives and reduces smoking.

Given the patient's medical context, her unfulfilled gestational desire and the technical difficulty of a third conization due to fibrosis of the remaining cervix, it was decided not to perform a third conization and to start treatment with Papilocare® for 6 months.

A clinical check-up was performed after 3 months, where complete disappearance of the vaginal condylomas was observed. A significant reduction in the cervical condyloma's size was measured, being now less than 1 cm [Figure 4]. When this clinical case was written cytology results were due.

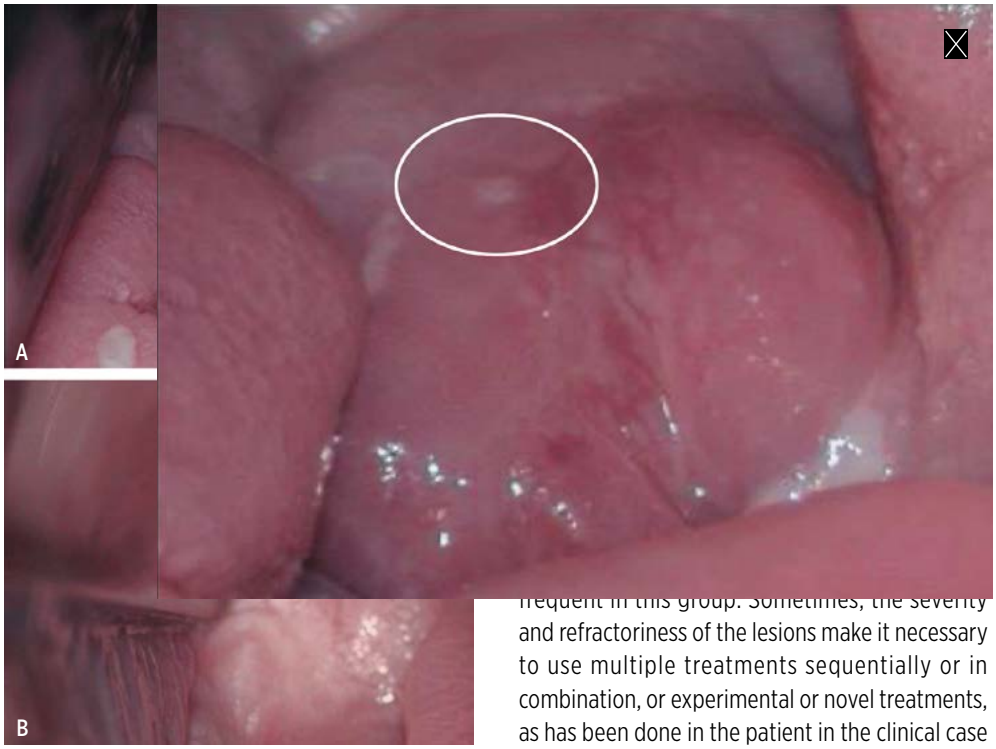

FIGURE 3. (A) White arrow shows a hyperkeratotic acetowhite lesion in the major lip of about 3cm suggestive cervical condyloma. (B) Magnification.

DISCUSSION

Immunosuppressed patients are highly susceptible to persistent HPV infection and are at increased risk of developing premalignant and malignant cervical lesions and condyloma acuminata. The prevalence of HPV in these populations often exceeds 30% and a high proportion of cytological changes are observed. Condyloma acuminata in these patients are more frequent, larger in size, occur at infrequent sites, are resistant to treatment and are recurrent. Therapies that activate the immune system (imiquimod and synecatechins) may be less effective while trichloroacetic acid and destructive treatments (cryotherapy, CO_2 laser) are more effective. Excisional therapy is indicated in cases where

frequent in this group. 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 has been done in the patient in the clinical case with Papilocare® with a very good response.

In these patients, the alteration of cytokines at the epithelial cell level favors the acceleration of the course of established infections and the reactivation of latent HPV infections. The persistence of condyloma lesions is due to low interferon production by NK cells as the CD4 lymphocyte count is affected. Low CD4 counts (< 200) behave as an independent predictor so that monitoring should be more stringent.

Early initiation of antiretroviral therapy and sustained adherence reduces the incidence and progression of premalignant lesions and ultimately the incidence of carcinoma.

Papilocare® is a *Coriolus versicolor*-based Vaginal Gel that combines the benefits of moisturization, tissue regeneration and vaginal microbiota balance. Additionally, it contains other ingredients with proven positive effects on HPV-dependent cervical lesions as well as viral clearance. Papilocare® as an adjuvant treatment

has been shown to help normalize ASCUS, LSIL and condyloma lesions in nine out of ten women and to clear high-risk HPV in more than 60% of cases in as little as six months of treatment. It offers cervical lesion and HPV clearance in comparison with the wait-and-see watchful approach, while having very good tolerability.

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FINALIST

Warty Lesion in a Patient Diagnosed with Differentiated VIN. Progression or HPV-Dependent Lesion?

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Summary

Here we present an unusual case of an HPV-dependent warty lesion found during a follow-up consultation due to a differentiated vulvar intraepithelial neoplasia in the context of Lichen sclerosus whose exegesis had been the patient's pluri-pathology.

Keywords: Differentiated VIN; Common type VIN; HPV; Progression.

MEDICAL HISTORY

A 91-year-old pluri-pathological and poly-medicated patient, with diabetes mellitus, COPD, atrial fibrillation, paroxysmal atrial fibrillation, hypertension, chromophobe renal cell carcinoma treated with radiofrequency in 2017, gammopathy monoclonal of uncertain significance and epidermoid carcinoma of the left jugal mucosa (T2N0M0) intervened in 2017. She has a previous hysterectomy for endometriosis.

Under follow-up for long-standing *Lichen sclerosus* treatment with clobetasol for maintenance.

At the last check-up, biopsies had been performed in 2 areas of sclerosis with a diagnosis of differentiated vulvar intraepithelial neoplasia (dVIN). The indicated treatment would be excision of the lesions, but given the patient's age and the multi-pathology, it was decided to follow a different approach with close check-ups and only treat if progression occurs. The patient came in for a check-up and reported an increase in pruritus and the appearance of a warty lesion.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS [Figures 1 & 2]

- Inner face of labia majora and minora with broad faint leukoplakic area typical of *Lichen sclerotic*, with 2 raised leukoplakic plaques hyperkeratotic below the hood 2 cm from the clitoris and in a fork below the introitus on the left, already biopsied, diagnosed of VINd and no change from previous exploration.
- Growing introitus warty lesion on the right lateral face that goes towards the vagina with 2-3 cm of newly appeared.

With these findings, a progression of the VINd is suspected and the new warty lesion is biopsied in vulva and vagina.

FIGURE 1 . ENLARGE IMAGE

FIGURE 2 . ENLARGE IMAGE

Pathological biopsy diagnosis: papillomatous lesion with hyperkeratosis and keratohyalin granules, suggestive of a viral wart.

In view of the discordance of results, an immunohistochemistry was requested, which corroborated the double origin of the lesions.

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of vulvar intraepithelial neoplasms (VIN) are very heterogeneous; therefore a biopsy is needed for histological examination in doubtful cases to stablish a differential diagnosis between differentiated VIN and common VIN.

Although it is possible to differentiate considering the clinical context, in some cases, as the one is presented here, a combination of immunohistochemistry with histology is needed. HPV-dependent lesions will show positivity for p16, Ki67 and detection of HPV itself. In contrast, differentiated VIN type lesions will frequently show p53 gene mutations.

The main difficulty for differential diagnosis between benign inflammatory dermatoses and differentiated VIN is that histological changes can be very subtle, therefore up to 40% of cases are underdiagnosed.

TREATMENT AND EVOLUTION

The viral wart was eliminated via cryotherapy. Subsequently, treatment was begun with imiquimod 3 times a week in combination with Papilocare® External Gel daily as a co-adjuvant for the elimination of the virus but also having a re-epithelializing effect in response to the inflammatory effect of imiquimod, as well as having a beneficial moisturising effect which is particularly interesting in this patient that presents a *Lichen sclerosus* in the entire vulva.

At the one-month check-up, the warty lesion completely disappeared, without changes in the VINd. The patient referred a clear improvement, and therefore an expectant approach was taken with frequent check-ups and maintenance treatment with clobetasol an in areas affected by *Lichen sclerosus* combined with Papilocare® External Gel as a moisturiser, and reepithelialising and HPV lesion limiting agent [Figure 3].

FIGURE 3 .

FINAL DIAGNOSIS

HPV-dependent vulvar lesion in the setting of differentiated VIN and *Lichen sclerosus*.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

There are two clearly differentiated entities of Vulvar Intraepithelial Neoplasia (VIN) which are: HSIL (common type VIN) related to human papillomavirus (HPV) and differentiated type VIN related to inflammatory dermatoses, mainly Linchen sclerosus. Their epidemiological factors, histology, clinical behaviour and potential for progression to cancer are clearly differentiated. The described case represents a particular case in which both entities coexist.

The common type of VIN, HSIL (cVIN), is more frequent, occurs in younger women and is often associated with HSIL lesions in other locations. On the other hand, differentiated type VIN, occurs generally in older women with a history of inflammatory dermatoses and has a higher progression rate to major vulvar carcinoma of 33% versus 6% for common VIN.

The 2015 International Society for the Study of the Vulvovaginal Disease (ISSVD) classifies these two entities and considers that LSIL (VIN1) has no carcinogenic potential and recommends to identify it as "viral wart or changes associated to HPV" with a symptomatologic treatment, but not as a preventive treatment for vulvar cancer.

Therefore, in this clinical case, the risk of progression to cancer is mainly due to the differentiated VIN, whose only effective treatment is surgical excision. However, in this case, the patient is an elderly and pluri-pathological patient, in which the adverse effects of a vulvectomy intervention could have deleterious effects, and the priority must be increasing her quality of life. Destructive treatment of the HPV-dependent lesion is however effective and less aggressive, and the maintenance therapy improves her quality of life. This being the treatment of Lichen sclerosus with clobetasol to reduce itchiness together with co-adjutant treatment with Papilocare® External Gel as a moisturising and re-epithelializing to limit HPV reactivation and improve vulvar trophism.

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FINALIST

Adjuvant Management with *Coriolus versicolor* Gel in the Treatment of Vulvar Intraepithelial Neoplasia. A Case Report

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Summary

Vulvar intraepithelial neoplasia (VIN), classified as VIN 1, 2 or 3, are precursor lesions of squamous vulvar cancer. It originates from persistent HPV infection, with the main clinical presentation being pruritus associated with pain or itching. The risk of progression of VIN to vulvar squamous cell carcinoma is accepted to be 7-10%[1].

Keywords: Intraepithelial vulvar neoplasia; Laser vaporization; HPV; *Coriolus versicolor*.

MEDICAL HISTORY

48-year-old patient. Referred to our cervical pathology office for vulvar condylomatosis and poor response to medical treatment.

- Allergic hypersensitivity to metronidazole. Allergy to fentanyl.
- Left trigeminal neuralgia.
- Traumatic brain injury in 2016. Seizures in childhood.
- A picture suggestive of mixed phenotype asthma in a patient with a history of smoking (smoker of 15-20 cigarettes/day).
- Carotid atheromatosis.
- Follow-up multinodular goiter.
- Migraines without aura. Hypercholesterolemia.
- Surgical interventions: appendectomy. Arthroscopy of left malleolus.
- G1C1 FM amenorrheic bumps. Stable couple for 5 years.
- Without sexual intercourse since the beginning of follow-up due to the psychosexual impact of the lesions.
- Not vaccinated against HPV.

PHYSICAL EXAMINATION AND TREATMENT

November 2020 [Figure 1]

External genitalia with extensive vulvar condylomatosis, covering the lower third of the labia minora. Normal and wide vagina. Cervix well epithelialized, lateralized.

- Colposcopy: inadequate. Type 3 TZ. No acetowhite lesions. Iodo-negative.

FIGURE 1.

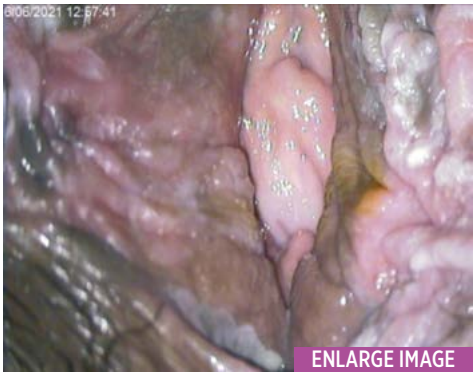

FIGURE 2.

- Vulvoscopy: vulvar condylomatosis with dense acetowhite over condyloma areas. No lesions suspicious for malignancy.

In view of the great symptomatology and given the results of pathological anatomy, it is proposed to perform a laser vaporization as well as complementary treatment with Papilocare® gel to help re-epithelialize and soothe the treated area[5].

- Cytology: LSIL + HR HPV (not 16/18)
- Vulvar biopsy: tissue with low-grade squamous intraepithelial lesion/LSIL (VIN 1)
- Endocervical curettage: abundant mucoid material and very isolated fragments of endocervical epithelium without relevant alternations.

June 2021 [Figure 2]

Attends 6-month follow-up visit

Refers treatment with Veregen® + Papilocare® and Hupavir® for 45 days proposed by private gynecologist.

- Examination: external genitalia present pigmented and leukoplastic lesions on both labia minora compatible with VIN1 / condylomas.
- Colposcopy: inadequate and unsatisfactory. Type 3 TZ. Vascularization: typical. Acetowhite: no pathological uptake. Iodo-negative: 0% compatible with normality in the exo-cervix. Endocervical biopsy performed.
- Vulvoscopy: both labia minora with pigmented, leukoplastic and hyperatotic lesions. A biopsy was performed on the left labia minora

The results of these tests are as follows:

- Cytology ASCUS + HR HPV
- Cervical biopsy: mucoid material and fragments of squamous and endocervical epithelium with minimal focus suggestive of low-grade squamous intraepithelial lesion/CIN1.
- Vulvar biopsy: low-grade squamous intraepithelial lesion/VIN 1 and minimal focus suggestive of high-grade squamous intraepithelial lesion/VIN2

Smoking cessation is insisted, and the use of Imunocare® associated with Papilocare® External Genital Gel and Papilocare® Immunocaps is recommended.

December 2021 [Figure 3]

Great improvement in mood with a 30-kilogram weight loss due to trigeminal neuralgia pain control as well as measurable changes.

Complete vaccination against HPV, reduction of smoking to 5 cigarettes per day.

- Gynecological examination: flat condylomas on almost the entire vulvar surface. Cervical-vaginal cytology is performed.

FIGURE 3.

- Vulvoscopy:
  labia minora
  labia minora
- LSIL cytolog
  cells, inconclusive for HSIL/CIN2
- Vulvar biopsy: high-grade squamous intraepithelial lesion (HSIL)/VIN 3, associated with HPV.

In view of these findings, and after presenting the case to the cervical pathology committee, a conization with diathermy loop and partial cutaneous vulvectomy was proposed which was later performed in February 2022.

Conization with diathermy loop:

- Uterine conization specimen with diathermy loop: low-grade squamous intraepithelial lesion (LSIL)/CIN 1. Focal involvement of the exocervical margin at 9 o'clock. Absence of endocervical glandular epithelium represented.
- Endocervical enlargement: loose fragments of squamous epithelium with intense thermal artifact not assessable.
- Endocervical curettage: absence of endocervical glandular epithelium. Minimal fragments of squamous epithelium without relevant alterations accompanied by hematic material.
- Simple vulvectomy specimen: Extensive high grade squamous intraepithelial lesion (HSIL)/

March 2022 [Figure 4]

In the review after the intervention, the patient reports a great improvement of the clinical condition with disappearance of the itching, despite the recency of the intervention.

She is currently applying Papilocare® External Genital Gel to re-epithelialize the tissue once a day and associating Papilocare® immuno-capsules. She has requested referral to the smoking cessation unit.

FINAL DIAGNOSIS

VIN 2 and 3 associated with HR HPV (not 16/18), CIN1. The patient will have the next follow-up visit in 6 months, where co-testing, colposcopy, and vulvoscopy will be performed, and later acting according to result.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Papillomavirus infection can occur throughout the entire anogenital area[1,2], with the cervix being the site with the most premalignant and malignant

lesions, but other regions such as those discussed in this case should not be forgotten.

The vulva usually presents multifocal, recurrent lesions with great aesthetic impact and their repair is usually associated with vulvodynia and dyspareunia[6].

Our patient presented with the following risk factors: being a heavy smoker, the significant number of drugs she used for pain control, and having a high susceptibility due to the disease she was suffering from.

Early diagnosis of VIN and its appropriate treatment[5,6] prevents squamous cell carcinoma of the vulva, but usually at the cost of excisional treatments which often have a great impact on a patients' self-image. The use of topical gels that improve re-epithelialization and help eliminate the virus will favor the management of these lesions and improve the self-esteem of patients, reducing the psychosexual impact of treatment.

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FINALIST

Healing of Acute Vulvar Ulcer after COVID-19 Infection with a *Coriolus versicolor* Extract based Re-Epithelializing Gel

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Summary

Here we present the clinical case of a 27-year-old woman who had with a single non-infectious vulvar ulcer (Lipschütz ulcer) after infection with SARS-CoV-2. The role of Papilocare® External Genital Gel treatment to accelerate the healing of this vulvar ulcers is tested.

Keywords: COVID-19; Lipschütz vulvar ulcer; Re-epithelialization; *Coriolus versicolor*.

MEDICAL HISTORY

A 27-year-old nulliparous woman with no medical or surgical history of interest. Ex-smoker, uses the vaginal ring as a contraceptive and was vaccinated with 3 doses of tetravalent HPV vaccine at 19 years of age. She is being followed up in the Lower Genital Tract Unit due to a low-grade cytological, confirmed by biopsy as CIN 1 and positive for HPV genotypes 39 and 66.

The patient reported the appearance of a painful lesion in the lower third of the right labium minora, of 36 hours' duration. She indicates the appearance of "a wound" that has grown in the last 12 hours, which causes pain and a "vulvar burning sensation". Afebrile, no alterations in vaginal discharge, urinary symptoms or abdominal pain. She denies risky sexual relations. The last sexual intercourse was 5 days ago, with her regular partner.

The patient indicates that she had a SARS-CoV-2 infection confirmed by a self-taken antigen test one week ago. Currently, the patient has no symptoms associated with SARS-CoV-2 persisting only a slight asthenia.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Examination of the lower genital tract revealed an approximately 1 cm annular lesion on the inner side of the lower third of the right labium minora. The lesion area is well defined, has a necrotic background with fibrin deposition. The lesion is also painful on palpation. There are no satellite lesions. [Figures 1 & 2]

On speculoscopy, the cervix and vaginal mucosa do not show significant alterations. No pathological leucorrhoea is found. Vaginal examination showed no pain on cervical mobilisation. No regional adenopathy was observed.

FIGURE 1. 1 cm Vulvar lesion in the inner face of the right labia minora.

FIGURE 2. Magnification shows a well limited lesion with a necrotic background and fibrin deposit.

Given the clinical features of the case, the suspected diagnosis is "acute Lipschütz vulvar ulcer" after infection with SARS-CoV-2. However, as a differential diagnosis, vaginal and endocervical exudates, and serology for sexually transmitted infections (HIV, syphilis, Hepatitis B and C, and Herpes) is requested. All the tests give a negative result.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in this case is that of acute vulvar ulcer, and the following must be fundamentally ruled out: syphilitic chancroid, genital herpes and Behçet's disease.

TREATMENT AND EVOLUTION

The treatment of this case is fundamentally symptomatic and should be aimed at relieving vulvar pain and promoting the healing of the ulcer. Usually, the process is self-limiting and resolves spontaneously within several days or a few weeks. In some cases, with a torpid course, topical corticosteroids may be useful.

In this case, analgesia is proposed with 400 mg ibuprofen on demand, up to a maximum of 1 tablet every 8 hours. It is recommended to keep the wound clean and dry to avoid maceration. Sexual intercourse is not recommended until complete healing.

To promote healing of the lesion, Papilocare® External Genital Gel is recommended twice a day until the next medical check-up. This preparation has a specific formulation with 7 components, including *Coriolus versicolor* fungus extract, the prebiotic Bioecolia®, hyaluronic acid, β-glucan, *Centella asiatica*, neem (*Azadirachta indica*) extract and Aloe vera extract with important healing and re-epithelialising properties.

The patient is scheduled for an appointment 6 days later to review the results of the tests requested and to check the evolution of the case. She reported disappearance of vulvar pain 24 hours after starting treatment with no need for analgesia, as well as almost complete healing of the vulvar lesion 4 days after starting treatment. The patient was completely asymptomatic at the follow-up visit [Figure 3].

FINAL DIAGNOSIS

Acute vulvar ulcer of Lipschtütz after SARS-CoV-2 infection.

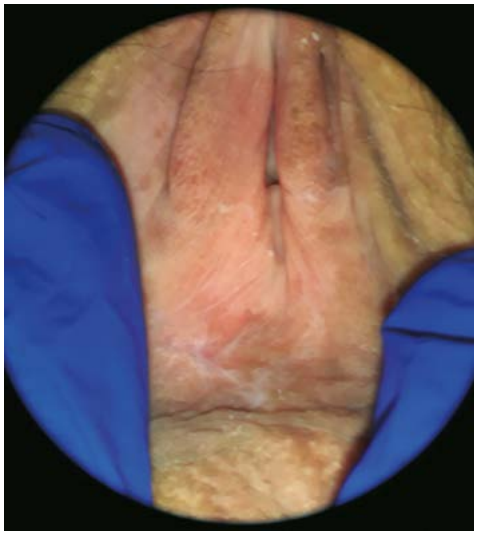

FIGURE 3. Image of the same area 6 days after starting treatment. The vulvar lesion has disappeared without scars.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Vulvar ulcer of Lipschütz is a clinical entity based on the occurrence of one or more acute vulvar ulcers in girls or young women, of unknown cause, in which venereal aetiology and other common causes of vulvar ulceration are ruled out[1,2]. Its aetiopathogenesis is poorly understood, but it has been linked to immunological mechanisms following viral infections. It may be related to a primo-infection by Epstein-Barr virus and other viruses typically affecting the ENT area, and which appear as a pseudo-flu-like picture of asthenia, myalgias, fever, etc.[3].

In the last two years there have been numerous publications reporting cases of acute vulvar ulcer following vaccination or infection by SARS-CoV-2[4-6]. In fact, some studies try to explain the pathogenesis of this process by relating the increase in cytokines and Tumour Growth Factor α (TNF-α) produced by SARS-CoV-2 with an increase in cell adhesion to the vascular endothelium and an altered endothelium and neutrophil function leading neutrophils to aphthosis[7].

Although the clinical practice, in most cases, is self-limited over time and the fact that lesions almost always heal without scarring, many studies recommend, in addition to symptomatic treatment, the use of substances that could promote faster healing of the lesions. Some case reports indicate that the use of oral corticosteroids would lead to rapid clinical improvement[8].

In this regard, the combination of ingredients of Papilocare® External Gel may be a very interesting treatment option in these cases, as the healing effect of the *Centella asiatica*, *Aloe vera* and β-glucans, are combined with the moisturising properties of hyaluronic acid and the immunomodulatory properties demonstrated by *Coriolus versicolor* extract [9,10].

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FINALIST

Effect of *Coriolus versicolor* on the Cervical Re-Epithelialization Post-Conization Process

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Summary

Conization is the treatment of choice for high-grade cervical dysplasia caused by HPV. The most frequent complication is bleeding. The *Coriolus versicolor* based vaginal gel accelerates the re-epithelialization process, decreases the risk of bleeding, and improves viral clearance rates after surgery.

Keywords: HSIL (CIN); *Coriolus versicolor*; Conization; Re-Epithelialization.

MEDICAL HISTORY

Two patients with similar characteristics, diagnosed with HSIL (CIN 2-3) in the cervical pathology office of our center by colposcopy-directed biopsy, were chosen.

PHYSICAL EXAMINATION

Patient 1

35 years old. G1P1. Only history of bronchial asthma. IUD user.

Screening cytology HSIL, HPV 16. Adequate colposcopy, type 1 TZ. No change on application of acetic acid. From 3 to 6 hours in TZ, iodine negative area: non-specific findings biopsied by HSIL cytology. Biopsy result: HSIL (CIN 2-3). Conization with diathermy loop under local anesthesia. Excision type 1 [Figure 1]. Electrocoagulation.

The histological study of the conization specimen describes a LSIL (CIN 1) contacting the endocervical margin. LEC without dysplasia.

Patient 2

28 years old. Nulliparous. No history of interest. HSIL screening cytology. Adequate colposcopy. Type 1 TZ. At 12 h in TZ, coarse stippling tab. Biopsy. HSIL (CIN 3) Conization with diathermy loop. Excision type 1 [Figure 2]. Electrocoagulation.

Histological study of conization specimen: HSIL (CIN 3) Free margins.

TREATMENT AND EVOLUTION

Both patients were given the same post conization instructions: relative rest, abstinence from intercourse, avoidance of immersion baths and tampons for 2 weeks.

FIGURE 1. Surgical site after conization in patient 1.

FIGURE 2. Surgical site after conization in patient 2.

Patient 1 was prescribed treatment with *Coriolus versicolor* (1 vaginal application daily until further control). No topical treatments were indicated for patient 2.

FINAL DIAGNOSIS

Both were evaluated 21 days after conization.

Patient 1 [Figure 3] had a favorable evolution, with no bleeding episodes. She had gone to the emergency room for yellowish leucorrhea, and the examination was normal.

Patient 2 [Figure 4] had experienced an episode of bleeding for which she had gone to the emergency room, and no treatment was necessary. She referred spotting since then. On examination, a fresher site was visualized, with granulation tissue and a bleeding point on the posterior lip, which was coagulated with silver nitrate.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASES

Conization is the treatment of choice for high-grade cervical dysplasia. It consists of excision of a cone-shaped portion of the cervix, surrounding the endocervical canal and including the entire transformation zone. It can be performed with cold scalpel, diathermy loop and/or laser. The diathermy loop is the most used procedure[1].

After surgery, patients are advised to rest and to avoid intercourse, tampons, and immersion baths, but there is no consensus on the use of topical treatments.

One of the most frequent complications after surgery is bleeding. This can occur immediately and up to 2 weeks after conization. The incidence of this type of event after conization with a diathermy loop is around 8%. There is little literature studying predisposing factors (cone size, etc.). Normally this type of complication is resolved with conservative measures[2].

There is literature supporting the use of *Coriolus versicolor* vaginal gel to accelerate the repair of cervicovaginal mucosal lesions[3]. In the patient in our clinical case, the treatment was shown to have a positive effect on the re-epithelialization of the cervical mucosa after conization compared to the patient who did not use it. It also reduced the risk of bleeding[4].

We also know that the vaginal microbiota of HPV-positive patients is more diverse than that of

FIGURE 3. Re-epith
post conization.

uninfected patie
shown to decre
HPV clearance.
patient in our st

The recomm
vaginal gel afte
easy for the patient to comply with and provides many benefits (accelerates the re-epithelialization process, reduces complications, improves the viral clearance rate, and improves the prognosis of cervical pathology).

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a pilot study in asymptomatic women. BMC Women's Health. 2017; 17(1): 21.

FINALIST

Resolution of Persistent HPV 53 Infection in an Immunocompromised Patient after Treatment with Papilocare®

DR. ANA BELÉN JIMÉNEZ GALLEGO

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Summary

We reviewed the clinical case of a patient with a history of immunosuppression due to treatment for rheumatoid arthritis with persistent HPV 53 infection and resolution after treatment with *Coriolus versicolor*-based gel (Papilocare®).

Keywords: Immunosuppression; High-Risk HPV; *Coriolus versicolor*; Genital warts.

MEDICAL HISTORY

- **Family History:** father with hypertension; mother treated for bipolar disorder.
- **Personal history:** 29 years old. Polyarticular juvenile idiopathic arthritis. SI: appendectomy, breast prosthesis. Allergy to Metamizol. Non smoker.
- **Obstetric & gynecological history:** nulli-parous. Menarche 13 years old. Previous normal cytological screening. Complete vaccination against HPV at 12 years of age. Normoregulated.
- **Treatment:** tocilizumab in monotherapy. Prednisone.
- The patient first visited our clinic in July 2019 due to the appearance of vulvar lesions compatible with condylomas. Subsequently she presented HPV test with positive result 53 (HR).

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

First Visit

Good general condition. Normal weight.

Vulva: raised lesions of umbilicated appearance on the right labium majora suggestive of Molluscum, but one of them differs in appearance and could be a papillomatous lesion. Another single lesion in the upper third of the left labium majora. Normal vagina.

Anteverted uterus with 2nd stage LE. Normal ovaries.

Second Visit (Follow-Up Control)

The patient has undergone CO_2 laser treatment after no response to podophyllotoxin ointment.

ENLARGE IMAGE

FIGURE 1.

Provides co-test: normal cytology. HPV positive for genotype 53 (HR).

GE normal, scar lesions after CO2 treatment. Vagina normal, no condylomatosis lesions.

Transvaginal Ultrasounds: homogeneous anteverted uterus with thin endometrium. Adnexa normal, with multiple peripheral follicles. No free fluid.

Colposcopy: adequate. TZ1. No acetic lesions are observed. Immature metaplasia. Schiller test negative.

Third Visit (Follow-Up Control)

The patient went for a new co-test one year after the previous one, similar result: normal cytology, persistence of HPV 53.

Colposcopy: adequate colposcopy, TZ 1, no acetowhite lesions. Schiller, negative vaginoscopy.

The patient is prescribed treatment with Papilocare®, which is carried out in a complete regimen for 6 months.

Fourth Visit (Follow-Up Control)

She goes for a new co-test, which is reported as negative cytology and negative HPV.

TREATMENT AND EVOLUTION

The patient has continued treatment throughout the review period with biologic therapies tocilizumab and prednisone, causing immunosuppression. From the gynecologic point of view, she has undergone 6 months of treatment with Papilocare® according to a standardized regimen. The first 21 days daily and then every other day for 5 additional months.

FINAL DIAGNOSIS

Persistency of HR HPV 53 for 2 years. Resolution after treatment with Papilocare®.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Immunosuppressed patients are especially susceptible to persistent HPV infection, presenting a higher risk of progression to high-grade lesions. Special care should be taken in this population, performing annual cytologic controls from the age of 25.

We know that treatment with Papilocare® has shown greater benefit than expectant management in patients with lesions associated with HPV. In the case of the patient presented here, there is a positive response to treatment with *Coriolus versicolor* gel, so it seems a suitable alternative as a co-adjuvant in these cases.

The patient had no adverse reactions to the treatment and had excellent tolerability.

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FINALIST

Vulvar Intraepithelial Neoplasia. Topical Treatment with Imiquimod and Adjuvant Treatment with Papilocare® External Gel. A Case Report

DR. ESTER MARTÍNEZ LAMELA

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Summary

A 52-year-old female patient consulted for a vulvar lesion of several months of evolution. A high-grade squamous intraepithelial lesion (HSIL-VIN common type) and the presence of HR HPV were confirmed. She was treated with topical Imiquimod 5% with complementary treatment with Papilocare® external gel. Complete remission was achieved after 12 weeks of treatment.

Keywords: Vulvar intraepithelial neoplasia; Human papillomavirus; *Coriolus versicolor*.

MEDICAL HISTORY

52-year-old woman, referred to the lower genital tract clinic for evaluation of vulvar lesion.

She has no medical history of interest. She smokes 12 cigarettes a day, has a steady partner and uses a barrier method for contraception. She is not vaccinated against HPV.

She presents with a normal cytological screening, according to protocols, and without alterations. She refers to finding a lesion at vulvar level in self-exploration of several months of evolution which has increased in size but does not produce any symptomatology.

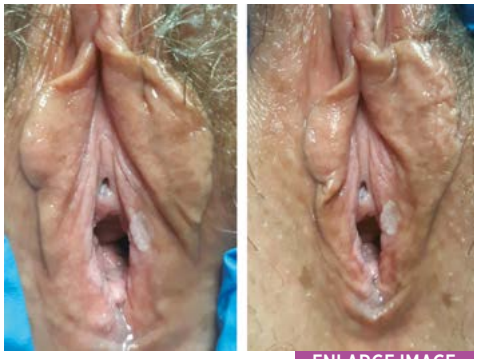
PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Exploration:

- External genitalia with isolated whitish lesion, located in the middle third of the left labium minora, slightly raised, with an irregular surface.
- Vagina and cervix macroscopically normal.

In view of these findings, a complete examination of the lower genital tract is performed:

- Cervical liquid cytology: satisfactory sample, presence of endocervical component, negative for malignancy.
- HPV genotype: high-risk 45.
- Colposcopy: transformation zone type 2, normal vascularization. Mature squamous epithelium. Schiller's test negative. Normal findings.
- Vaginoscopy: normal.
- Vulvoscopy: after application of 5% acetic acid, a multifocal lesion is observed: weak acetowhite at the entrance of the introitus and the inner part of the right labium minora over its entire length, with no other superimposed images. On the left side, the lesion described is dense



ENLARGE IMAGE

FIGURE 1.

ENLARGE IMAGE

FIGURE 2.

acetowhite, raised, with irregular border and a normal vascularization pattern normal [Figure 1]. A #4 punch biopsy is performed.

Pathological anatomy confirms a high-grade squamous intraepithelial lesion: HSIL (common type VIN).

TREATMENT AND EVOLUTION

Since it was a common type VIN, and there were no signs of occult invasion, a destructive treatment was decided.

Topical treatment with Imiquimod 5% is prescribed before bedtime on the lesion, three times a week. As a complementary treatment, given that the rest of the lesions are compatible with changes caused by HPV, the application of Papilocare® External Genital Gel is indicated daily.

In the clinical control at 6 weeks, the patient showed good tolerance to the treatment. Vulvoscopy showed the disappearance of the lesions located in the right introitus and labium minora, with persistence of the lesion on the left side, but with clear improvement. Therefore, the same treatment regimen was maintained for 12 weeks, reaching complete remission [Figure 2].

DISCUSSION

Vulvar intraepithelial neoplasia (VIN) is considered a precursor lesion to vulvar carcinoma. The 2015 classification by the International Society for the Study of the Vulvovaginal Disease (ISSVD) establishes two patterns for VIN: HSIL (common type VIN) and differentiated type VIN, with clearly differentiated epidemiological factors, histology, clinical behavior, and potential for progression.

HSIL (common type VIN) is related to oncogenic HPV types.

Only 50% of VIN lesions are symptomatic. This fact reinforces the importance of performing a systematic and thorough vulvar examination.

There is no characteristic lesion of VIN, and the clinical findings are highly variable with respect to color, surface, and topography.

In terms of treatment, the most conservative strategies possible should be designed to preserve vulvar anatomy and functionality, always ensuring satisfactory results in terms of efficacy.

Imiquimod is an immune response modulator with an antitumoral effect. Its activity is due to stimulation of local cytokines and cellular immunity. It can produce significant local effects.

The application of *Coriolus versicolor* based gel has demonstrated a wide efficacy in the resolution of cervical lesions associated with HPV. It also improves hydration and repair of a damaged mucosa favoring the normal re-epithelialization process.

Although more studies are needed, it appears that adjuvant treatment in vulvar lesions caused

by HPV may be an excellent option as an adjunct to destructive topical treatments, improving their tolerability and HPV clearance.

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FINALIST

Vaginal Gel with *Coriolus versicolor* in the Treatment of Vaginal Intraepithelial Neoplasia (VaIN) in a Menopausal Patient

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Summary

Vaginal intraepithelial neoplasia (VaIN) is considered the precursor lesion of vaginal cancer. These lesions are infrequent and difficult to diagnose, which, together with the limited knowledge of their natural history, makes clinical management of VaIN a real challenge.

Keywords: VaIN; HPV; *Coriolus versicolor*; Vaginal Gel.

MEDICAL HISTORY

We present the case of a 56-year-old woman who underwent a simple total hysterectomy 10 years ago for an intracervical neoplasia (CIN) associated with papillomavirus (HPV) genotype 16. Of additional interest, she is also diagnosed with relapsing-remitting multiple sclerosis with immunosuppressive treatment.

The patient attended her annual check-up and was asymptomatic except for a slight sensation of vulvovaginal itching and decreased vaginal discharge, symptoms that were initially attributed to the genitourinary syndrome of menopause.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Physical examination was normal, except for evidence of significant vulvovaginal atrophy, which made examination difficult. A vaginal cytology was performed as part of the protocolized follow-up due to her previous pathology, which is reported as squamous cell atypia of uncertain significance (ASCUS). Vaginoscopy revealed a faint lugol area in the right corner of the vaginal vault, which was biopsied and found to be a low-grade intraepithelial lesion or LSIL (VaIN).

TREATMENT AND EVOLUTION

At first it was decided to take a watchful waiting approach and a new review in was scheduled in 6 months, during which a treatment with local estrogens was prescribed to improve the tropism of the vaginal epithelium and alleviate the patient's symptoms.

At 6 months we found a slight improvement in the referred symptoms, as well as a more

satisfactory examination. However, after repeating the vaginoscopy and biopsy, the results still showed persistence of the lesion. At this point it was decided to start topical treatment with a Coriolus versicolor based vaginal gel (Papilocare® Vaginal Gel). The patient applied it daily for one month, and, subsequently, every other day until completing 6 months of treatment.

FINAL DIAGNOSIS

After 6 months of treatment with Papilocare® Vaginal Gel, the patient underwent a new examination. A vaginal cytology was taken and reported as normal, and a vaginoscopy was performed in which the previously observed weak lugol area in the angle of the vagina was no longer evident. In addition, the patient reported a clear improvement in her symptoms.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Vaginal intraepithelial neoplasia (VaIN) is a rare and often asymptomatic entity. Depending on the degree of epithelial maturation involvement, they are classified into high-grade intraepithelial lesions or HSIL (VaIN) and low-grade intraepithelial lesions or LSIL (VaIN)[1]. Human papillomavirus (HPV) infection has been identified as the causative agent in up to 90% of VaIN cases, with HPV 16 being the most frequent genotype[2].

Since most lesions are asymptomatic, the incidence of VaIN is difficult to know. In Spain, it is estimated that VaIN constitutes 2% of all HPV-associated lower genital tract pathology[3].

The goal of treatment of VaIN is to prevent its progression to invasive vaginal cancer. However, 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. In cases of patients with LSIL (VaIN), observation without treatment is recommended, justified because most of these low-grade lesions regress spontaneously[4]. However, immunosuppressed patients are an exception, as in the case of the patient described.

An important part of the treatments available are topical treatments, the main advantage of which is that they can be applied to the entire vaginal mucosa. The most used to date have been fluorouracil (5-FU), trichloroacetic acid (TCA) or imiquimod. However, they all share an important side effect: local irritation, which can often be intolerable for patients and is a frequent cause of abandonment of treatment.

The *Coriolus versicolor* based vaginal gel (Papilocare® Vaginal Gel) is presented as an alternative treatment for this type of lesions. In addition to *Coriolus versicolor* extract, this gel contains hyaluronic acid (moisturizing effect), beta-glucan (anti-inflammatory), Bioecolia® (prebiotic), Centella asiatica (regenerating), Azadirachta indica extract (re-epithelializing agent) and Aloe vera[5].

The studies available to date, focusing on the efficacy of the gel in women with HPV infection and low-grade cervical lesions, have shown an improvement in cytology and colposcopy results, and even HPV negativity in up to 67% of cases after treatment[6].

In addition to these beneficial effects at the level of HPV lesions, the largest study available to date (PALOMA), conducted in 91 HPV-positive women with low-grade cytology and abnormal colposcopy, demonstrated good tolerance to treatment, as well as numerous secondary beneficial effects, including a higher percentage of re-epithelialization and decreased stress, which confers high adherence to treatment[7].

To date, there are no studies available on the effect of this vaginal gel on VaIN and it will probably be difficult to find any in the future due to the low incidence of this type of lesions. However, due to the available literature on its effect on cervical lesions and its high tolerability, it is an effective treatment alternative to be taken into account when a VaIN is found, as in the clinical case presented.

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FINALIST

Treatment of Erythroplasia and Cervical HPV in a Young Patient with a *Coriolus versicolor* Vaginal Gel

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Summary

The human papillomavirus (HPV) is the most frequent sexually transmitted disease, in addition to being the causative agent of almost all cervical neoplasms and their precursor lesions. Infection by this virus has a high incidence during the first years of sexual life, although most infections are transient and almost 90% of cases resolve spontaneously within 18-36 months, particularly in the case of lower-risk viruses. This viral "clearance" is attributable to local innate immunity; however, this local immunity is insufficient to guarantee permanent protection, so new infections by the same or a different virus are possible. Approximately 10% of infections are persistent and usually involve the highest risk viruses and can evolve into preneoplastic and neoplastic lesions. HPV infects the skin and some mucous membranes, presenting selectivity according to the type of HPV. It enters the epithelium through several mechanisms: microtrauma during sexual intercourse, direct contact with infected skin and objects; and during pregnancy and perinatal period ascending and vertical passage is possible. The latency period from infection to clinical expression varies from months to years. Sometimes it can produce symptoms such as post-coital bleeding.

Keywords: Cytology; Coital bleeding; HPV; Cervical cancer prevention.

MEDICAL HISTORY

27-year-old woman under follow-up in the lower genital tract pathology clinic for testing HPV positive and experiencing coital bleeding in the last months.

- Family history: negative for breast, ovarian, and/or endometrial cancer. Grandparents gastric and lung cancer. No hereditary diseases.
- Personal History: no genetic diseases. No known drug allergies. No surgeries.
- Obstetric and Gynecological History: Nulliparous. Stable couple. CM: combined oral hormonal contraception.
- HPV vaccination: 3 registered doses (11/2009; 01/2010; 05/2010)

Negative cytology controls with positive HPV 52 (high oncogenic risk) since June 2020. She attends a consultation in August 2021 for periodic control and reports coital bleeding during the last few months.

PHYSICAL EXAMINATION

Normal external genitalia. Vaginal mucosa of normal appearance. Erythroplastic cervix, without active bleeding or signs of infection. Nabothian cysts [Figure 1].

- Colposcopy: Adequate. Completely visible squamocolumnar junction (SCJ). Type 1 TZ. Nabothian cysts.

FIGURE 1. Initial examination, acetic stain shows erythroplastic cervix with no active bleeding or signs of infection. SCJ completely visible. Type 1 TZ, Nabothian cysts are observed.

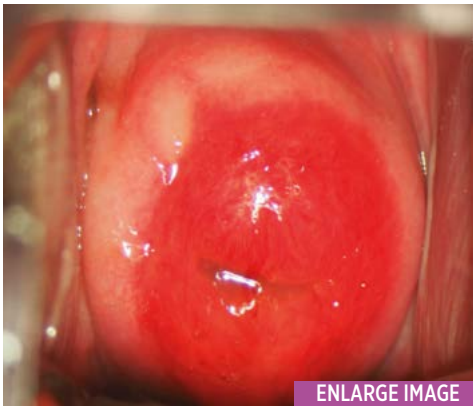

FIGURE 2. Acetic acid staining shows that after two months of treatment with Papilocare® there is an improvement of erythorplasia and reduction of ectopia. Nabothian cysts are observe.

1. No preparation: Ectopia (3/3). Normal vascularization.
2. Acetic:
   - Normal findings: mature squamous epithelium. Ectopia: yes. Metaplastic epithelium: yes.
   - Abnormal findings: no.
3. Schiller: uniform Lugol's uptake.
4. Biopsies: no.
5. Endocervical curattage: no.

- **Colposcopic diagnosis:** Normal colposcopic findings.
- **Vaginoscopy:** normal..

Diagnostic suspicion of post-coital bleeding: ectopia associated with contraception method.

Treatment with Papilocare® Vaginal Gel 1 application every night for 21 days during the first month of treatment and then continue with an application every 48 hours for another 5 months. The patient attended for results and evolutionary control after two months, reporting a significant improvement in coital bleeding.

RESULTS

- HPV genotype: 52 (high-risk).
- Endocervical exudate: Neisseria gonorrhoeae is not isolated.
- Chlamydia PCR: negative. Gonococcus PCR: negative.
- Vaginal exudate: no yeast or trichomonas. Gram: normal vaginal flora.
- Cytology satisfactory, negative for malignancy.

After two months of treatment, we can observe an improvement in the erythroplasia as well as in the patient's symptoms. [Figure 2].

It is recommended to continue with the prescribed treatment until completing 6 months of treatment.

In February 2022, after completing the treatment, she went for a check-up and underwent another examination in which the erythroplasia practically disappeared and cytology and determination of HPV was performed.

In March results were given. HPV was found to be negative, and the cytology was negative for malignancy.

In view of these results, a new control with cytology and HPV test is recommended within one year according to the recommendations of the AEPCC

DISCUSSION

Cervical ectopia is a benign condition in which glandular cells of the endocervix are present

in the ectocervix. The cervix has an unstable histologic structure with two permanently confronting epithelia, the squamous poly-stratified vaginal-exocervical and the glandular cylindrical endocervical epithelia. The reserve cells below the glandular epithelium are in a metaplastic process of re-epithelialization since they retain the capacity to grow and differentiate into mature forms of squamous epithelium (most frequently) or glandular epithelium. This process is called metaplasia. This generates an extensive area in the neck that is identified as a transformation zone, which is very susceptible to HPV infection.

Post-coital bleeding may indicate the existence of cervical intraepithelial neoplasia (CIN). Up to 11% of patients consulting for this reason have cervical cancer, and the risk increases the older the age of the patient presenting with post-coital bleeding. In a study by Cohen et al. in 2019, 48.9% of patients consulting for post-coital bleeding required cervical biopsy for colposcopic changes, of which 30.3% reported CIN 1. 0.7% of women consulting for coital bleeding had high-grade dysplasia (CIN 2 or higher). Therefore, post-coital bleeding should be considered as a risk factor for cervical dysplasia.

Ectopia is usually an incidental finding in up to 50% of women. Its most common symptoms are post-coital bleeding and non-malodorous leucorrhea. It only requires treatment if the symptoms affect the patient's daily life.

Papilocare® is a sanitary product in the form of a gel for vaginal application. It is based on *Coriolus versicolor* and other Phyto-therapeutic ingredients such as hyaluronic acid, centella asiatica, and aloe vera, which allow its use as a moisturizer and repairer of the vaginal mucosa. It has the advantage of being a less aggressive treatment for the patient and is convenient to apply, since the patient does not need to travel to the office but is instead applied at home. For this reason, they can be a first step in the treatment of symptomatic cervical ectopia before moving on to other more aggressive treatments.

Coriolus versicolor is a fungus of Chinese origin that contains β-glucan polysaccharides with known immunostimulant properties, anti-microbial and anti-tumor activity. This fungus 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.

In patients with HPV infection, it has been observed to aid in the regression of low-grade squamous intraepithelial lesions of the cervix, as well as in viral clearance.

The PALOMA clinical trial has been able to demonstrate normalization of HPV ASCUS/LSIL lesions (cytological normalization and concordant colposcopy) at 6 months of treatment in 85% of women treated with Papilocare® Vaginal Gel versus 65% in the control group. The PALOMA study has also demonstrated viral clearance at 6 months of treatment in 63% of women with high-risk HPV compared to 40% in the control group.

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FINALIST

Application of Genital Gel with *Coriolus versicolor* in the Treatment of Condyloma Acuminata in a Pregnant Woman

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Summary

Condyloma acuminata in a 36-week pregnant woman treated with trichloroacetic acid and Papilocare® Vaginal Gel with excellent clinical results.

Keywords: Condyloma acuminata; Gestation; Papilocare®; *Coriolus versicolor*.

MEDICAL HISTORY

A 33-year-old woman, 36 weeks pregnant, consults for new genital warts. She presents genital discomfort with pruritic sensation and is very concerned about whether it could interfere with the birth canal.

She has had normal check-ups until the beginning of pregnancy, and the last cytology performed 1 year ago was normal. She has had an episode of pelvic inflammatory disease due to Chlamydia trachomatis, which resolved with antibiotic treatment.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

External genitalia with multiple condyloma lesions, mainly in the introitus and vulvar fork, extending to the perianal region. Vaginal mucosa and cervix without lesions.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should be made with vulvar papillomatosis, a physiological finding that differs in morphology, as it presents papillae with independent bases, while condyloma acuminata are acetowhite lesions that have a common base with a cockscomb surface and papillae. Other papular lesions are molluscum contagiosum and seborrheic keratosis.

TREATMENT AND EVOLUTION

The possibility of active vs. expectant management of condylomatosis lesions is explained to the patient. The patient wishes active treatment. Application of trichloroacetic acid magistral formula (80-90% concentrate) with weekly application in the office for a maximum of 10-12 weeks. Complementary treatment is also performed with *Coriolus versicolor*

FIGURE 1. Decrease in the number of lesions in the first 4 weeks of treatment.

vaginal gel 1 cannula/day for a month, followed by 1 cannula/every other day.

The patient evolved adequately, with a striking decrease in the number of lesions until their complete disappearance in 5 weeks [Figure 1].

FINAL DIAGNOSIS

Condyloma acuminata in full resolution.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Condyloma acuminatum is a common and highly infectious sexually transmitted infection[1]. Condyloma acuminata are the clinical expression of infection by certain HPV types considered to be of low oncogenic risk, mainly HPV types 6 and 11[2,3].

During gestation, a state of immunological tolerance occurs, which, together with the effects of progesterone and vascular changes, results in a reduced immune response to HPV[4].

In general, treatment is preferred to expectant management during pregnancy, although the risk of vertical transmission in the perinatal period is very low. The greatest risk of transmission to the newborn is the maternal history of genital condylomatosis during pregnancy and not its passage through the birth canal, so cesarean section is not considered indicated for termination of pregnancy[4].

The treatment aims to reduce perinatal exposure and prevent the growth and proliferation of lesions which, in cases of large outgrowths, may make vaginal delivery difficult or impossible, although this was not the case in our patient. The main medical options are considered contraindicated or there are no studies that have demonstrated safety in humans[4,5], so trichloroacetic acid treatment was decided in accordance with the Spanish Association of Cervical Pathology. It was decided to associate Papilocare® given the cellular immunity-enhancing effect of *Coriolus versicolor*[1-3].

Therefore, and as a conclusion of the clinical case presented, the use of trichloroacetic acid and the vaginal gel based on *Coriolus versicolor* seems to be a safe and effective treatment option in pregnant patients.

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FINALIST

Combined Treatment with Papilocare® Vaginal Gel and Immunocaps for High-Grade Lesion in a Pregnant Woman

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Summary

Human Papillomavirus (HPV) infection is necessary for the development of cervical cancer and its precursor lesions. In most cases, it is transient, asymptomatic infection. There are multiple HPV serotypes, among which HPV 16 and 18 deserve special attention, due to their greater aggressiveness and persistence.

Although it does not usually cause complications to the mother or foetus, a diagnosis of premalignant lesions and HPV infection during gestation, requires strict follow-up, both by cytology and colposcopy to prevent further complications.

Keywords: Human Papillomavirus (HPV); Gestation; Papilocare®.

MEDICAL HISTORY

A 34-year-old patient in week 25 of pregnancy, comes for consultation to the Cervical Pathology Unit after a consultation with an obstetric specialist, who determined High Grade cytologic alterations (HSIL) in the cytology tests, and a PCR showing the presence of High-risk (HR) HPV including HPV serotype 16.

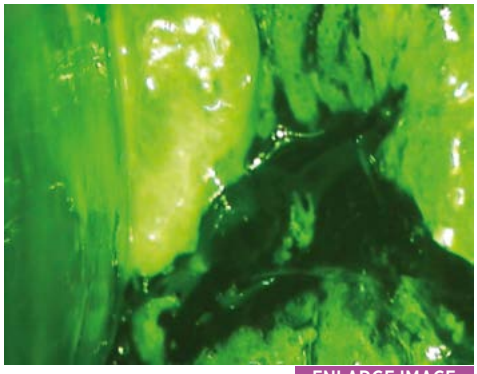
- Known Medical History:
  - Diseases: No.
  - Surgical Interventions: Adenoidectomy. Ankle lesion which affected articular cartilage.
  - Toxic Habits: smoker, 8 cigarettes per day
  - Contraceptive Method: no.
- Obstetric History:
  - AO: G2P1.
- Ginaecological History:
  - Menarche: 14 years old.
  - Menstrual Formula 3-4/28-35.
  - Date of Last Period: 30/06/2021.
  - EIRS 17.
  - NPS 4.
  - Not vaccinated against HPV.

The patient had a first consultation at week 25 of pregnancy. Patient is informed about the cytology results and colposcopy is advised, including biopsies if needed.

PHYSICAL EXPLORATION AND COMPLEMENTARY TESTS

Week 25 of Pregnancy

Colposcopy allows the observation of a type 1 transformation zone entirely. The area is cleaned



ENLARGE IMAGE

FIGURE 1.

ENLARGE IMAGE

FIGURE 2.

with saline and observed under a green light filter. Between 11 and 1 o'clock the exploration shows the presence of anomalous vessels in the upper lip, having morphological alterations (i.e. disrupted vessels or altered diameters) [Figure 1].

Acetic acid staining shows a dense aceto-white area from 12 to 2 o'clock in which the "ridge sign" is observable, which is a dense area where the white becomes a pearlier colour [Figure 2]. A coarse mosaic and coarse stippling are also observed, all of which are signs of major changes.

A biopsy was performed at 12 o'clock with an anatomical-pathological result of CIN 2 on extensive LSIL-affected area. Given the pregnancy, the patient is advised not to undergo surgical treatments and is prescribed with Papilocare® Vaginal Gel plus Papilocare® Immunocaps as an oral co-adjuvant treatment. The patient is also advised to quit smoking. Based on the protocols, the patient is scheduled a follow-up consultation after 12 weeks.

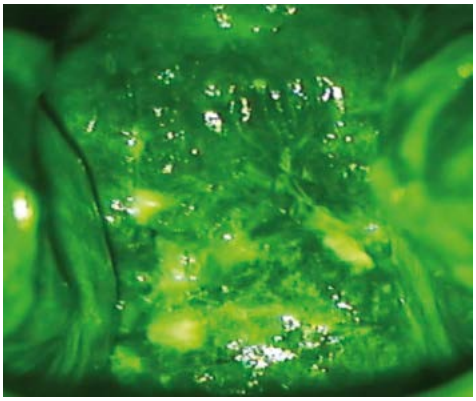


FIGURE 3.

Week 37 of Pregnancy

The patient came back to the clinic after 12 weeks for a follow-up consultation (pregnancy week 37). The patient declared that she had reduced her tobacco consumption to 3 cigarettes per day and adhered to the prescribed Vaginal Gel and oral caps.

The gynaecological examination showed a hypertrophic cervix with intense gestational deciduosis, due to the time of pregnancy. Colposcopy examination showed a cylindrical epithelium, with a type 1 transformation zone, and a large extension of the epithelium from the inside of the canal towards the outside. Observation with the green light showed an improvement in vascular morphology and distribution [Figure 3]. After staining with acetic acid, a large aceto-white area was observed between 11 and 2 o'clock, with mosaic and coarse stippling inside [Figure 4].

A biopsy was taken at 1h, with the diagnosis of CIN 2-3, with extension to the endocervical glandular epithelium.

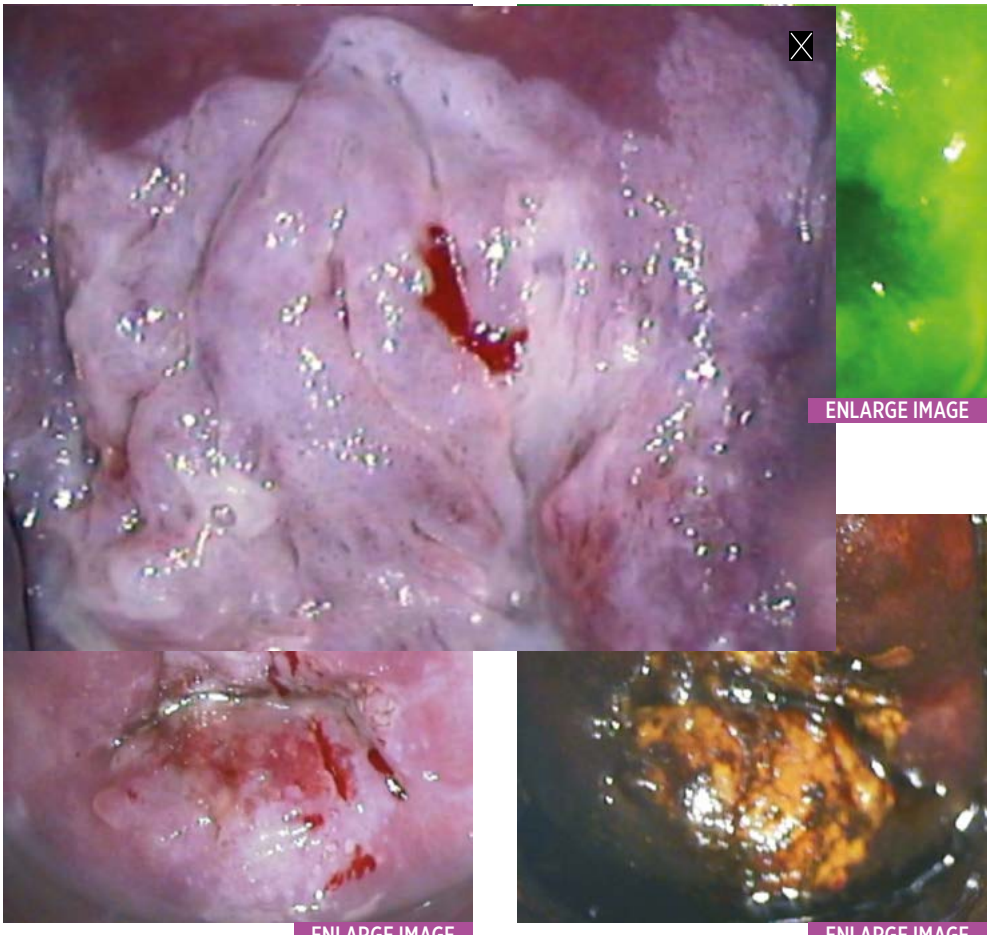


FIGURE 6.

FIGURE 7.

Given that delivery is expected within the next weeks, Papilocare® Vaginal Gel plus Papilocare® Immunocaps treatment was maintained. A new post-partum appointment is scheduled in 8 weeks' time.

In week 40 of pregnancy, the patient gave birth by vacuum extraction to a new-born weighing 3,100 g without any pathology. Apgar 9/10.

After 48 hours of hospital admission, the patient and the new-born were discharged, and a new appointment was made 8 weeks after delivery with the Pathology Department at the Cervical Pathology Clinic.

Post-partum control

At 8 weeks post-partum, the patient attended the Cervical Pathology Clinic, where a new examination, cytology and colposcopy were performed.

The colposcopy shows a clear improvement compared to previous visits during pregnancy. A type 1 TZ is still visible, and after application of green light, no abnormal vessels are seen [Figure 5]. Acetic acid staining shows a decrease in the acetowhite area, not only in extent, but also in the intensity of the pathological uptake [Figure 6]. Iodine staining shows a weak negative area [Figure 7].

Biopsies are taken at 12, 1 and 6 o'clock, and endocervical curettage is performed. The results of the Pap smear show:

- Cytology: LSIL.
- Biopsy of the Cervix: Low-grade squamous lesion, corresponding to CIN 1
- Endocervical curettage: no signs of dysplasia

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Most HPV infections are transient and clear spontaneously without leaving any further complications. It is known that HPV persistence, in particular with genotype 16, favours the progression of these cervical alterations to premalignant lesions.

Low immunocompetence is considered a risk factor for development of HPV persistence. During pregnancy patients are considered as being partially immunocompromised and therefore at higher risk of HPV persistence and lesion progression. Therefore, the administration of a treatment to boost immune system and which may create a more unfavourable environment for viral replication can help us to hold or even regress these pathological cervical changes.

Surgical treatment of HSIL/CIN 2-3 during pregnancy is associated with a high rate of complications. On the other hand, the rate of progression to cervical cancer in the short term is low. Therefore, current guidelines are not recommending surgical intervention in pregnant women. Additionally, up to 20% of patients will spontaneously show a postpartum regression and HPV clearance. In our clinical case, the combined treatment of Papilocare® Vaginal Gel plus Papilocare® Immunocaps may have contributed to the regression of the cervical lesions after delivery. Although this clinical case shows encouraging results, further research is needed with prospective studies and adequate cohorts.

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FINALIST

Treatment with *Coriolus versicolor*-based Vaginal Gel for Vaginal HPV Persistency after Hysterectomy. A Case Report

DR. MARÍA MAGDALENA PORTO QUINTÁNS

Hospital Álvaro Cunqueiro

Summary

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world. However, it is usually a transient infection that resolves spontaneously. HPV persistency favours the development of lesions, being HPV 16 and 18 genotype carriers those with higher risk of developing lesions.

HPV infection accounts for about 90% of Vaginal intraepithelial neoplasia (VaIN) cases. VaIN is an asymptomatic and rare entity. It accounts for 0.4% of all premalignant lesions of the lower genital tract (LGE). VaIN lesions are classified into low-grade lesions or LSIL (VaIN I) and high-grade lesions or HSIL (VaIN II-III) which are the precursors of vaginal cancer.

Alteration of vaginal microbiota favours HPV persistency. Treatment with a *Coriolus versicolor*-based vaginal gel have been described to favour the mucosal reepithelialisation and reduce vaginal bacterial diversity, contributing to the HPV clearance.

Keywords: HPV; VaIN; vaginal re-epithelization; excisional treatment; Hysterectomy; *Coriolus versicolor*.

MEDICAL HISTORY AND ANAMNESIS

43-year-old patient came to the Colposcopy and Cervical Pathology Unit due to diagnosis of LSIL with presence of suspicious cells, although the result was not conclusive of HSIL.

The patient tested positive for HPV genotype 18.

Personal history: no known medical allergies, no diseases. G2P2. Beginning of relations at the age of 20, stable partner, condom use, non-smoker and not vaccinated against HPV virus. No treatments or toxic habits.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

- Normal external genitalia and vagina. Cervix well epithelialized.
- Colposcopy: Normal colposcopy without any alteration. Type 2 TZ. After application of acetic acid, dense acetowhite epithelium is visualised between 11-12 h, which corresponds to mustard yellow on application of lugol.
- Biopsies: adenocarcinoma of the endocervix in situ.
- MRI: no tumour is visualised in the cervix.

FIGURE 1. VaIN I.

FIGURE 2. Negative vaginoscopy.

TREATMENT

Hysterectomy and bilateral salpingectomy are performed.

Anatomy-pathology results reveal an endocervical adenocarcinoma in situ, with no evidence of infiltrating carcinoma.

HPV vaccination with the Gardasil® nonvalent vaccine is indicated. The patient is advised to maintain the use of barrier methods during sexual intercourse as well as increase physical exercise and having a healthy diet.

EVOLUTION

- 1st check-up: cytology resulted in ASCUS, and the PCR showed the presence of High-Risk (HR) HPV but not 16 and 18. Vaginoscopy with negative Bx.
- 2nd check-up: cytology resulted in ASCUS, HR-HPV+, negative vaginoscopy.
- 3rd check-up: LSIL, HPV +, Vaginoscopy with minor changes in upper and left edge of colpotomy. A biopsy was taken resulting in VaIN 1 [Figure 1]. Due to of lesion and AR-HPV persistence, treatment with *Coriolus versicolor*-based vaginal gel (Papilocare®) was prescribed for 6 months: one daily application for 21 days and then every other day, treatment is not applied during the period and the patient is scheduled for a follow up visit in 6 months.
- 4th check-up: cytology results showed normalization, testing for HPV was negative, indicating the clearance of the HR-HPV, vaginoscopy resulted also negative [Figure 2].

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HPV infection can potentially affect any part of the genital area, although the most frequently infected area is the cervix. Nonetheless, it can also produce lesions in the anus, vulva and vagina, as it is illustrated in this clinical case.

Although it is not very frequent, it should be noted that even if a hysterectomy is performed, HPV can still persist in the vagina. Therefore, barrier methods are important to prevent new lesions in the vaginal region.

In this clinical case, the patient was advised to keep using barrier methods (condoms), exercise and eat a healthy diet to increase immunity.

Recently, a new conservative treatment, a *Coriolus versicolor*-based vaginal gel (Papilocare®) has become available, which represents a new local conservative approach that contributes to mucosa re-epithelialization, a critical factor favouring viral clearance and normalization of low-grade cytological alterations.

In this case, the patient underwent a hysterectomy. However, after 3 follow-up visits, the

patient still showed altered cytological alterations evolving from ASCUS to LSIL and biopsy resulted in VaIN I changes, and PCR test demonstrated HR-HPV genotype 18 persistency. Given this situation, the patient was prescribed with a 6-month treatment with a *Coriolus versicolor*-based gel. The patient came back then for a final follow-up consultation showing a complete normalization of the cytological alteration as well as HR-HPV 18 clearance.

The importance of this case lies in the fact that the viral persistence, together with non-regression of cytological alterations, is associated with progression to a more advance status that is a risk factor for cervical carcinoma. Thus, viral persistence generates anxiety in many patients. Given the length of the process, it can have a negative impact in their quality of life and create situation of mistrust in their doctor.

Treatment with a *Coriolus versicolor*-based vaginal gel (Papilocare®) has proven beneficial over expectant management in women with HPV-positive or not, with low-grade cellular lesions, showing increased cyto-normalization and viral clearance rates. It also contributes to anxiety reduction, improving patient's quality of life, partly because it empowers the patient to actively take part in the disease management, as well as being a well-tolerated treatment.

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Vaginal Gel in the Adjuvant Treatment of Cervical Dysplasia due to HPV: A Case Report

DR. MARÍA JOSÉ LOZANO JIMÉNEZ

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Summary

Human papillomavirus (HPV) is the most common sexually transmitted infection among young sexually active individuals and can be contracted and transmitted by both women and men. There are more than 200 types of HPV, and each can infect different tissues, such as the skin and mucosa of the anal-genital area.

Persistent infection with an oncogenic type of HPV is the major risk factor for the development of cervical dysplasia and cervical cancer. HPV is associated with approximately 100% of cases of cervical cancer.

Keywords: Human papillomavirus; Sexual transmission; Cervical dysplasia.

MEDICAL HISTORY

38-year-old female patient consulted for post-coital bleeding and intermenstrual spotting.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

A gynecological examination with cytology and HPV sampling is performed.

The cytology showed ASC-H (atypical cervical cells that cannot rule out a high-grade lesion) and the PCR was positive for HPV 16.

A colposcopy was performed as indicated, and a dense acetowhite epithelium was observed at 12 o'clock.

This was biopsied and sent to pathology. The biopsy result reported a high-grade squamous lesion (CIN 3).

DIFFERENCIAL DIAGNOSIS

When a patient consults for the above-mentioned symptoms, ectopia, cervicitis, presence of cervical polyps and endometrial polyps, among other entities of interest, must be discarded.

TREATMENT AND EVOLUTION

A conization is performed, anatomical pathology confirms the presence of the lesion and the existence of lesion-free margins of the surgical piece performed.

The patient is indicated to undergo HPV vaccination and to start treatment with Papilocare® Vaginal Gel.

A control is performed 3 months later: the cytology is reported as negative for malignancy, HPV 16 remains positive, and colposcopy is normal.

A new control is performed at 6 months: the cytology is reported as negative for malignancy, HPV 16 and all high-risk oncogenic HPVs are negative, and the colposcopy is normal.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HPV requires a lesion, or to integrate itself in an epithelial transition zone, such as the one that exists in the cervix, anus, or tonsils, in order to infect cells.

An essential part of HPV infection management is prevention, for which vaccines are a valuable tool. The quadrivalent HPV vaccine has been available since 2006 and the literature considers the degree of protection it offers against genital warts and cervical cancer to be very significant.

As a pathophysiological mechanism, it has been proved that the virus integrates its genome in that of its host, always preserving the E6 and E7 oncogenes, with loss or interruption of the E2 gene. This is important to note because in pre-invasive lesions of the cervix, the viral genome is found in episomal (circular) form, i.e., outside of the cellular genome and with the complete E2 gene.

HPV can continually stimulate tumor growth, which favors the generation of random mutations, usually over a long period of time, in the cell genome, with the expected consequence that some of them confer greater oncogenic capacity to the neoplastic cell. Based on experimental data generated from the work of zur Hausen, it has been postulated that for the virus to evolve to an invasive phenotype, the successive loss of different tumor suppressor genes is required.

Several studies have emerged indicating that there are four circumstances that may be related to HPV clearance or persistence and its ability to colonize cervical cells, those being the following:

- Viral type: this is the best-known variable that conditions the capacity of cell integration and associated oncogenic risk. Types 16 and 18 clearly lead this risk.
- The immune system status of the host. It is well known that immunocompromised patients are at increased risk for the development of HPV-dependent lesions. Therefore, improving the local immune status at the site of HPV action can presumably be a strategy to facilitate HPV clearance.
- The status of the vaginal microbiota, the balance of which ensures vaginal health. We have recent data which strongly suggest that this balance conditions the pathogenesis of cervical cancer.
- The histologic structure of the uterine exo-cervix. HPV needs mitotically active cells to integrate. The cells in the cervical transformation zone that are undergoing metaplastic re-epithelialization meet this condition and are therefore perfect targets for HPV anchoring.

Papilocare® Vaginal Gel is the first patented treatment indicated for the prevention and treatment of lesions caused by HPV. It is made of natural ingredients with proven efficacy in the regression of intraepithelial lesions and HPV negativization.

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Regression of High-Grade CIN after Treatment with Papilocare®

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Summary

A 25-year-old woman consulted for presenting with altered cytology: LSIL, being positive for both HPV 16 and 51. A colposcopy was performed, finding an extensive area of fine mosaic and a small area of thick mosaic. A biopsy was taken, with result: CIN 2 (high-grade). After 6 months of treatment with Papilocare®, a co-test was repeated: negative. A control colposcopy was also performed: normo-epithelialized cervix. Co-test at one year was normal.

Keywords: Cytology; Colposcopy; HPV; Papilocare®.

MEDICAL HISTORY

February 2020

25-year-old female presenting from a private gynecologist for altered cytology (LSIL) and positive results for both HPV 16 and 51 (high-risk). The patient also had previous cytology (2019) with the same result. Therefore, it was decided to perform a colposcopy.

- Personal History: none of interest. No toxic habits.
- Obstetric and Gynecological History:
  - Nulligravid
  - Menarche at age 12
  - Menstrual Type: regular 4/30
  - Contraceptive method: condom
  - Not vaccinated against HPV
- Gynecological examination: without significant findings.
- Colposcopy: satisfactory. Type 1 TZ. Using acetic acid an extensive acetowhite area is observed, from 11 to 4 o'clock, without reaching the endocervical canal of fine mosaic (minor changes) and a small area at 3 o'clock of coarse mosaic (major changes). When applying Lugol's solution it continues to show a negative Lugol zone from 11 to 4 o'clock. Two biopsies were taken at 12 o'clock and at 3 o'clock.
- Biopsy 1: CIN 1 (low-grade).
- Biopsy 2: CIN 2 (high-grade).

Given the patient's age, it is proposed to postpone conization and treat with Papilocare® Vaginal Gel and HPV vaccination.

September 2020

The patient attends the clinic for a check-up. She has not been vaccinated but has continued treatment with Papilocare®.

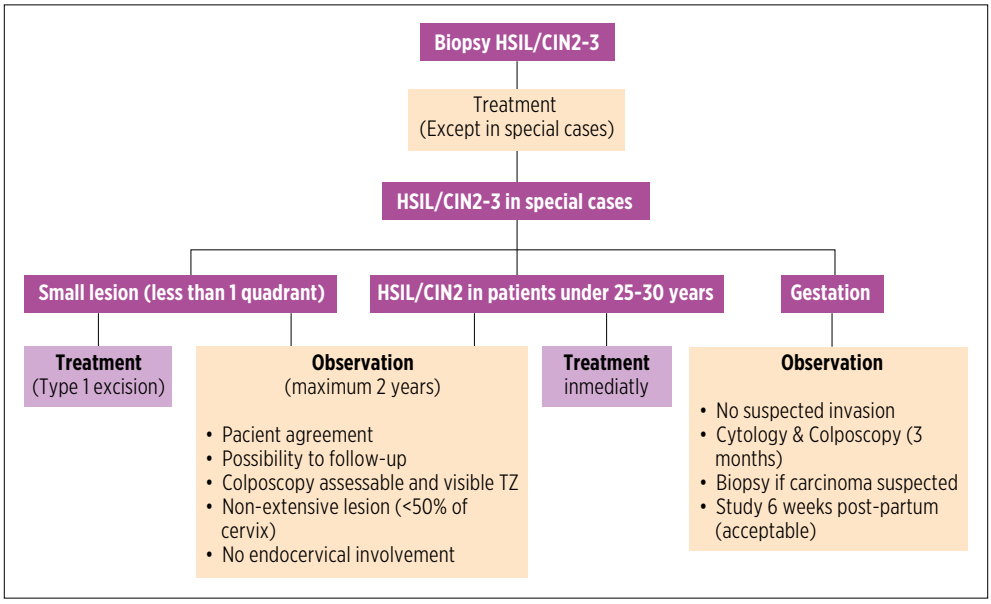

FIGURE 1. SEGO: Cervical Cancer Prevention Protocol (2013).

- Co-test: negative.
- Colposcopy: satisfactory. Type 1 TZ. Normo-epithelialized cervix. No acetowhite or lugol-negative areas.

  The benefits of vaccination are insisted.

September 2021

- Co-test: negative.
- Pending a new co-test in one year.

DISCUSSION

Cervical pathology screening with cytology (Papanicolaou) or HPV detection is not indicated in women under 25 years of age. There is a very high prevalence of infection in this age group, but the infections are transitory and resolve spontaneously in the vast majority of cases. HPV lesions will not usually occur in this age group and, if they do, almost all resolve without treatment.

In young women (under 25 years of age or even under 30 years of age) with high-grade lesions, an acceptable option is to maintain a wait-and-see approach with the aim of avoiding conization. The likelihood of progression is very low in a short time, while the rate of regression is not negligible.

In these cases, treatment with Coriolus versicolor may be a valid option to maximize the probabilities of regression.

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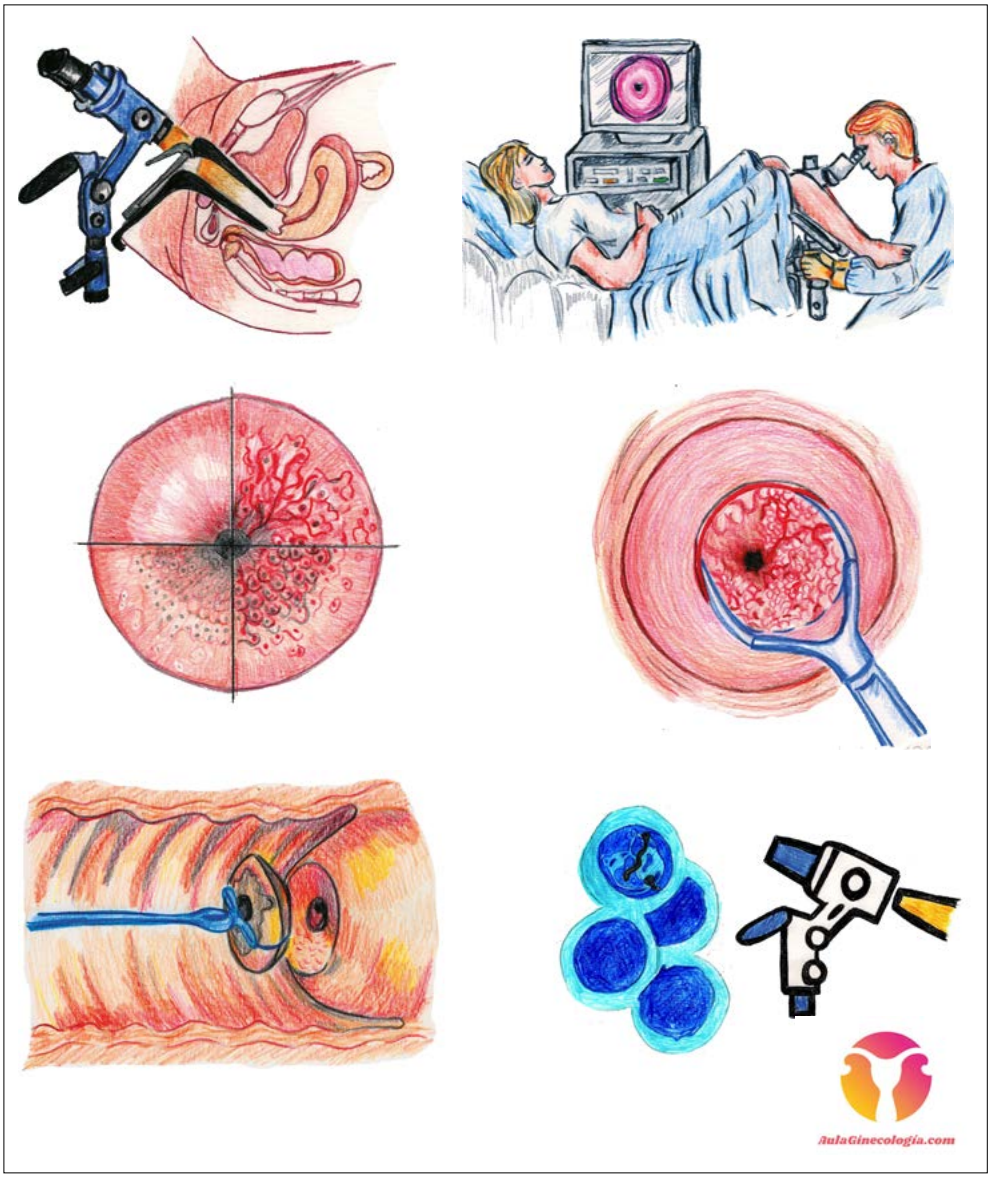

FIGURE 2. Original drawings: www.aulaginecologia.com

Persistent LSIL in a Hysterectomized Patient Treated with a Vaginal Gel. A Case Report

DR. ANA CRISTINA GONZÁLEZ CEA

Hospital Clínico Universitario Santiago de Compostela

Summary

This case is about a patient with a previous subtotal hysterectomy and a diagnosis of persistent LSIL, who was treated with Papilocare® Vaginal Gel.

Keywords: Hysterectomy; LSIL; Papilocare® Vaginal Gel.

MEDICAL HISTORY

Female, 44 years old. G0P0A0..

Personal History:

- No known allergies.
- Myomectomy in 2008.
- Subtotal hysterectomy (for myomatosis) preserving ovaries in 2016.
- Cholecystectomy.

REASON FOR CONSULTATION

The patient undergoes annual check-ups, detecting an LSIL cervical lesion (HPV 51 positive).

TREATMENT AND EVOLUTION

- A cervical colposcopy-biopsy was performed, confirming the cytological result.
- Bi-yearly follow-up is recommended, with no improvement of the lesion that worsens to HSIL.
- Cervical conization was performed, confirming the HSIL lesion.
- Cytological control and treatment with Papilocare® vaginal gel daily for 1 month and every other day for at least 3 months, is proposed.

FINAL DIAGNOSIS

- At the next cytological control, the lesion had disappeared, and her cytology has remained normal to date.
- The patient is recommended to periodically undergo treatment with Papilocare® Vaginal Gel.

DISCUSSION

Cervical lesions caused by human papillomavirus have increased alarmingly in recent decades. Their consequences for the women who suffer from them are in many cases serious health problems and affect their sexual and personal lives. Papilocare® Vaginal Gel may help to improve the results in the treatment of these lesions, thereby improving their perception of the disease.

Papilocare® Vaginal Gel in A-GUS Cytology Post-Conization: A Case Report

DR. YASMINA PULIDO TERRADO

Hospital Universitario Arnau de Vilanova

Summary

The human papillomavirus affects 90% of sexually active women. The prevalence of HPV infection in women over 30 years of age is lower, but they have a higher percentage of persistence, leading to a higher risk and incidence of precursor lesions after this age. In most cases, LSIL/CIN1 lesions resolve spontaneously without the need for any type of treatment, unlike high-grade HSIL/CIN 2-3 lesions, which are often persistent, with low probability of spontaneous regression and with a significant risk of malignant transformation[1].

Keywords: HPV; HSIL; CIN 2; A-GUS; Treatment.

MEDICAL HISTORY

50-year-old woman with a history of positive HPV, with negative cytology of 2 years of evolution, with HSIL result in last cytology. Secundiparous and asymptomatic.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient was referred for consultation for HSIL cytology. A colposcopy was performed, with visualization of two areas suggestive of grade 2 changes, so biopsies were performed with a result of CIN 3.

TREATMENT AND EVOLUTION

A colposcopically guided conization is performed with negative endocervical and exocervical margins, as well as vaccination. In the post-conization control, cytology was performed with AGUS result, negative HPV and negative endocervical and endometrial biopsies. Adjuvant treatment was started for 6 months with Papilocare®. In the two subsequent controls the patient presented normal examination with negative cytology and HPV

FINAL DIAGNOSIS

After initial treatment with conization and subsequent treatment with Papilocare® Vaginal Gel for 6 months, the patient presented negative controls and was discharged from the unit.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

In this case it is curious how, after treatment with conization and negative margins, the

patient presented an A-GUS cytology which, with complete vaccination and adjuvant treatment with Papilocare®, was able to negativize.

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Application of a Vaginal Gel with *Coriolus versicolor* in the Treatment of Low-Grade Cervical Dysplasia in Patients in the Post-Menopausal Stage

DR. BEATRIZ CONTRERAS GONZÁLEZ

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Summary

Human papillomavirus infection is the most common sexually transmitted infection worldwide. In most cases the infection is transient in nature. However, immunosuppression is the main risk factor for viral persistence and the development of cervical lesions.

Keywords: HPV; Persistent HPV infection; LSIL; Menopause; Genitourinary syndrome of menopause.

MEDICAL HISTORY

69-year-old female patient, with no family history of interest. Type 2 diabetic in treatment with basal and rapid insulin according to capillary blood glucose levels. Type 2 obesity with a BMI of 37. G2P2 (2 eutocic deliveries) with natural menopause at 49 years of age and without hormonal treatment. Stable sexual partner for 40 years and has intercourse without the use of a barrier.

The patient has been followed/ been in consultation with cervical pathology since 2015, after being referred there due to the result of LSIL in a cervical-vaginal cytology. There, a sample was taken to evaluate the presence of HPV which was positive for HR-HPV (however, not type 16 nor 18). After normal examination and colposcopy, an annual follow-up with the usual recommendations was proposed. Four revisions are performed in the following years, one check-up a year. During these visits cytology results alternate between negative, ASCUS and LSIL with persistence of the HR-HPV type (not type 16 nor 18) and colposcopies giving normal findings.

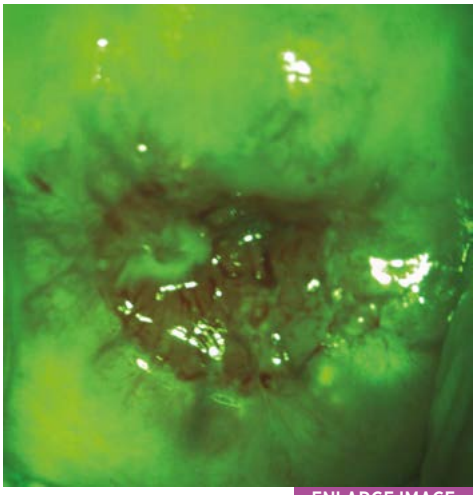
In the follow-up visit of 2019, parting from the basis of cytology findings of LSIL in the previous year with HR-HPV persistence (not types 16 nor 18), the patient reports superficial dyspareunia, which has caused her to become almost unable to maintain sexual intercourse, as well as experiencing occasional post-coital bleeding and urinary incontinence with feelings of urgency and mild stress, with no other added clinical manifestations. Cervantes scale was performed with a score of 31.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Physical examination revealed external and internal genitalia with moderate atrophy, and a cervix, macroscopically healthy, with a multiparous appearance. Bachmann Index 8. Colposcopy is

ENLARGE IMAGE

FIGURE 1.



ENLARGE IMAGE

FIGURE 2.

adequate with a type 2 TZ and normal findings due to atrophy [Figures 1 & 2].

DIFERENTIAL DIAGNOSIS

With the diagnostic suspicion of a genitourinary menopausal syndrome with a low cytological grade cervical dysplasia in addition to a persistent and long-standing HR-HPV infection, a follow-up visit is again proposed, and topical treatment is initiated.

TREATMENT AND EVOLUTION

We started treatment with Papilocare® Vaginal Gel for 6 months. The first month: 21 applications, one application every day, and the following 5 months, one application every other night, alternating this time with the use of Estradiol cream. This time a clinical control is performed after 6 months once the treatment with Papilocare® was finished. Clinically, she showed a slight improvement in dyspareunia, no more post-coital bleeding, and a slight improvement in urinary urgency. On examination, she maintains mild atrophy in external genitalia with improvement of atrophy in internal genitalia, Bachmann Index of 12 and colposcopy with findings similar to previous ones.

A new control is proposed in 6 months, now alternating the use of topical Estradiol with Idracare vaginal moisturizing gel.

At the last visit, the patient reported great improvement of genital dryness, with less dyspareunia and the ability to now participate in sexual intercourse without pain. Partial improvement of urgency and urinary incontinence with significant increase in quality of life. A new Cervantes scale was performed with a result of 27. Examination showed improvement in atrophy with Bachmann Index of 14 and colposcopy with normal findings [Figures 3 & 4]. SA new cervical-vaginal co-test was performed with a negative result for cervical-vaginal cytology dysplasia and for the first time a negative result for HR-HPV.

FINAL DIAGNOSIS

Persistent HR-HPV-positive infection, low-grade cervical dysplasia, and genitourinary syndrome in a postmenopausal patient.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Squamous intraepithelial lesions of the cervix are the precursors of cervical cancer. Screening

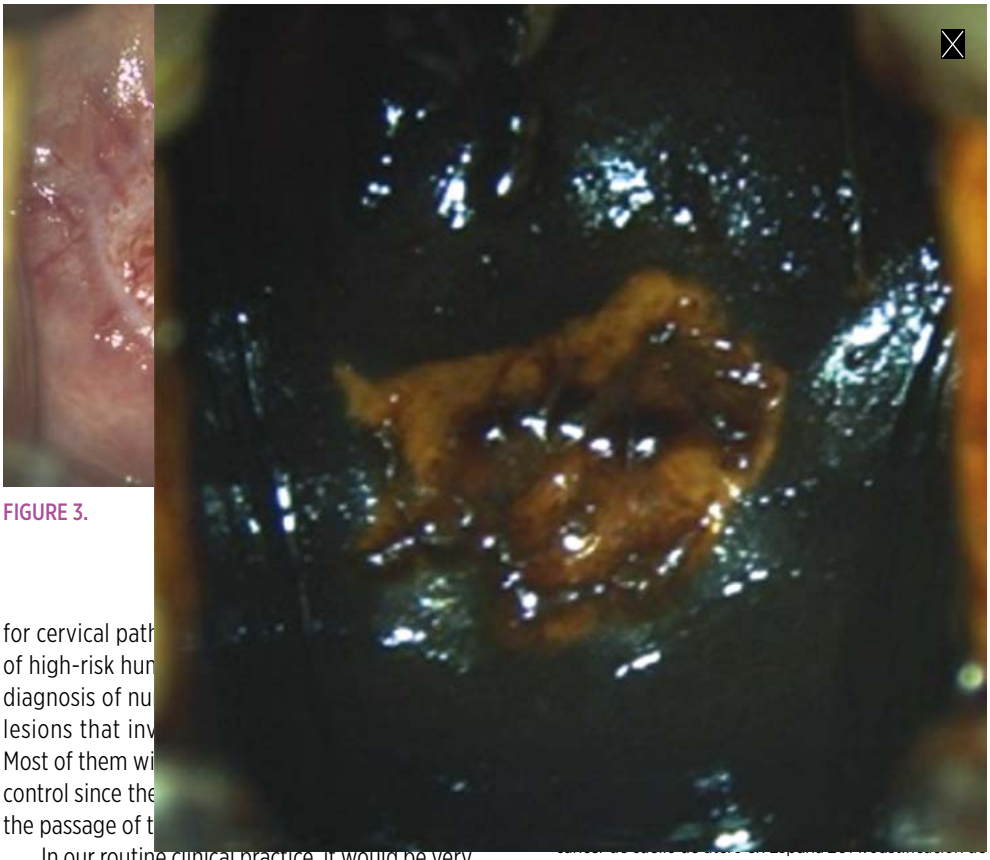


FIGURE 3.

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In our routine clinical practice, it would be very useful to have treatments that help to eliminate the HPV infection avoiding its persistence and, at the same time, enhancing the regression of cervical dysplasia if there is any.

The scientific evidence available shows a correlation between immune status and viral persistence. In the case described, the patient had a persistent HR-HPV infection, in this case her immune system was not being able to fight the viral infection, and so it was necessary to perform some type of intervention that would favor the elimination of the virus. Providing adequate hydration and favoring the vaginal microbiota could be an appropriate strategy to prevent persistent HR-HPV infection and enhance the regression of low-grade intraepithelial lesions in postmenopausal patients, also improving

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HPV-Associated Pathology (Vaginal: VaIN, Vulvar: VIN, Anal: AIN) after Hysterectomy for CIN 3 in an HIV Patient. A Case Report

DR. GEMMA TAMARIT BORDES

Hospital de Manises

Summary

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, but in most cases, it will not have any clinical repercussions. However, in immunosuppressed patients, the risk of cervical dysplasia is higher, as well as the risk of developing HPV lesions in less common locations. In this article we report a case of a patient with HIV (human immunodeficiency virus) and persistent HPV, who, despite not being immunosuppressed, developed multiple lower genital tract and anal lesions, which required several treatments.

Keywords: Dysplasia; HPV; HIV.

MEDICAL HISTORY

A 38-year-old patient who came to the Hospital de Manises for a follow-up visit in July 2015. As personal history, she referred to being a carrier of HIV and having undergone antiretroviral treatment for the past 10 years. She also had celiac disease, was allergic to naproxen and was a smoker. She had undergone surgery for peritonitis due to appendicitis, left adnexectomy and right ovarian wedge. As for history of HPV pathology, she had a conization in 2005, in 2007 CIN1 was found in biannual control, and in 2008 she had a perianal condylomatosis treated with cryotherapy. Nulligravid.

PHYSICAL EXAMINATION

A cytology was performed, and the result was LSIL (low-grade cervical dysplasia). In a follow-up visit during March 2016, a new cytology resulted LSIL again. The patient went for a colposcopy in April and a biopsy was taken which could not rule out HSIL (high-grade cervical dysplasia).

TREATMENT AND EVOLUTION

In the presence of a possible HSIL, a simple laparoscopic hysterectomy was indicated as the patient refused to undergo conservative surgery, discarding procreative desire. This intervention was performed without incident in June 2016, and the anatomopathological result of the piece was an extensive HSIL CIN2 moderate dysplasia with the exocervical border affected by CIN1.

A co-test was performed at 6 months after surgery, with result of ASCUS (atypical cells of uncertain significance) and HPV 52 and 58. In

February 2017, a vaginoscopy was performed in which minor changes were observed, which were then biopsied with a result of VaIN 1 (low-grade vaginal dysplasia).

In June 2017, a new control was carried out, observing at this time not only the vaginal lesion, but also, an additional lesion in the vulva of about 2 cm on the external face of the left labium minora. Samples were taken from both locations, being on this occasion the result VaIN 3 and VIN 3 (high-grade vaginal and vulvar dysplasia). The patient had been previously diagnosed in May 2017 with a breast carcinoma (treated with lumpectomy, BSGC, radiotherapy and tamoxifen), as well as a superficial acral fibromyoma of the foot, treated by tumor resection. For this reason, she decided to undergo medical treatment with Imiquimod 5%, applied 2 or 3 times a week, according to tolerance, monitoring evolution by vulvoscopy and vaginoscopy.

In June 2018, in view of the persistence of VIN 3 and VaIN 3, despite medical treatment, a partial colpectomy and excision of the vulvar lesion under colposcopy control were performed. During this procedure a perianal acetowhite lesion was found and biopsied.

The result of the analysis of the different pieces were: VaIN 3 with one affected lateral edge, VaIN 1 with affected edge, VaIN 2, VaIN 2-3 with one affected lateral edge, and AIN 3 (high-grade anal dysplasia), which is why the patient was then referred to a specialist in coloproctology.

In February 2019 the patient underwent surgery: excision of external hemorrhoids and extensive biopsies in all four quadrants. She obtained three results of AIN 1 and three results of AIN 2-3.

In September 2018 and March 2019, vulvoscopy and vaginoscopy were performed presenting normal vulva and VaIN 1.

Due to the presence of dysplasia in different localizations despite multiple surgical interventions, the committee decided to treat with Imiquimod 5% continuously applied in the anal canal with the finger and in the vagina with a tampon at night, 3 times a week.

To perform an anoscopic control, a revision was scheduled, under sedation, in November 2019 and the following was performed: vaginal resection: VaIN 1-2, vulvar biopsy: inflammatory, anal mucosa rection: AIN 1, 2, and 3 without infiltrative lesions.

After this intervention the patient has continued with Imiquimod 5% and controls every 6 months. The findings have been compatible with VaIN 1. Throughout this evolution, HPV testing has always resulted positive for HPV 52.

The patient has been recommended treatment with Coriolus versicolor at vaginal and vulvar levels, alternating with Imiquimod.

The patient was vaccinated with 3 doses of Cervarix.

The last control was in October 2021.

DIFFERENTIAL DIAGNOSIS

- Anal squamous cell carcinoma: Symptoms of anal cancer may include changes in bowel habits and changes in and around the anal area that may include bleeding and itching, pain or pressure, mass, fecal incontinence, or fistula. Some patients have no symptoms at all, and others have nonspecific symptomatology.
- Carcinoma of the vulva: manifests as a lump or ulcer on the vulva that often causes itching. Although it can occur at any age, vulvar cancer is diagnosed more frequently in older women, associated with dermatoses. However, in younger women it is associated with HPV

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HIV-related immunodeficiency has complex effects on female genital HPV, including increased risks of infection, multiple types, persistence, reactivation, and the risk of developing pre-invasive and invasive disease.

Normalization of immunity with retroviral drugs improves cellular immunity, but even so, the risk of HPV-related malignancy remains higher than in the general population and occurs at younger ages. Early initiation of antiretroviral therapy allows for better immunological memory through existing antibodies and T-cell clones and improves long-term outcomes.

Interactions between HIV and HPV should influence public health decisions to prioritize HPV vaccine implementation, secondary prevention of cervical cancer, and early screening programs for HIV-infected women and early initiation of antiretroviral therapy.

VaIN is the precursor lesion of vaginal cancer. It is an uncommon and asymptomatic entity, which can easily go unnoticed in the lower genital tract examination. Its diagnosis represents 0.4% of all premalignant lesions of the lower genital tract, although these figures probably underestimate the real prevalence.

HPV infection is causally implicated in up to 90% of VaIN cases. This justifies that VaIN lesions are associated with multi-centric lesions of the anogenital tract.

There is no evidence as to which is the most appropriate therapeutic modality for all cases of VaIN; however, excisional treatments, such as partial or total colpectomy, classically used, present significant morbidity. This circumstance has led to the increased use in recent years of destructive treatments, with fewer adverse effects and acceptable healing results.

The natural history of VaIN is very different in the subgroup of patients with previous hysterectomy for CIN or cervical cancer. Women after hysterectomy for CIN or with a history of cervical cancer require long-term gynecological controls (up to 20 years), as the interval between surgery and the onset of VaIN ranges from 4 to 13 years.

Persistence of VaIN after treatment is defined as evidence of the same degree of vaginal lesion after treatment or follow-up observation. This situation is quite uncommon, except in immunosuppressed patients who usually present extensive, multifocal and multicentric disease. Before a new treatment, the balance between the importance of eliminating the vaginal lesion and the need to preserve vaginal function and minimize the morbidity represented by the sum of treatments should be assessed. Imiquimod should be considered in case of therapeutic failure after a first destructive or excisional treatment, or in the case of persistence and/or the recurrence of lesions in areas difficult to access.

VIN is considered the precursor lesion of vulvar squamous cell carcinoma. Early diagnosis and adequate treatment of VIN is the only secondary prevention method currently available to avoid the development of this neoplasm. The management of patients diagnosed with VIN represents an important challenge in healthcare practice. The great variability in the clinical presentation, the high risk of occult invasion at the time of diagnosis, the multiple therapeutic options available without a defined optimal treatment, and the high percentage of recurrences observed after treatment, underlie the complexity of this pathology. HSIL lesions (common type VIN) usually affect women aged around 40-45 years, with a second peak after 55 years, and are those associated with HPV infection. In contrast, differentiated type VIN is frequent in older women, generally over 60 years of age. The incidence of common type VIN is clearly higher in HIV-positive patients than in the general population. Data from a study evaluating a cohort of 2,791 women over 13 years shows an incidence of VIN of 0.42 vs. 0.07 per 100 women/year, respectively.

Simple local excisional treatment is the treatment of choice in differentiated type VIN and in cases of HSIL (common type VIN) with lesions that do not require destructive or topical treatments. Topical treatments for VIN have emerged as an alternative to surgery, although most of the studies published with this type of

therapy refer to isolated cases or short series. Currently, although the FDA has not approved any topical treatments for VIN, they are recommended in certain situations and are accepted by scientific societies. Imiquimod treatment can be used as a single or combined treatment for isolated unifocal or multifocal lesions, after ruling out occult invasion.

Anal intraepithelial neoplasia (AIN) is a precursor lesion of anal squamous cell carcinoma. Epidemiological studies have shown that the populations with highest prevalence correspond to patients with HIV infection, patients with a history of anal or genital condylomas, patients with a history of cervical intraepithelial neoplasia and, in general, groups with a higher prevalence of HPV infection, such as smokers. While there are established protocols for the diagnosis, follow-up, and treatment of HPV-associated lower genital tract pathology, this is not the case for anal dysplasia, probably because anoscopy must be performed under sedation due to its painful nature and the fact that anal cytology is not validated.

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Role of Papilocare® in the Conservative Management of Moderate-Grade Cervical Lesions (CIN 2) in Patients under 25 years of age

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Summary

Low grade premalignant lesions and HPV infections are often found in cytologic screening of young women. In the present case, a high-grade lesion (HSIL) was found and treated with Papilocare®.

Keywords: CIN 2; Regression; Papilocare®; HPV.

MEDICAL HISTORY

A 23-year-old female patient, nulliparous and vaccinated against HPV, with no toxic habits nor other personal history of interest, underwent a cytology at her health center at her own request due to changes in vaginal discharge. She maintains heterosexual sexual relations and does not have a steady partner. She reports approximately five sexual partners to date of cytology.

After finding a high-grade lesion (HSIL) and the presence of bacterial vaginosis, she was referred to the gynecology department for evaluation. The patient comes to the gynecology office after having undergone treatment with vaginal probiotics for bacterial vaginosis. She reported improvement of the symptoms.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Endocervical exudate is taken for HPV detection and colposcopy.

Positive culture for HPV 45 and 56. Satisfactory colposcopy. Type 1 transformation zone. Presence of major changes at 3 and 9 o'clock. Positive Schiller test. Cervical biopsy reported by pathological anatomy as CIN 2.

TREATMENT AND EVOLUTION

Given that between 40-74% of these types of lesions can regress after 2 years, the option of conservative vs. excisional treatment is offered. Regression in these cases is more frequent in patients under 25 years of age, those with non-extensive lesions (< 50% of the cervix) and in the absence of cofactors that facilitate progression, such as smoking[1,2]. In this case conservative treatment with serial colposcopies was recommended. The patient requested information about treatment to help the regression of the cervical lesions. Papilocare® Vaginal Gel and the usage of condoms are recommended. This vaginal gel with its action on vaginal microbiota,

cervical epithelialization and improvement of local immunity, could be beneficial in this patient[3,4].

A colposcopy was performed after three months showing major changes at 3 h, with a directed biopsy with a result of CIN 2 and a new colposcopy at 6 months with minor changes that turned out to be a CIN 1. A new colposcopy was performed again at 6 months with satisfactory and negative colposcopy, so it was decided to perform cytology and HPV testing at one year, both of which were negative.

FINAL DIAGNOSIS

Given the correct evolution and regression of the cervical lesion, a new co-test was decided at three years, and routine screening would be performed if the tests were negative

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

About 5% of the world's cancers are attributed to HPV, especially the following high-risk genotypes: 16, 18, 31, 33, 33, 35, 39, 45, 51, 52, 56, 58 and 59. HPV is necessary to cause cervical cancer. Most HPV infections do not cause lesions and the virus is cleared within 12-24 months. Smoking, exposure to hormonal treatment and immunodeficiencies can increase the risk of progression of premalignant lesions caused by HPV[5].

The incidence of cervical cancer under the age of 25 years is low and routine screening has not shown any benefit in reducing the incidence[6]. However, in screening young women, premalignant lesions and HPV infections are often found.

The aim of conservative treatment is to avoid surgical intervention in those cases of CIN 2 with a greater capacity for spontaneous regression.

A non-negligible regression rate has been demonstrated in patients with a histological diagnosis of HSIL/CIN2 who are younger (< 25 years), have small lesions and no endocervical involvement in the first 24 months. Negative HPV testing at follow-up is associated with a higher probability of regression[7,8].

Avoiding surgical treatment, especially in young patients, means reducing the morbidity associated with cervical Lletz, such as higher rates of preterm delivery, low birth weight or premature rupture of membranes. Papilocare® Vaginal Gel is a good tool for the treatment of low-grade lesions, and with its contribution to HPV clearance at 6 months, it could be considered as a good adjuvant therapy in the conservative management of high-grade lesions[9].

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Role of *Coriolus versicolor* in the Treatment and Prevention of Condylomas. A Clinical Case Report

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Summary

We present the case of a patient diagnosed with persistent and recurrent vulvar condylomas. Genital warts are the most frequent clinical manifestation of HPV. In Spain 22,000 new cases are diagnosed in women each year, while at the European level it is estimated that approximately 8% of the population has been diagnosed with this lesion at least once in their lives[1]. Condyloma acuminata or genital warts are the clinical expression of infection by certain types of human papillomavirus (HPV) considered to be of low oncogenic risk (6 and 11). They are currently considered one of the most frequent sexually transmitted diseases with an increasing incidence in most populations[2]. There are multiple forms of presentation and extension of the lesions (from very localized 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 individualize when choosing between the different procedures available (excisional, destructive, topical, etc.). We must not forget the high rate of recurrence after treatment due to the appearance of new lesions in the treated or untreated areas[3]. Genital HPV infection is one of the most common sexually transmitted infections. However, condyloma acuminata are not included in the surveillance systems of most countries, and therefore global epidemiology data are limited. The incidence of new cases according to systematic reviews (considering men and women) ranges from 118 to 205 per 100,000 habitants. The peak incidence rate in women is observed between 20 and 24 years of age, and in men between 25 and 29 years of age[3,4].

Keywords: Condylomas; HPV; Wart; Vulva; Immunosuppression

MEDICAL HISTORY

A 39-year-old asymptomatic patient, presented with warty lesions on the vulva of 3 months of evolution. No family or personal history of interest. As gynecological-obstetric history, she had an adequate cervical cancer screening, with the last cytology 3 years ago, so a new Pap smear was taken. The patient had previously been treated

for the same reason at 37 years with sinecatechins (Veregen®) ointment twice daily until resolution. The patient recalled this treatment negatively due to intense stinging, local itching, and discomfort, and therefore she asks about alternative therapies. She smokes 5 cigarettes a day, started sexual intercourse at 16 years of age, does not use contraceptives and is not vaccinated against HPV.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

5 raised warty lesions were observed, some pinkish and some brown, more pigmented, ranging in size from 1 mm to 5-6 mm [Figure 1].

Vulvoscopy with colposcope and staining with 2% acetic acid was performed. Vaginoscopy and colposcopy were also performed, ruling out the presence of condylomas in the vagina, cervix, and perianal region. Cytology was normal.

Physical examination is the gold standard in the diagnosis of this pathology. Colposcopy of the vulva after application of acetic acid is not recommended as a routine examination but can be useful when intraepithelial neoplasia or initially invasive cancer in the vulva and anal area is suspected. It helps to delineate the lesion and to choose the biopsy site. However, it should be made clear that aceto-white epithelium in the vulva is a nonspecific finding.

Biopsy of lesions should not be performed in a standardized manner, only if the response to treatment is not as expected, in the presence of signs of suspected malignancy or in girls with suspected sexual assault[5].

DIFFERENTIAL DIAGNOSIS

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

FIGURE 1. Condylomas after topical treatment with Verrutop®. Two millimetric "mirror" lesions persist in the perianal region that finally disappear with the application of Papilocare® Vaginal Gel for 5 months of maintenance.

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

TREATMENT AND EVOLUTION

Before starting a treatment plan, an adequate explanation is necessary so that the patient understands the evolution of the process, the purpose of the treatment as well as the therapeutic possibilities, the possible adverse effects, and the percentages associated with healing and recurrence.

In this patient's case, we started a first session by applying Verrutop® [Nitrizinc Complex TM: organic acids (acetic, lactic and oxalic), inorganic (nitric), copper and zinc salts] on the vulvar area over the condylomas. This product allows application 1 or 2 more times in the same session if necessary. In this patient, a second round was applied on two mirrored condylomas in the perianal region.

Subsequently, the patient is informed of the possibility of complementing adjuvant treatment with *Coriolus versicolor* (Papilocare® External Genital Gel) for 5 weeks, at night, in the area treated for condylomas. It is insisted that the objective of this adjuvant therapy is to help re-epithelialize and protect this area. At the end of the treatment, the patient is clinically reevaluated, and the lesions disappear completely, and no new warts are observed.

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

FINAL DIAGNOSIS

Recurrent vulvar condylomas.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Although the experience regarding this case is positive for the use of Papilocare® External Genital Gel, studies with a larger number of cases are needed to draw statistically significant conclusions.

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HPV and Condylomatosis in Childhood. Topical Treatment with Vaginal Gel based on *Coriolus versicolor*: A Case Report

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Summary

The presence of anogenital condylomas in childhood is a controversial situation since there are doubts about their route of transmission and epidemiology. Due to the high rates of spontaneous regression of the infection, an expectant attitude can be adopted.

We present the case of a healthy 2-year-old girl with multiple millimetric perianal condylomas, who experiences persistence of condyloma lesions after expectant management.

Keywords: Childhood; Condyloma; Warts; HPV; *Coriolus versicolor*.

MEDICAL HISTORY

Healthy 26-month-old girl, with no medical or surgical history of interest and correct vaccination, presenting multiple millimetric anal condylomas.

Normal socio-familial environment without detecting risk factors for sexual abuse in the anamnesis. The children's section of the *Consellería de Bienestar*, after evaluation of the case and family environment, ruled out sexual abuse.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

LThe patient came to the outpatient clinic referred by her pediatrician after her mother observed multiple verrucous pedunculated lesions smaller than 1 cm located in the perianal area, of recent appearance in the last 3-4 weeks [Figure 1].

After a thorough examination and the ruling out of lesions in other locations, a biopsy of the condyloma lesion was performed for pathology and HPV typing by in situ hybridization and polymerase chain reaction (PCR). The pathology study confirmed the diagnosis of condylomas and human papillomavirus (HPV) typing revealed HPV genotypes 6 and 11.

To establish the mechanism of HPV infection in the patient, a gynecological examination of the mother was performed by liquid cytology (co-test). The results obtained revealed: negative cytology for malignancy and co-infection with HPV serotypes 11, 16, 53.

TREATMENT AND EVOLUTION

After reassuring the mother of the child, explaining the high rates of spontaneous regression

FIGURE 1. Initial examination: multiple perianal myometric condylomas

FIGURE 2. Follow-up: persistence of perianal condylomas.

FIGURE 3. Follow-up after treatment with Papilocare® external genital gel: partial resolution of central perianal condylomas.

of the infection, a watchful waiting attitude was adopted. At 6 months, no change in the perianal condyloma lesions was observed [Figure 2].

Given the persistence of the lesions, treatment was proposed with imiquimod 5% (off-label), 3 applications/week. However, after the first week of treatment, the child's mother decided to terminate the treatment due to poor tolerance by the patient (intense erythema, pain and itching in the perianal area that prevented the child from resting).

FINAL DIAGNOSIS

Finally, it was decided to maintain a wait-and-see attitude with topical application of Papilocare® External Genital Gel, based on *Coriolus versicolor*, as an adjuvant treatment. This treatment was applied with good tolerance by the patient every 12 hours for 45 days

At the follow-up visit, partial resolution of the more central perianal condylomas and slight growth of the peripheral condylomas were observed [Figure 3].

It was decided to continue with topical treatment for 30 more days and after 45 days the complete disappearance of the perianal condyloma lesions was observed [Figure 4].

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The presence of anogenital condylomas in children is a controversial situation, since there are doubts about their route of transmission and epidemiology[1-4].

The main routes of transmission of human papillomavirus (HPV) to the anogenital area in children are the following[5,6]:

1) Perinatal route, from clinical or subclinical lesions in the birth canal. Due to the long incubation and latency time of HPV, this route

ere the family
ablished, and the
lack of hygiene,
tc.) will be ruled
y history, it is of
ish the possible
by looking for
h other persons
STDs, without
onset of sexual
exual abuse.
examination,
complementary
microbiological
Ds as well as

he social variant
ion to the close
ist, pediatrician
or dermatologist, the help of social workers is also necessary.

from vulgar warts on the hands of children or caregivers.

3) From adult genitalia.

The epidemiology is summarized in Table 1.

According to the literature consulted, we consider that in the case of a minor affected by HPV we should perform:

As for the treatment of condyloma acuminata in childhood, due to the high rate of spontaneous regression, a wait-and-see approach can be adopted in principle. Interferon treatment seems to be effective in extensive and resistant

TABLE 1

Agent	Human papilomavirus (HVP-6, 11)
Contagion	Direct, vertical, indirect (?)
Susceptibility	60-70 % of those exposed
Transmissibility	Up to 1 year
Incubation period	6 – 20 weeks (3 months)
Age	Adolescence
Station	No predominance
Immunity	No subsequent immunity
Localization	Genitalia and perianal
Predisposing Factors	Low socio-economic level, STD
Evolution	Chronic with recurrences

condylomas, although experience in childhood is scarce, so medical treatment of condylomas in children is not recommended as the first line of treatment.

Additionally, it is important to follow up for at least one year due to the risk of recurrence.

Finally, after the positive outcome derived from the topical use of external genital gel with *Coriolus versicolor* in our patient, it would be interesting to have more information regarding the experience and results of the use of Papilocare® External Genital Gel for the elimination of vulvar and anal condylomas, either alone or as a complement to other classic treatments.

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Low-risk Cytology and Persistent HPV 16 Infection in the Post-Treatment Follow-Up of Severe Dysplasia

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Summary

A 30-year-old woman who, after undergoing cervical conization for severe dysplasia, presents persistent positivity for high-risk HPV, as well as cytology with a low-grade lesion. Therefore, an active role in the follow-up care was decided.

Keywords: HPV; Cervical dysplasia; *Coriolus versicolor*; Vaginal gel; Prevention.

MEDICAL HISTORY

A 30-year-old woman, with no family or personal history of interest, with a BMI of 21 kg/m^2, regular treatment with oral contraceptives for 2 years, nulliparous, smoker of 5 cigarettes/day, with a stable partner and no relevant gynecological symptoms. Cytologic screening for cervical cancer performed at her primary care center showed HSIL results.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

In view of the HSIL cytological result, a colposcopy was indicated, showing a type 1 transformation zone (TZ), with dense acetowhite epithelium in the posterior region of the cervix on application of acetic acid, and negative iodine to the Schiller test. Three directed biopsies were taken with results of CIN 2 and 3, after which conization was performed, resulting in extensive moderate and severe epithelial dysplasia (CIN 2-3), with clear contact of the dysplasia with the exocervical surgical margin, and endocervical curettage with high-grade dysplasia.

DIFFERENTIAL DIAGNOSIS

In case of an altered cytological result, with suspicion of high-grade dysplasia, a colposcopy is performed to assess the cervix and biopsies are taken to confirm or rule out lesion, cataloging the degree and/or existing invasion.

- Mild cervical dysplasia
- Moderate/severe cervical dysplasia
- Carcinoma in situ
- Cervical cancer

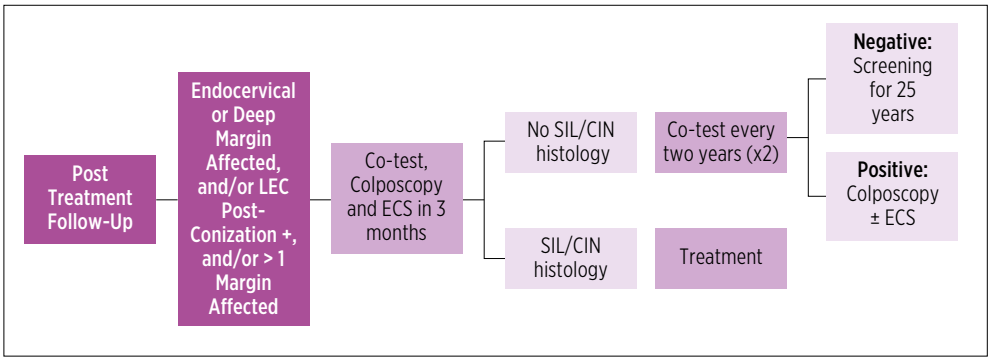

FIGURE 1. Follow-up algorithm for patients after conization for CIN 2-3. *(Source: "Prevention of Cervical Cancer 2022" Guidelines of the AEPCC)*[1].

TREATMENT AND EVOLUTION

As mentioned above, a conization was performed. The surgical specimens (exocervical and endocervical) both presented affected margins. Since this was a patient without fulfilled reproductive desires, the indicated approach according to the current AEPCC guidelines, is close follow-up with co-testing, colposcopy and endocervical study (ECS) at three months [Figure 1][1].

In the follow-up visit at 3 months the following result was obtained:

- Cytology: ASCUS.
- HPV test: positive for HPV 16 and 33.
- ECS: no alterations.
- Colposcopy: directed biopsy was taken, with results indicating focal coilocytic changes and fragments of epithelial hyperplasia and inflammation (without suspicion of dysplasia).

The next follow-up visit was in one year, as recommended, with co-testing, and in this case a positive HPV test for subtype 16 and triple negative cytology was obtained. In view of the persistence of positive HPV 16, a new colposcopy was performed, and biopsies were taken (exocervical), resulting in mild focal dysplasia (CIN 1) with chronic endocervicitis.

In view of these results, treatment with vaginal gel with *Coriolus versicolor* is indicated for six months, and it is decided to perform the next control with co-test in one year. In this control, a negative HPV test and a negative cytology were obtained.

FINAL DIAGNOSIS

High-grade cervical dysplasia and persistent HPV 16.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Cervical cancer is the most common pathology related to HPV, 99.7% of which is caused by persistent infection with high-risk HPV[2]. More than two hundred HPV types have been identified, with around fifteen types causing cervical cancer[3] (mainly types 16 and 18). Screening for HPV and cervical dysplasia as early prevention has significantly decreased the risk of death from cervical cancer. Additionally, when combined with colposcopy, we increase the probability of detecting cervical dysplasia[4]. Lesions can usually be treated simply and effectively[4]. In the follow-up of cervical pathology, HPV test negativity is associated with a lower long-term risk of cervical cancer, with persistent detection being an important risk indicator of unfavorable outcomes, despite normal cytology[5]. No current treatment completely eradicates HPV[6]. The availability in recent years

of the HPV vaccine is contributing to the decrease in the incidence of genital warts[6] and cervical cancer. However, in Europe, a *Coriolus versicolor*-based vaginal gel is the first and only treatment for the prevention and treatment of low-grade HPV-dependent lesions[7]. Its composition favors virus clearance, offering increased rates of repair of low-grade lesions (such as ASCUS or LSIL) as well as HPV clearance, as opposed to the usual practice based on untreated controls[7]. According to the PALOMA study[8], treatment with this vaginal gel has been shown to have better clinical benefit compared to the conventional watchful waiting for high-risk HPV-infected patients and for treating HPV-related cervical lesions, after a six-month treatment period[8].

In the case of our patient, after having been treated with cervical conization for high-grade dysplasia with affected endocervical margins, persisting high-risk HPV positivity and presenting a cytology with an ASCUS result, we found clearly adequate characteristics to indicate treatment with this vaginal gel, which favors clearance of the virus and disappearance of the lesion. Additionally given the persistence of the virus and the fear of disease progression, most women affected by this pathology request a treatment that favors resolution. The vaginal gel with *Coriolus versicolor* offered us a safe and tolerable treatment, which reduced the patient's stress while waiting for the new follow-up visit. In the last follow-up she presented a negative HPV test and normal cytology. As mentioned above, in cases of greater stress for both the patient and the physician, taking an active attitude in the follow-up, especially in those patients at higher risk, can have a positive result.

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Use of an External Genital Gel based on *Coriolus versicolor* as Adjuvant Treatment after two Vulvar Interventions for Common Type Vulvar Intraepithelial Neoplasia (VIN)

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Summary

Immunosuppressed patient (multiple sclerosis treated with cladribine) with vulvar lumpectomy for common type vulvar intraepithelial neoplasia (VIN) and after 6-8 months a second intervention for the same reason with laser vaporization. After the second surgical intervention, an external genital gel based on *Coriolus versicolor* was applied as an adjuvant treatment, which proved to be effective. At present the patient's vulva is unaltered and she is asymptomatic.

Keywords: Common type VIN; Vulvar lumpectomy; Laser vaporization; HPV; *Coriolus versicolor*.

MEDICAL HISTORY

- Age: 50 years.
- Family History: father with lung cancer.
- Personal History: no known drug allergies. Anxiety. Hypercholesterolemia. Multiple Sclerosis. Surgical interventions: Herniated disk. Tubal ligation.
- Usual treatments: omeprazole, mirtazapine, tranxilium, venlafaxine, simvastatin, cladribine, silodyx.
- Toxic Habits: smoker 10 cig/day
- Gynecological-Obstetric History: Menarche: 14 years. Menopause: yes. LMP: 48 years. G2P2A0. Cytological screening within the normal range. Not HPV vaccinated.

She starts controls in the Cervical Pathology Unit of our center due to vulvar pruritus of several months of evolution.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

- External genitalia with a whitish raised plaque of approximately 2-2.5 cm in the lower third of the left labium minora. On vulvoscopy, a lesion with well-defined borders and a reaction to 5% acetic acid is observed.
- Normal vaginal. Normal cervix. No leukorrhea. No other suspicious lesions.
- Updated cervical cytology: negative for malignancy.
- Serology: negative.
- Biopsy of vulvar area described (punch): VIN common type, p16 positive.

DIFERENTIAL DIAGNOSIS

Given the great heterogeneity in the clinical presentation of VIN, many vulvar disorders can be

confused with this entity. In clinically doubtful cases, histological study will allow us to differentiate it from condyloma acuminata, seborrheic keratoris, psoriasis, lichen simplex chronicus and lichen sclerosus.

TREATMENT AND EVOLUTION

HPV vaccination, nonavalent vaccine, was started.

Lumpectomy of the vulvar lesion was performed since it was a unifocal lesion. Result: common type VIN, free margins.

At one month after surgery: correct healing and normal vulva.

Six months after surgery, in a new review: raised plaque was observed. This time heterogeneous but with erythematous areas larger than the previous one (3-3.5 cm) covering the middle and lower third of the left labium minora. New biopsy: common type VIN, p16 positive.

Laser vaporization of the described lesion was performed.

One month after surgery: healing is correct, but minimal persistent erythematous area in the middle third of the left labium minora, without being raised, is observed where the patient continues to present occasional itching.

After this second surgery, treatment with a *Coriolus versicolor* based external genital gel was proposed. During the first month the patient used two applications per day and subsequently, one application per night until completing six months.

At 6 months after surgery: normal vulvoscopy. Patient asymptomatic, no pruritus. A punch was performed on the scar zone in the middle third of the left labium minora, resulting in normal histology.

Currently, she continues with follow-up control vulvoscopies in our Cervical Pathology office, within normality, and the patient remains asymptomatic.

FINAL DIAGNOSIS

Common type VIN which required a vulvar lumpectomy and a laser vaporization, as well as adjuvant treatment with a *Coriolus versicolor* based external genital gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Vulvar intraepithelial neoplasia is an underdiagnosed entity. It is a lesion that precedes vulvar squamous cell carcinoma. There are two clearly differentiated entities: common type VIN (HSIL) related to HPV and differentiated type VIN associated with chronic inflammatory dermatoses such as lichen sclerosus and lichen simplex chronicus.

There are different epidemiological characteristics between common type VIN and differentiated type VIN. Common type VIN lesions usually affect women aged around 40-45 years, with a second peak after 55 years of age (50 years in our case). In contrast, differentiated type VIN is frequent in older women, generally above 60-65 years of age.

The following discussion will focus on common type VIN

The causative agents for common type VIN are oncogenic HPV genotypes, with HPV 16 being involved in most cases. As in HPV-related precursor lesions of other anatomical locations, in 90% of cases, infections are transient and will resolve spontaneously in about 2 years due to the body's immune response. Immunosuppression is therefore frequently associated with viral persistence and development of intraepithelial lesions. The patient in our case is immunosuppressed (multiple sclerosis treated with cladribine). Smoking is also frequently associated with common type VIN and we can also see this reflected in our case.

The lesions are usually polymorphous (frequently raised or papillomatous and pigmented), and multifocal, located in mucosal areas devoid of hair, preferably in the lower third of the vulva. Unlike most of the cases, our lesion is unique, in that it is single, but is elevated, pigmentated and located in an area devoid of hair. In fact, it is in the middle and lower third of the left labium minora. The associa-

tion with intraepithelial lesions in other anatomical areas of the anogenital tract is frequent, although it does not occur in our clinical case.

Examination with the colposcope and acetic acid (vulvoscopy) allows a magnified examination and a more detailed inspection and is useful for identifying suspicious lesions and directing biopsy.

There is no ideal treatment for patients with VIN, although there are specific recommendations that guide the most appropriate therapeutic approach. Treatment of patients with VIN is recommended in all cases. Excisional treatment will be imperative in cases of differentiated type VIN and in cases of common type VIN with high risk of hidden invasion. In cases where invasion can be ruled out, destructive and/or combined therapies may be used. In our clinical case, we first started with excisional treatment (excision of the entire lesion with a safety margin of 0.5 cm around the visible lesion) since it was a unifocal lesion. After persistence we decided to apply laser vaporization as it is recommended in common type VIN of localized areas in the introitus or in non-hairy areas once invasion is ruled out as in our case.

The *Coriolus versicolor* based external genital gel has moisturizing and re-epithelizing properties for the external genital area mainly indicated to treat warts caused by the human papilloma virus. In our patient, it has been used for a vulvar intraepithelial neoplasia secondary to human papilloma virus, showing its usefulness and efficacy in this proposed case, both for helping re-epithelialization after surgery and for its collaboration in the clearance of HPV.

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Consequences of not Complying with Population-Based Cervical Cancer Screening Protocols in Terms of Age of Onset. A Case Report

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Consulta Privada - Raquel León del Pino

Summary

Cervical cancer screening performed prior to the established age which progresses from ASCUS to normal through HSIL/CIN 3.

Keywords: Screening; HPV; Squamous intraepithelial lesion; Conization; *Coriolus versicolor*.

MEDICAL HISTORY

25-year-old female patient, with BMI within normal range, and no medical or surgical history of interest, non-smoker. Nulliparous. Family history: mother with breast cancer at the age of 50. The patient underwent cervical cytology screening for cervical cancer at her Primary Care Center before the established age according to current protocols due to anxiety about her mother's history, and the result was ASCUS (squamous cell atypia of uncertain significance).

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

With the result of ASCUS cervical cytology, the patient was referred to the hospital for lower genital tract pathology (LGTP) for further study.

In the physical examination, both general and gynecologic, including speculoscopy, there are no findings of interest.

A co-test was performed with positive results for high-risk HPV 16, 45, 51, 52, 59, 68 and negative cervical cytology. In view of these results, colposcopy was performed, as well as a biopsy with result LSIL/CIN 1 and with this, an expectant attitude is taken and follow-up with cytology at 6 months. In this cytology the result was HSIL/CIN 3, indicating excisional treatment by cervical conization and endocervical curettage (ECC), confirming the same anatomopathological diagnosis in the histology of the conization specimen, with a negative result for ECC, and free surgical margins.

DIFERENTIAL DIAGNOSIS

In the presence of altered cervical cytology and positivity for HPV, colposcopy with biopsy is performed to rule out:

- Low-grade squamous intraepithelial lesion (LSIL)/Cervical intraepithelial neoplasia grade I (CIN 1).
- High-grade squamous intraepithelial lesion (HSIL)/Cervical intraepithelial neoplasia grade 2 (CIN 2).
- High-grade squamous intraepithelial lesion (HSIL)/Cervical intraepithelial neoplasia grade 3 (CIN 3) or carcinoma in situ.
- Cervical cancer (CC).

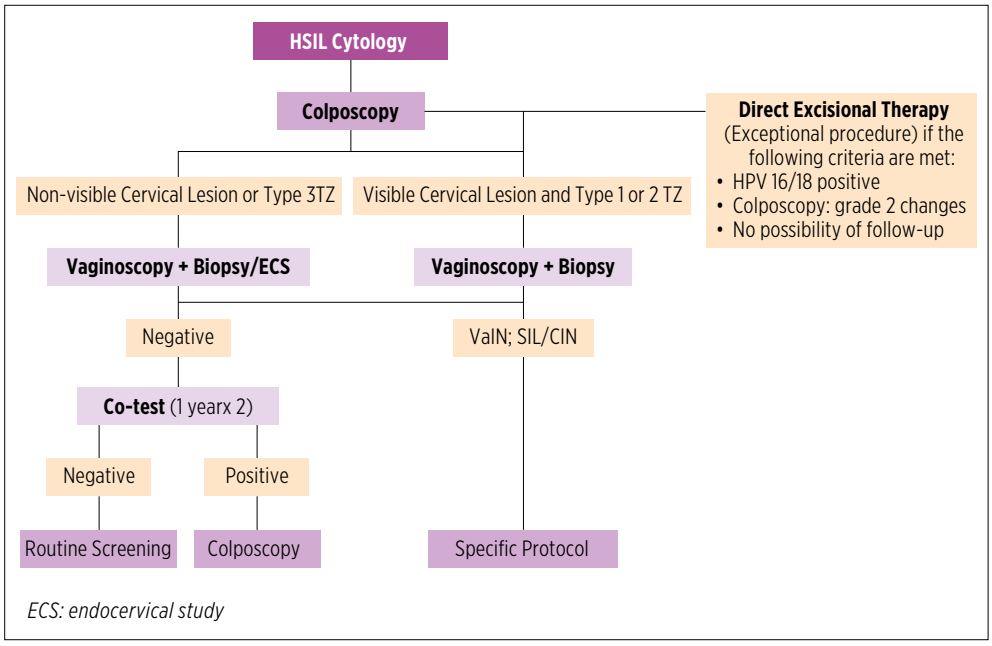

FIGURE 1. Algorithm: Cytology HSIL (AEPCC Guidelines).

TREATMENT AND EVOLUTION

With the histological diagnosis of HSIL/CIN 3/ Carcinoma in situ, the patient is closely followed up, with appointments every 6 months since the conization:

- 1st control. Co-test + Colposcopy + exocervical biopsy with result: ASCUS cytology, HPV 16 and 45, colposcopy with major changes, and negative biopsy.
- 2nd control. Co-test with result: negative cytology, HPV 16 and 56.
- 3rd control. Due to HPV 16 persistency, a colposcopy, exocervical biopsy and LEC are performed.
  - Colposcopy: adequate, UEC visible, type 1 TZ. No altered vascularization at present. Acetic, dense acetowhite epithelium of rapid appearance in region covering time zone 9 and 12 of small size. Visible open glandular orifices. Lugol's or Schiller's test positive in the same area described. Biopsy is taken at 9 and 12 o'clock. LEC is performed. The 3 samples were sent to Anatomic pathology in separate bottles for study. Correct hemostasis is performed with silver nitrate.
  - Results: 9 o'clock biopsy negative. 12 o'clock biopsy CIN 1. LEC negative.
  - With these results, conservative treatment using a Coriolus versicolor based vaginal gel is indicated for six months and a follow-up visit is scheduled in one year[3].
- 4th control. Co-test with the following results: HPV and cytology both negative

FINAL DIAGNOSIS

Patient with persistent HPV 16 (on follow-up after CIN 3 conization with free margins), who after treatment with Coriolus versicolor for six months is discharged, passing to the established population screening, with negative HPV and cervical cytology.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

It is important to follow the current AEPCC[1,2] guidelines since we may encounter complicated situations when deciding on a therapeutic approach, such as this case in which the screening program for uterine cancer had been initiated before the age of 25 (the established age for beginning). Although the patient arrived at the PTGI office with altered results and at the age of 25, but without considering the age at which sexual relations began, vaccination status or other risk factors.

Figure 1 shows the algorithm for HSIL[1] cytology.

According to the current AEPCC guidelines[1], the incidence of cervical cancer under 25 years of age is extremely low and screening has not demonstrated any benefit in reducing the incidence, as it has little or no impact on the rates of invasive cervical cancer up to the age of 30 years. On the contrary, screening in young women results in the detection of a high number of cases with minor cytological alterations and transient HPV infections, the study of which translates into high economic cost, overdiagnosis and overtreatment of lesions with little malignant potential.

Before the age of 25 years, primary prevention of cervical cancer should be promoted, and HPV vaccination should be recommended, as well as health measures aimed at family planning and prevention of other sexually transmitted diseases. Our patient was recommended vaccination after the HSIL biopsy result and completed it with three doses.

According to current guidelines, it is not recommended to perform cytology before the age of 25, but in case of pathology, it is recommended to complete the study[1,4].

We should avoid overtreatment when lesions are confirmed if they have a low risk of progression.

In the same edition of the current AEPCC guidelines, we have a section on the attitude to follow when faced with HSIL cytology in women aged 25 years [Figure 2][1].

Recommendation

- Refer for colposcopy (low level of evidence, strong recommendation in favor of)
- Direct excisional therapy is not considered an acceptable option (moderate quality of evidence, strong recommendation against).

Justification

Colposcopy allows for directed biopsy and to adapt clinical conduct to the definitive histological result.

In women younger than 25 years, the rate of spontaneous regression of HSIL/CIN 3 is very high (up to 73%) and it is estimated that less than 5% are at risk of progression to long-term uterine cancer.

Immediate treatment is overtreatment for an unacceptable percentage of women under 25 years of age and may have an unfavorable impact on the reproductive potential of these patients.

FIGURE 2. Attitude to follow when faced with a HSIL cytology in women 25 years or younger (AEPCC Guidelines).

Although in our case, perhaps driven by the patient's anxiety, it was decided to perform an excisional treatment[5].

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Regression of Low-Grade Intraepithelial Lesion after Treatment with Vaginal Gel containing *Coriolus versicolor*

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Summary

Efficacy of conservative treatment with *Coriolus versicolor* gel in the resolution of low-grade epithelial lesions.

Keywords: Cervical cancer; Cytology; Cervical cancer precursor lesions; HPV.

INTRODUCTION

Human papillomavirus (HPV) infection is the most frequent sexually transmitted disease in mankind. Its persistence over time is a necessary cause for the development of cervical cancer and a contributing factor in the etiology of up to 5% of all human tumors.

Scientific evidence shows that HPV infection is necessary but not sufficient for the development of pre-cancerous and cancerous cervical lesions. There are more than 200 HPV subtypes known today and only a few have oncogenic potential. There are 15 high-risk HPVs that affect the cervix, of which five (types 16, 18, 33, 31 and 45) are associated with the highest risk, with subtypes 16 and 18 causing 60% of CIN 3 and 70% of cancers.

Viral persistence is the most important indicator of injury. Age, immunosuppression, smoking, chlamydial infection, and oral contraception are factors that favor viral persistence. These same factors are risk markers for cervical cancer.

MEDICAL HISTORY

47-year-old woman presenting for cytology with changes suggestive of low-grade squamous intraepithelial lesion (LSIL).

- Family history: negative for breast, ovarian, and/or endometrial cancer. No hereditary diseases.
- Personal history: depression in treatment. No known drug allergies. Smoker of 10 cigarettes/24 h.
- Surgical history: adenoidectomy, amygdalotomy, umbilical herniorrhaphy, and hysteroscopic polypectomy.
- Obstetric and gynecological history: G6A3P2C1 CM: vasectomy couple. MT: 5/28.
- Gynecologic cytology:
  - Satisfactory specimen for evaluation.
  - Limited evaluation due to absence of endocervical/transformation component.
  - Benign cellular changes.
  - Presence of microorganisms, suggestive of bacterial vaginosis.

FIGURE 1. ENLARGE IMAGE

FIGURE 2. ENLARGE IMAGE

  - Cellular changes suggestive of low-grade squamous intraepithelial lesion (LSIL)
- HPV genotype 33 (Hisk-Risk oncogenic), HPV genotype 54.
- Examination: external genitalia and vaginal normal, macroscopically well epithelized multiparous cervix, no leucorrhea.
- Colposcopy: adequate. Type 1 TZ. Without preparation: normal vascularization.
  - Acetic:
    - Normal findings: mature squamous epithelium/Ectopia: no/Metaplastic epithelium: no.
    - Abnormal findings: Acetowhite epithelium: G1/Radial: 11 hr-1 hr/Quadrants: 1% of cervix: minimal.
    - Suspected invasion: no.
  - Schiller: TZ with no uniform lugol uptake except in the region described above where uptake is nil.
  - Biopsies: radial 11 hr. The result of the biopsy informs us of a low-grade dysplasia CIN 1.

TREATMENT AND EVOLUTION

In view of these results, treatment with a *Coriolus versicolor* vaginal gel is proposed to the patient daily for one month and then every 48 hours for 5 more months, resting on the days of menstruation. After this time of treatment, the patient comes for a follow-up visit. A cytology, a new HPV test and a colpovaginoscopy are performed. This time the colpovaginoscopy did not show any evident alteration and therefore no biopsy was taken. The cytology showed cellular atypia of uncertain significance and the HPV test was negative.

The patient is currently scheduled for a follow-up in one year according to the AEPCC recommendations.

DISCUSSION

Coriolus versicolor has a cellular-immunity-enhancing effect and improves cervical re-epithelialization by reducing the epithelial conflict zone which has intense cellular activity and represents the perfect target for HPV integration. It also normalizes the vaginal microbiota, and it has been demonstrated that its polysaccharides and beta-glucans have antioxidant, immunomodulatory and antitumor properties.

Treatment with Papilocare® has demonstrated better clinical benefit than the conventional watchful waiting approach in clinical practice for

HPV-positive patients, especially those with high-risk HPV.

In patients with HPV infection, it has been observed to influence the regression of low-grade squamous intraepithelial lesions in the cervix, in addition to a significant effect on the negativization of the virus.

An increasing number of studies support the advantages in cervical re-epithelialization with the use of Coriolus versicolor and the positive effect on the elimination of the virus and the cells affected by it. The PALOMA study has been able to demonstrate viral clearance at 6 months of treatment in 63% of women with high-risk HPV compared to 40% in the control group.

It is a therapy that has been available on the market for several years now and no significant side effects have been described after its use, so it should be offered as a treatment in all cases of mild intraepithelial dysplasia with association to positive HPV risk test from the time of diagnosis. The use of conservative treatments that will help eliminate HPV lesions is important since the risk of disease progression is secondary to persistent HPV infection.

This possibility of easy-to-apply treatment with few side effects would help to reduce health care costs by increasing follow-up intervals and reducing morbidity derived from invasive diagnoses and unnecessary treatments. It would also reduce anxiety in a significant number of patients.

In this clinical case, the use of Papilocare® improved the results of HPV-DNA, cytology and colposcopic testing in agreement with the data presented by most of the published studies.

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Internal Genital Gel with *Coriolus versicolor* in the Treatment to Control and Help Revitalize the Cervical Transformation Zone to Prevent the Risk of Lesions (ASCUS/LSIL) caused by HPV: A Case Report

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Clínica Mileniun-Dent

Summary

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, affecting up to 90% of sexually active individuals. Although most patients clear the infection spontaneously, viral persistence is associated with the development of lesions such as those of the cervical transformation zones (ASCUS/LSIL). Other studies indicate that HPV persistence is more likely in individuals with an altered microbiota. Guo Y-l et al. showed that women with HPV persistence had a prevalence of bacterial vaginosis of 11% versus only 5% of women who had cleared the virus. Similarly, King et al. observed that women with bacterial vaginosis had delayed viral clearance (hazard ratio: adjusted 0.84, 95% CI: 0.72-0.97).

Keywords: HPV; Altered microbiota; *Coriolus versicolor*.

MEDICAL HISTORY

A 54-year-old female patient, with no history of interest, came to the clinic for an asymptomatic check-up.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient comes to the gynecology office because of a partner with genital lesions. The patient has no external symptoms, and normal external genitalia.

Speculoscopy: neck with slight erosion.

PCR for HPV is performed.

Cytology, colposcopy, and biopsy are ordered for lesions in the couple. The patient is scheduled in 30 days in consultation to collected results.

After 15 days, the patient is called for consultation for pathological findings:

- **Cytology:** (ASCUS).
- **Colposcopy:** satisfactory, focal Lugol's negative lesion was observed at 6 hr and biopsied.
- **Cervical biopsy, 6 hours.** Exocervical mucosa with moderate acute cervicitis and marked reactive changes. The reactive changes secon-

dary to inflammation, do not allow ruling out of the presence of dysplasia. Clinical correlation is recommended.

- Positive for **HPV** types 26, 53 (Probably High-Risk) and 66 (High-Risk).

TREATMENT AND EVOLUTION

Treatment is prescribed with Papilocare® Vaginal Gel for HPV and Papilocare® Immunocaps for the partner for 6 months; follow-up in 6 months with cytology and colposcopy.

The patient attended after three months of treatment and at her request PCR and cytology were performed.

- **Spectroscopy:** healthy cervix
- **Cytology:** negative
- **HPV** positive for 62/81

After three months of treatment, the disappearance of the lesions and clearance of high-risk viruses is verified, with the appearance of other low-risk viruses, although the patient is not discharged and continues with Papilocare® Vaginal Gel and Papilocare® Immunocaps.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

In this case it is striking how, after only three months of treatment with Papilocare® Vaginal Gel and Papilocare® Immunocaps for the couple, recovery is observed in cytology (ASCUS), cervical lesions and biopsy, as well as the clearance of HPV genotypes 26, 53 (Probably High Risk) and 66 (High-Risk).

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Spontaneous Reversal of CIN2-3 in a Pregnant Patient with HPV 18

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Summary

Spontaneous reversal of CIN 2-3 in a pregnant patient colonized by HPV 18, who was administered a *Coriolus versicolor*-based vaginal gel.

Keywords: Gestation; intraepithelial neoplasia; *Coriolus versicolor*.

MEDICAL HISTORY

30-year-old female patient, with no family or personal history of interest, anovulatory drug user and active smoker of approximately 20 cigarettes a day. She came for consultation due to the finding of HSIL in cytological screening.

She began sexual relations at 15 years of age and was not immunized against HPV.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

The patient has normal external genitalia, with macroscopically normal vulva, vagina, and uterine cervix and apparent friable ectopia on rubbing.

Colposcopy is adequate with a type 1 transformation zone (complete visibility of the squamous-columnar zone). When acetic acid was applied, areas of raised acetowhite epithelium with thick mosaic vascularization and partial iodine uptake, suggestive of grade 2, were discovered [Figures 1 & 2], so it was decided to perform a biopsy and endocervical sampling for identification and genotyping of HPV.

TREATMENT AND EVOLUTION

The biopsy result reports extensive CIN 2, with areas of CIN 3, intense positivity for K i67 and p16. Endocervical genotyping is positive for HPV 18.

After informing the patient of the various therapeutic options, a cervical conization was agreed upon.

In the weeks prior to the operation, the patient consulted because she had become pregnant due to failure of the contraceptive method, expressing her

FIGURE 1. Initial colposcopy.

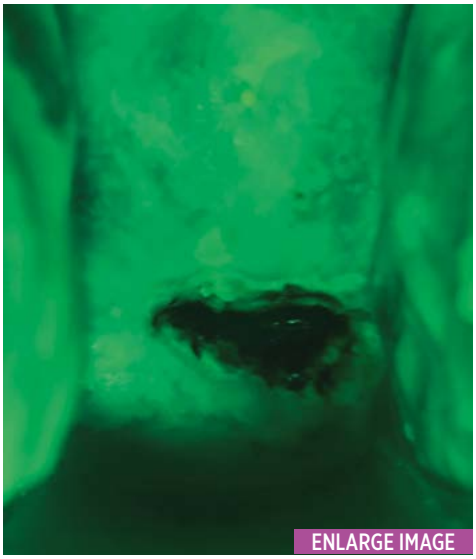

FIGURE 2. Initial colposcopy with green filter.

desire to continue with the pregnancy. In view of the risks inherent to surgical manipulation of the cervix during pregnancy, in agreement with the patient, an expectant management was proposed with periodic colposcopy controls, and the associated administration of Papilocare® Vaginal Gel, according to the recommended regimen of 1 vaginal cannula daily for 21 days, followed by the administration of one cannula every other day until completing 6 months of treatment.

At 11 weeks of gestation, adequate colposcopy with type 1 transformation zone revealed a cervix with obvious regression of the lesion [Figures 3 & 4], which could be confirmed histologically (CIN 1). HPV identification and genotyping remained positive for HPV 18. The patient is currently being followed up in her 18th week of gestation, and there have been no side effects associated with the treatment.

FINAL DIAGNOSIS

Spontaneous reversal of CIN 2-3 in a pregnant patient colonized by HPV 18, who was administered a *Coriolus versicolor* based vaginal gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Cervical intraepithelial neoplasia is a pre-malignant lesion that precedes the development of invasive cervical cancer. It is a dynamic lesion that can progress to invasive cancer, persist over time or regress spontaneously.

The treatment of choice in patients with CIN 2-3 lesions is conization, a procedure that is not free of complications, especially during pregnancy. Although spontaneous regression can occur in up to 65% of cases, the management of these lesions during pregnancy remains controversial.

Cervical cancer is the most common pregnancy-associated gynecologic neoplasm in mankind; it has an incidence of between 1/1,200 to 1/10,000 pregnancies, including carcinomas in situ and postpartum women[1]. However, there is currently no conclusive data on the biological effects of the tumor on pregnancy, the associated perinatal outcomes and the appropriate timing of cervical intervention[2,3].

There is evidence of the possibility of spontaneous regression of cervical intraepithelial

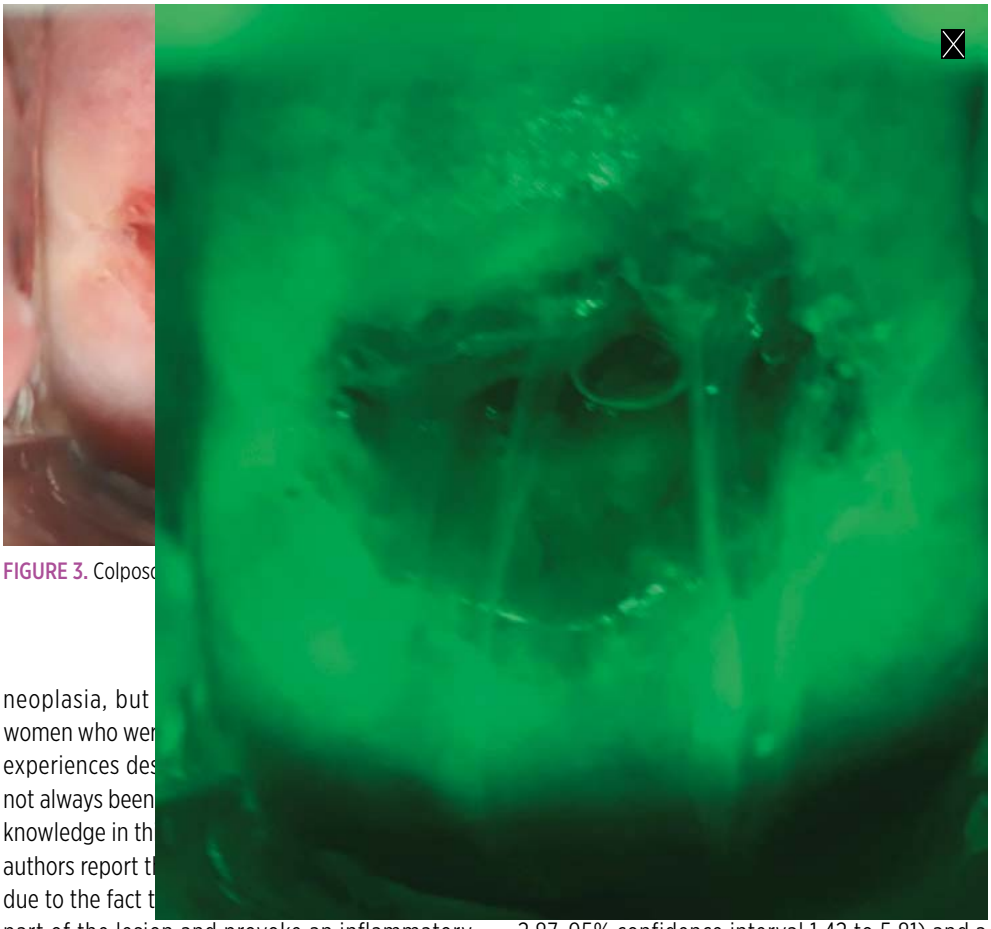

FIGURE 3. Colposc

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due to the fact t
part of the lesion and provoke an inflammatory reaction sufficient enough to favor its reduction and disappearance. On the other hand, other authors suggest that it is the interval period that has an influence, and others that it is the route of delivery[4].

Gestational prognosis is affected by the diagnosis of cancer. A large study shows that women diagnosed with cervical cancer during pregnancy or in the postpartum period have higher rates of spontaneous or induced prematurity, and low and very low birth weight newborns[5]. However, when cervical intraepithelial neoplasia is treated with conization, either by cold knife, laser or diathermy loop, there is a higher subsequent risk of perinatal mortality and other serious problems in pregnancy[6].

2.87, 95% confidence interval 1.42 to 5.81) and a significant risk of preterm delivery (2.78; 1.72 to 4.51), extremely preterm delivery (5.33; 1.63 to 17.40) and birth weight less than 2. 000 grams (2.86; 1.37 to 5.97). Laser, described in only one study, was also associated with an increased chance of low birth weight. On the other hand, ablative treatment with cryotherapy or laser was not associated with an increased risk of serious birth complications; however, radical diathermic ablation was associated with a higher frequency of perinatal mortality, preterm delivery and low birth weight[6].

In view of this background, the possibility of maintaining an expectant management course with the vaginal administration of Papilocare® to try to promote regression of the cervical

intraepithelial lesions was considered in the case presented. Although its use during pregnancy is not standardized, there is no formal contraindication to its use since there is no data suggesting a possible risk of any of the product's components for pregnancy.

Although the most frequent factors associated with the regression of lesions are: age less than 25 years, small lesions, negative HPV status, and absence of HPV 16 infection, more studies are needed to deepen our understanding of the prognostic factors of cervical dysplasia during pregnancy[7].

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Treatment with Papilocare® for Inflammation and Ectopia associated with ASC-H in a Young Patient

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Summary

Human papillomavirus lesions are very prevalent nowadays. Sometimes they can be asymptomatic or present mild symptoms such as inflammation or post-coital bleeding, especially when associated with ectopia.

Keywords: Ectopia; Human papillomavirus; ASC-H; Colposcopy.

MEDICAL HISTORY

An 18-year-old female patient who comes for consultation due to dysmenorrhea and post-coital bleeding. She refers to participating in sexual intercourse without contraception and does not have a steady partner. She provides the result of a recent cytology performed despite being outside the age range indicated in the current protocols. Its results are as followed: Inflammation and atypia associated with ASC-H and finding of key cells associated with bacterial vaginosis.

The patient was vaccinated against HPV with two doses at 9 years of age.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Examination revealed normal external genitalia, without objectionable lesions, eutrophic vagina, and cervix with extensive bleeding ectopia on rubbing. Nonspecific leucorrhea.

Transvaginal ultrasound showed a normal uterus and appendages.

Adequate colposcopy was performed, with a type 1 transformation zone, and fully visible squamocolumnar junction. Wide ectopia, without atypical or vascular vessels. Minor changes are observed at 12 and 16 hours, basically fine punctation and mosaic. Schiller and Lugol's test without suspicious areas.

Given the findings, it was decided not to perform a directed biopsy.

DIFFERENTIAL DIAGNOSIS

A diagnosis of bacterial vaginosis and ASC is established, ruling out high-grade lesions, as well as a friable ectopia.

TREATMENT AND EVOLUTION

We indicated treatment with Papilocare® one application daily for 21 days and then every other day for one month. In addition, we associated previous treatment with clindamycin ovules 100 mg at night for three days, as well as oral probiotics for one week.

The patient came for a follow up visit after finishing treatment and she informed us that she had only been treating with Papilocare®, she had not taken the probiotics nor administered the vaginal clindamycin.

Speculoscopy showed very slight periorificial ectopia that no longer bled to the touch, non-specific leucorrhea and eutrophic vagina without lesions. It was decided to perform a new cytology and culture.

The cytology reported the absence of suspicious intraepithelial lesions, and the culture continued to show Gardenella bacterial vaginosis.

FINAL DIAGNOSIS

Finally, we obtain a previous diagnosis of inflammation, ectopia and ASC-H, which disappears after short-term treatment with Papilocare®.

On the other hand, there is a bacterial infection by Gardenella.

DISCUSSION

Human papillomavirus (HPV) infection is currently one of the most frequent sexually transmitted infections in our environment. Although HPV vaccines are widely distributed and included in the vaccination schedule, they do not cover all serotypes of the virus, so the existence of cytological alterations associated with HPV is still frequent, appearing increasingly in young patients who have not yet begun cervical cancer screening.

Given that in the age group < 25 years old, we know that the clearance of the virus and disappearance of lesions is achieved in most patients, we must be as conservative as possible in their treatment, and this is where treatment with Papilocare® becomes very important, which in addition to acting against the cervical lesion, improves viral clearance and helps the re-epithelialization of the ectopia, improving abnormal bleeding and post-coital bleeding.

Assessing treatment response and improvement in symptomatology through clinical cases and trials is key to be able to universalize and standardize the currently available treatments and guidelines.

In the patient in question, it was decided to prolong the Papilocare® regimen until completing 6 months of treatment, in addition to recommending again treatment with vaginal clindamycin and oral probiotics.

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Perianal Condylomatosis in an Immunocompromised Patient

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Summary

Perianal condylomatosis in an immunocompromised patient with endocervical high-risk HPV, which remits after application of *Coriolus versicolor*-based gel.

Keywords: Multiple sclerosis; Alemtuzumab; Perianal condylomas; *Coriolus versicolor*.

MEDICAL HISTORY

38-year-old female patient with no family history of interest on treatment with alemtuzumab acetate for recurrent relapsing multiple sclerosis. Referred to the lower genital tract pathology office for recent appearance of perianal warty lesions with cytological finding of ASCUS and positive endocervical hybridization test for HPV 31 and 51. She has not been vaccinated against HPV.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

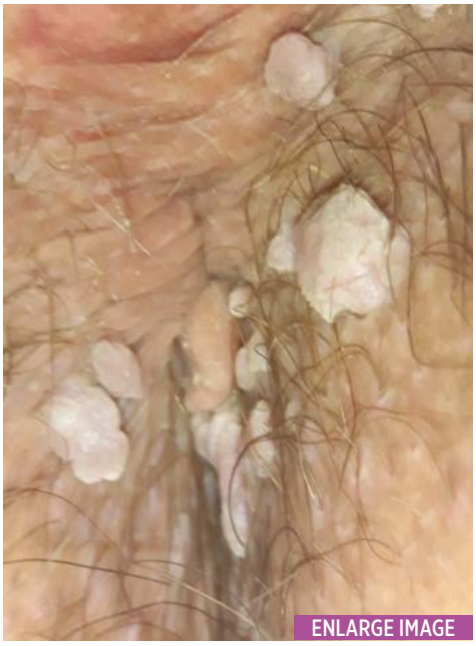
Physical examination reveals multiple perianal condyloma acuminata. They manifest as lesions of different colors, sizes and shapes that appear around the anal margin, forming, on the upper edge, a larger formation that could be considered a "cockscomb" [Figures 1 & 2].

The vagina is normal and the colposcopic examination is adequate, with a type 1 transformation zone (complete visibility of the squamo-columnar zone) with no colposcopic findings of note. The anoscopy also found no alterations of interest.

Often any perianal symptoms are attributed to the presence of hemorrhoids, since it is the most well-known anal disease; however, the differential diagnosis of perianal pathology includes anal fissures and fistulas (which cause pain and bleeding) and perianal condylomas, which are a common sexually transmitted disease.

TREATMENT AND EVOLUTION

At the beginning, treatment was started with a regimen of self-administration of sinecatechin ointment 3 times a day for a maximum of 16 weeks,



FIGURES 1 & 2. Images at the time of initial diagnosis

which the patient abandoned a week after starting treatment due to local irritative symptoms.

After discussing the possible therapeutic alternatives and their possible associated side effects with the patient, she asked us for surgical excision of the lesions with laser; to which we proposed as a last alternative prior to surgery, treatment with Papilocare® External Genital Gel once a day, which the patient accepted after explaining its safety profile.

After 4 weeks, there was a notable reduction in the number and volume of the condylomas, without the patient having presented any side effects [Figures 3 & 4]. Eighteen days later, the patient called for consultation referring the complete disappearance of the condylomas, which we observed a week later in consultation, where we indicated to continue with the usual regimen of Papilocare® External Genital Gel every other day.

At the present time, 6 months after diagnosis, the patient is being followed up by our Lower Genital Tract Pathology Unit; she is asymptomatic and the hybridization for endocervical HPV is only positive for serotype 31.

FINAL DIAGNOSIS

Perianal condylomatosis in an immunocompromised patient with endocervical high-risk HPV, which remits after application of *Coriolus versicolor*-based gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Anal condylomas are benign lesions caused by the HPV virus. The appearance of such lesions, warts and small growths around the anus are a frequent cause of concern for patients. They can appear either in the perianal area or inside the anus. Initially, they appear as small painless pink

FIGURES 3 & 4. Fo

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the affected areas. Up to two thirds of patients have anal itching, half of them bleed with defecation and some express a sensation of perianal wetness. Only a small proportion of patients have pain, although the intensity of symptoms also depends on the size of the lesions and their location in the anal canal[1,2].

Under normal conditions the immune system can counteract HPV by blocking the formation of lesions that are the first step towards the appearance of tumors. However, in some people, the immune system is weakened to the point of being unable to fight the virus, which can then act more rapidly and

Although the most studied immunosuppression in relation to the pathology of the lower genital tract is infection by the Human Immunodeficiency Virus, there are other causes of immunosuppression such as iatrogenesis produced by various therapies used in certain processes of autoimmune etiology such as scleroderma or multiple sclerosis[3,4]. In the present case, the patient was being treated with alemtuzumab, a humanized antineoplastic monoclonal antibody, which causes lysis of lymphocytes by binding to the CD52 antigen, a highly expressed, non-modulatory surface

glycoprotein present on the surface of normal and malignant T and B lymphocytes, as well as monocytes, thymocytes and macrophages. All this makes alemtuzumab a drug with a special capacity for immunosuppression[3,4].

None of the therapeutic options for anogenital condylomatosis are totally satisfactory on their own, and even less so when used in immunosuppressed patients who are associated with significant recurrence rates. Therefore, it is recommended to combine treatments and closely monitor patients, especially during the first three months, which is when most recurrences occur.

When condylomas are very small and located only around the skin of the anus, they can be treated with topical drugs that are applied directly on the lesion: podophyllin 0.5% or topical 5 fluoruracil. This procedure requires several applications over several weeks and must be applied by the specialist. Sinecatechins are green tea leaf extracts (Camellia sinensis) and are also effective in the topical treatment of lesions. On the other hand, the self-application of Imiquimod[5] has also been described. The application of a *Coriolus versicolor* based gel (Papilocare®) can help a obtain a favorable evolution and reduction of condyloma lesions[6].

Other forms of treatment consist of electrocautery, surgical resection, or a combination of both. Surgical excision is preferred in patients with large condylomas or numerous lesions. Condylomas located within the anal canal are not amenable to medical treatment and require surgery for cure[5,7].

Following the positive result, more experience is needed in the use of Papilocare® for condyloma removal, either alone or as an adjunct to other classical medical or surgical treatments such as CO_2 laser, especially in immunocompromised patients.

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Viral Clearance and Resolution of Lesions in At-Risk Subgroups with Vaginal Gel containing *Coriolus versicolor*

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Summary

Genital infection by human papillomavirus (HPV) is the causative agent of almost all cases of cervical cancer (CCU) and its precursor lesions. Specifically, high-risk oncogenic HPV genotypes (HR-HPV) 16 and 18 account for 70% of cervical cancer cases and 10 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 greater persistence of infection, which is a risk factor for the progression of premalignant lesions, has been demonstrated in cases of HR-HPV and in women over 30 years of age. The various studies of *Coriolus versicolor*-based Vaginal Gel are extremely promising as it has provided strong clinical evidence of improved clearance, re-epithelialization, restoration of vaginal microbiota and increased immunity compared to standard clinical practice.

Keywords: HPV; High risk; Clearance; *Coriolus versicolor* gel.

MEDICAL HISTORY

A 43-year-old patient under regular follow-up in consultation, with a recent cytology finding of low-grade squamous intraepithelial lesion (LSIL) associated with HR-HPV types 33 and 58. The patient had no personal or family history of interest.

PHYSICAL EXAMINATION AND DIFERENTIAL DIAGNOSIS

The patient came for a consultation after diagnosis and colposcopy were already performed, showing an area of thin acetowhite epithelium with mosaic that translates with lugol in the entire anterior lip. A cervical biopsy was performed at 10h, with a histological result of LSIL/CIN1 [Figures 1 & 2].

TREATMENT AND EVOLUTION

The diagnosis is carefully explained to the patient and the importance of healthy lifestyle habits and HPV vaccination is emphasized.

We began a treatment regimen with a *Coriolus versicolor* based vaginal gel for 21 days in a row during the first month and then on alternate days for 6 months (interrupting during menstruation). At the 6-month follow-up visit, a colposcopy was repeated which showed great effectiveness of

ENLARGE IMAGE

FIGURE 1 .

ENLARGE IMAGE

FIGURE 2 .

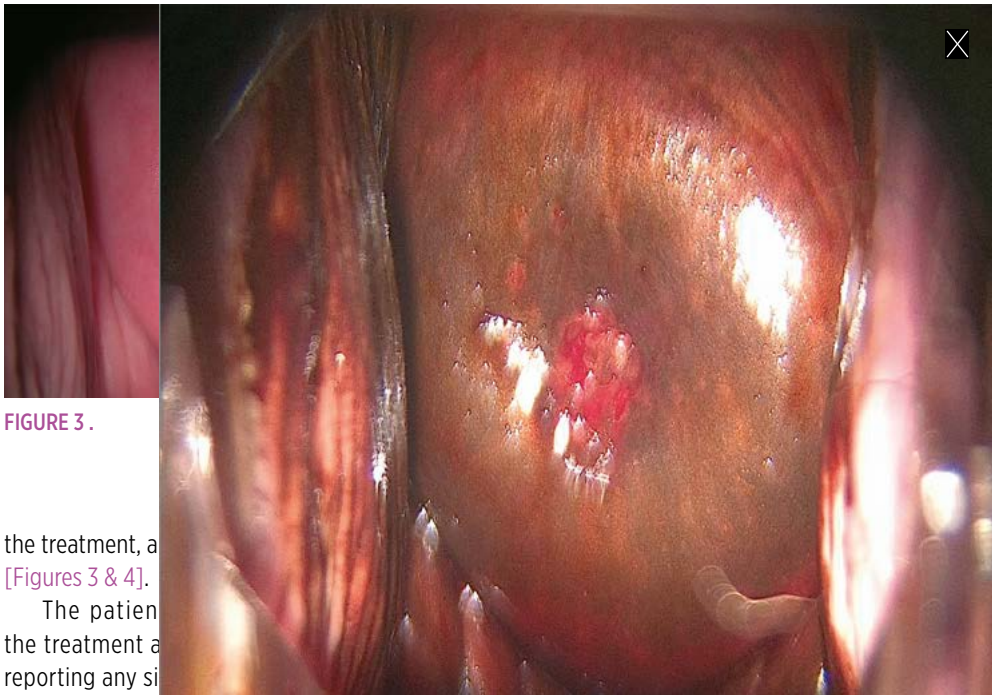

FIGURE 3 .

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control at 6 months, in which the patient presented normal cytology and negative HPV test.

FINAL DIAGNOSIS

Resolution of cervical lesion caused by HR-HPV and viral clearance after treatment with *Coriolus versicolor* gel in a patient over 40 years old.

We must consider the options available to us to promote the clearance of HPV infections and treatment of lesions, in a safe and effective manner. The efficacy of the *Coriolus versicolor* based vaginal gel was evaluated in the PALOMA clinical study in patients diagnosed with high-risk genotypes. The results demonstrated its efficacy in

the normalization of cervical lesions at 6 months in 88% of those treated vs. 56% in the control group and a clearance rate of 63% vs. 40% in the control group. The data obtained in the PALOMA clinical study have been reinforced both by a real-life observational clinical study and by 6 independent studies, all of them achieving stable clearance rates for HR-HPV ranging from 50-70%. These data reinforce the existing evidence of the beneficial effect of treatment with the *Coriolus versicolor* based vaginal gel on HPV lesions.

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Vaginal Gel with *Coriolus versicolor* as a Treatment for Low-Grade Intraepithelial Lesions and as an Adjuvant in the Clearance of Infection by Human Papillomavirus 16

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Summary

Human Papillomavirus (HPV) infection is one of the most prevalent sexually transmitted infections today. Approximately 75% of sexually active women become infected with HPV in their lifetime. Ninety percent of these infections are usually transient and resolve within 2 years of infection; however, the virus can remain latent and cause mucosal lesions in the lower genital tract, mainly at the cervical level[1].

The gradual development of the immune response has been described as the most likely mechanism for HPV clearance. However, it is known that the maintenance of healthy lifestyle habits and the reestablishment of an optimal vaginal flora will aid in the regression of intraepithelial lesions and in the viral clearance process[2].

Keywords: HPV infection; Cervical lesions; Vaginal flora; Treatment.

MEDICAL HISTORY

44-year-old patient. No steady partner. Not vaccinated against HPV. Obstetric history: G1P1.

No other history of interest. Previous cytology one year ago, negative for malignancy.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient consulted for an altered cytology result in June 2021, squamous intraepithelial lesion of uncertain significance (ASCUS) and HPV test positive for HPV 16.

A colposcopy was performed at the office showing: type 1 TZ, minor changes, areas of faint acetowhitening at 10 and 1 h, which were biopsied, obtaining an anatomopathological result of low-grade cervical intraepitelial neoplasia (CIN 1).

TREATMENT AND EVOLUTION

HPV vaccination and adjuvant treatment with Papilocare® Vaginal Gel in cannulas is proposed.

Colposcopy was performed at 6 months observing: Type 1 TZ, minor changes and metaplasia, negative lugol zone at 10 hours.

FINAL DIAGNOSIS

A biopsy was performed again at 10 h, obtaining the following result: intraepithelial mucosa without evidence of dysplasia. The HPV test was repeated and found 35, 52, 53, 58, 54 and 62/81.

We continued treatment with Papilocare® and scheduled a follow-up appointment in 6 months.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

This case shows the temporary change that can occur in a patient after infection with a high-risk HPV type, in this case HPV 16. We can see how after infection with a high-risk virus, intraepithelial lesions can begin to appear, which over time and depending on the behavior we take, can regress or not[3]. In this case, an active management was taken and both HPV vaccination and Papilocare® Vaginal Gel were started immediately, which may have facilitated viral clearance of type 16 and helped in the regression of the low-grade intraepithelial lesion. It is also noteworthy that despite having found the presence of new HPV viral types, colposcopy showed a clear improvement compared to previous ones, which leads us to conclude that the use of Papilocare® combined with healthy lifestyle habits and vaccination allows us to take a step forward and obtain positive results in the follow-up of low-grade lesions and high-risk HPV viral infections; however, more studies with large and diverse populations are needed to confirm these findings[4,5].

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LSIL/CIN 1 Treated with a *Coriolus versicolor* Vaginal Gel (Papilocare®). Viral Clearance and Resolution of the Cervical Lesion

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Summary

Genital infection by the human papillomavirus (HPV) is the causative agent of almost all cases of cervical cancer (CC) and its precursor lesions. Adequate and sustained screening of healthy women by cervical cytology has reduced the incidence and mortality from cervical cancer by up to 80-90%. The various studies of a *Coriolus versicolor*-based Vaginal Gel are extremely promising in terms of viral clearance and lesion regression.

Keywords: HPV; *Coriolus versicolor*; Clearance.

MEDICAL HISTORY

41-year-old female patient with no medical or surgical history of interest who came to the clinic requesting a gynecological check-up, asymptomatic. Cytology result LSIL associated with HR-HPV 39. Previous review 4 years ago with negative cytology result. Not vaccinated against HPV.

PYSICAL EXAMINATION AND DIFERENTIAL DIAGNOSIS

Colposcopy is offered and thin acetowhite epithelium is evidenced at the squamocolumnar junction, which is biopsied with histological result of LSIL/CIN 1 [Figure 1].

TREATMENT AND EVOLUTION

The patient is advised to have a new control in 6 months, smoking cessation and regular use of condoms is recommended. Nonavalent HPV vaccination is recommended.

At 6 months a new cytology was performed and LSIL persisted, the colposcopic findings were similar to the previous ones and the biopsy result was LSIL/CIN 1. Treatment was offered with Papilocare® Vaginal Gel for 6 months according to the guideline recommended in the technical data sheet and a new evaluation once the treatment was completed. At the next review a co-test was performed which was negative and the colposcopic examination was normal.

ENLARGE IMAGE

FIGURE 1 .

FINAL DIAGNOSIS

LSIL/CIN 1 of one year's evolution treated with *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal Gel) with resolution of the cervical lesion and viral clearance..

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Papilocare® is a medical device in the form of a vaginal gel based on *Coriolus versicolor* and other phytotherapeutic ingredients. *Coriolus versicolor* is a fungus of Chinese origin that contains β-glucan polysaccharides with known immunostimulant and antimicrobial properties as well as antiviral 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 on low-grade squamous intraepithelial lesions has been observed, as well as viral clearance.

The PALOMA clinical trial has been able to demonstrate normalisation of HPV-associated ASCUS/LSIL lesions (cytological and colposcopic) after 6 months of treatment in 85% of the women treated with Papilocare® Vaginal Gel compared to only 65% in the control group. The PALOMA® study has also been able to demonstrate viral clearance at 6 months of treatment in 65% of women with high-risk HPV versus 40% in the control group.

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Usefulness of *Coriolus versicolor* in the Treatment of the Lesions Produced by the Human Papillomavirus

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Summary

Anogenital human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. Its presence can lead to precancerous and cancerous lesions of the cervix, vulva, vagina, penis, anus and oropharynx[1]. Due to its high prevalence, it is critical that the sexually active population undergoes screening by cytology for early diagnosis of cervical, vulvar, vaginal, penile, anal and oropharyngeal HPV lesions, and treatment to minimise the possibility of more serious lesions developing. The study by co-testing (morphological study of the cells by cytology combined with the detection of the HPV genotype present) is essential to know whether we are dealing with a high-risk or low-risk HPV, since genotypes 16 and 18 are the most prevalent and the most carcinogenic[2]. In depth knowledge regarding which type of lesion and HPV genotype are involved allows us to develop a risk-based follow-up and treatment strategy based on the individual risk of our patients[3]. Cervical conisation is the treatment of choice for high-grade cervical lesions. However, in the absence of specific treatments for patients who are HPV carriers and/or have low-grade cervical lesions, adjuvant treatments are needed to help improve local immunity and contribute to viral clearance in order to prevent the development and/or progression of low-grade cervical lesions.

Keywords: Cytology; LSIL; HPV 16; Papilocare®.

MEDICAL HISTORY

A 45-year-old woman, under follow-up in our consultation since 2017 after a diagnosis of breast cancer in the left breast. At that time, she underwent a complete gynaecological check-up that included a conventional cytology, which resulted negative for intraepithelial lesions or malignancy.

She was a nulligestive patient, former smoker since 2012, with no other clinical history of interest.

In October 2020, during her follow-up in the gynaecological oncology consultation, a co-test was performed obtaining a result of squamous cells of uncertain significance (ASCUS) with a positive HPV test for high-risk virus: HPV 16.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

After receiving the cytological result of ASCUS & HPV 16, the patient was scheduled for colposcopy, which was adequate and in which an iodine negative area was visualised at 12 h and biopsied.

The result of the cervical biopsy was a low grade squamous intraepithelial lesion (LSIL).

TREATMENT AND EVOLUTION

The patient was referred to the cervical pathology unit for a closer follow-up. Due to its proven effectiveness in the prevention of new infections by other HPV genotypes, she was advised to receive the HPV vaccine[1] (which she completed by administering the recommended three doses), as well as the use of condoms during sexual relations. At this time the patient mentioned that she had not participated in sexual relations for several years.

Additionally, Papilocare® was prescribed according to its usual dosage. Treatment was prescribed for 6 months with good compliance.

FINAL DIAGNOSIS

In accordance with the current protocol[3], a co-test was performed one year later, with the cytology result being negative for malignancy and the HPV result being negative for high-risk genotypes.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

With this case we intend to illustrate the usefulness of adjuvant treatment with Papilocare® to both promote the elimination of high-risk HPV genotypes and to promote regression of low-grade cervical lesions. The use of a *Coriolus versicolor*-based gel has been shown to improve the re-epithelialisation of the cervix as well as the vaginal microbiota[4,5], generating an environment that supports natural immunity to clear viruses, and favouring the repair of lesions already present.

As HPV infection is most prevalent among sexually active young women, employing this treatment strategy may help reduce the number of high-grade lesions, and thus the need for more aggressive treatments (such as conization) that may be more uncomfortable for the patient, and which may have negative impacts in the future (e.g. for possible future pregnancy). Additionally, providing a treatment option for patients with high-risk HPV and/or low-grade lesions, rather than just an expectant management by follow-up, helps to reduce the anxiety that an HPV diagnosis may generate in patients.

The evidence available so far[4,5] has shown that Papilocare® is effective in both clearing high-risk HPV infections and in clearing low-grade cervical lesions, and therefore, we should keep this treatment in mind as an adjuvant treatment.

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Co-adjuvant Treatment with Papilocare® Vaginal Gel for High-grade Cervical Lesions

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Summary

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

Keywords: Human papillomavirus (HPV); Genital lesions; Cervical Cancer; Conization; Colposcopy.

MEDICAL HISTORY

A 26-year-old woman, ex-smoker without any other toxic habit, with no medical or surgical history of interest except for hypothyroidism under treatment with Eutirox® 25 µg. As gynaeco-obstetric history she was nulligestive, eumenorrheic and not vaccinated against HPV. She uses condoms as a contraceptive method.

Diagnosed during cytology screening in primary care with low-grade squamous intraepithelial lesion (LSIL). Due to this, she was referred to the general gynaecology clinic.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

At the general gynaecology consultation, a general and gynaecological physical examination was performed, in addition to obtaining a full patient medical history. The patient reported being asymptomatic.

The examination revealed eutrophic external genitalia and vagina, with normal discharge and a well epithelialized cervix with no obvious macroscopic lesions.

Given the finding of LSIL in a 26-year-old woman, a referral was made for consultation to the cervical pathology clinic. The cytological study was completed with a colposcopy, which was found to be adequate. A lesion was observed at 12 hours, occupying 25% of the cervix in the upper outer quadrant. The lesion was classified as the dense staining of the rapidly appearing acetowhite epithelium. Two directed biopsies were performed, the pathological findings of which reported a high-grade squamous epithelial lesion (HSIL/CIN 2-3).

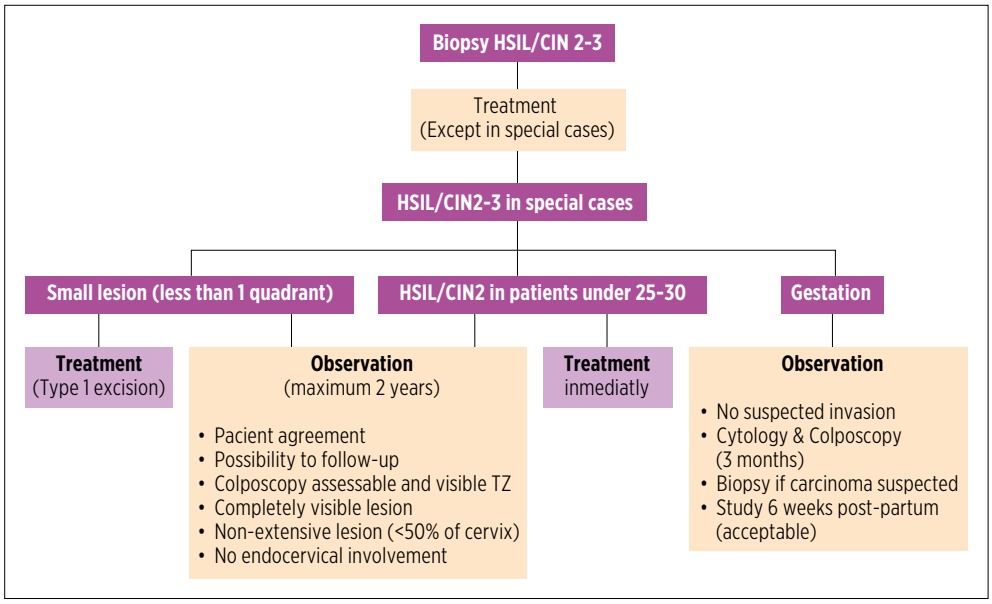


FIGURE 1. Diagram showing the decision sequence after a HSIL/CIN2-3 result in an informative biopsy, complete algorithm elaborated by the Spanish Society of Cervical Pathology and Colposcopy.

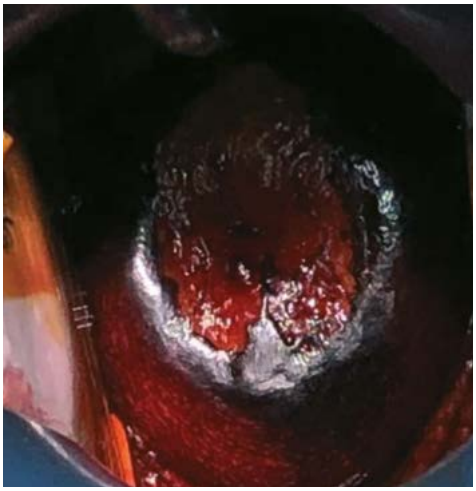
Based on the recommendations of the Spanish Society of Cervical Pathology and Colposcopy, we opted for immediate excisional treatment [Figure 1].

TREATMENT AND EVOLUTION

Fifteen days after obtaining the anatomopathological report from the colposcopy, a conisation was performed with a Lletz diathermic loop guided by iodine staining [Figure 2].

After an infiltration of paracervical anesthesia with 10 cc of Mepivacaine in 4 different points, the application of iodine revealed an iodine-negative zone at 12 h, and a subsequent colonization was performed with a diathermy loop [Figures 3 & 4], obtaining a cone that was sent for anatomopathological study. Finally, the bleeding surgical bed 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 1 application daily for 21 days.

FIGURE 2. Macroscopic vision of the cervix previously to the initial conization.



FIGURES 3 & 4. Iodine staining application, also known as Schiller test, before the conization (A), slight magnification from a different angle (B).

FINAL DIAGNO

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its precursor lesions, including vulvar, vaginal, penile and anal cancer, oropharynx carcinoma, anogenital warts and recurrent respiratory papillomatosis.

HPV causes warts and malignancies in both men and women, although the total burden of HPV-related cancers in men is about one-third of that in women. While warts are the most common clinical symptom, neoplasms are the most serious manifestation. The percentages of cancers caused by HPV vary according to the anatomical site, thus virtually 100% of cervical cancers, 90-93% of cancers in the anal canal, 12-63% of oropharyngeal cancers, 36-40% of penile cancers, 40-64% of vaginal cancers, and 40-51% of vulvar cancers are attributable to Papillomavirus infection. Cervical cancer is the most important HPV-associated outcome, but the incidence of other cancers, including anal, oropharyngeal, vulvar, and skin cancers 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 frequent malignant disease in the female population, and if we consider health disparities, cervical cancer is the third most common cause of death for women in underdeveloped countries[3]). Current figures report that 527,624 women are diagnosed with cervical cancer each year, and 265,672 die from the disease[3,4].

Regarding cervical cancer screening, cytology has been the standard method of secondary prevention. Since its introduction, wide coverage has significantly reduced cervical cancer mortality. Subsequently, advances in knowledge of virus carcinogenesis led to the emergence of HPV testing as a more sensitive method of screening. However, given the high prevalence of the virus in the population, HPV testing has a high number of false positives, which has a significant impact on the physical and mental health of patients, given the subsequent overdiagnosis and overtreatment. For this reason, new cervical cancer screening strategies are currently being developed based on molecular markers of the virus and of the patients' genome[4].

However, the best available method of prevention is prophylactic HPV vaccination, which should be targeted at females aged 10-14 years, before the onset of sexual activity[5]. Since its introduction into the market in 2006, the different HPV vaccines have been successful in reducing the prevalence of anogenital warts and high-grade cervical lesions caused by HPV of genotypes included in the vaccine, and also with cross-protection to other genotypes not included[4,5].

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

Occasionally, patients may be able to complement excisional treatment with a topical treatment to help eliminate the virus and the lesions caused by it. To this end, the efficacy of Papilocare®, a vaginal Gel based on *Coriolus versicolor* extract, has been evaluated on low- and high-grade HPV-related cervical lesions[8,9]. In 2021, a multicentre trial was developed in 91 HPV-positive women with low-grade changes. The results concluded that treatment with Papilocare® is safe and effective in the treatment of low-grade cervical lesions as well as in eliminating the virus[8]. In the same year, Criscuolo et al. carried out a retrospective observational study to evaluate the efficacy and safety of the gel in women with high-risk HPV carriers. The results showed a negative HPV test in 67% of treated patients compared to 37.2% of

the controls, leading the authors to conclude the efficacy and safety of this treatment based on the evidence examined[9].

It can be concluded, based on the reviewed literature and this clinical case report, that early management in specialised consultations is fundamental in the treatment of HPV lesions. Current knowledge of the viral aetiopathogenesis and carcinogenic potential is an improvement in terms of diagnosis and treatment of processes where the virus is involved. As a result, currently available treatments such as Papilocare® Vaginal Gel, which has shown a beneficial effect, can be beneficial as an adjunctive treatment in high-grade cervical lesions.

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Human Papillomavirus Clearance & Disappearance of Recurrent Condyloma after using *Coriolus versicolor*-based Vaginal Gel in a Patient Previously Conizised due to a Grade 3 Cervical Dysplasia

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Summary

Human Papillomavirus (HPV) infection persistence in patients after excisional treatment has a high risk of non-clearance or recurrence of the lesion.

A *Coriolus versicolor*-based gel have shown to improve viral clearance rates, improve the cure rate and reduce the risk of recurrence in patients with persistent HPV infection, becoming a possible tool to use as an adjuvant treatment.

Keywords: Human papillomavirus; ASCH; *Coriolus versicolor*; Condyloma.

MEDICAL HISTORY

Here we presented the clinical case of a 42-year-old woman referred to the cervical pathology department after a triple smear cytology in the context of cervical cancer screening with a result of ASCH.

Her medical history includes intolerance to metamizole, and arterial hypertension treated with 5 mg enalapril daily. The patient had no previous surgeries and reported smoking 5 cigarettes a day for 20 years. The patient's gynaeco-obstetric history includes menarche at the age of 14 and a history of 2 previous vaginal deliveries and a first trimester abortion. Her cycles were regular, and she did not use contraception as she currently has a stable partner with a vasectomy. Her first sexual intercourse was at 15 years of age and the number of sexual partners in her life has been 3. She is unvaccinated for HPV. The last cytological control she had undergone was during her last pregnancy, 8 years ago, with negative results.

PHYSICAL EXAMINATION, COMPLEMENTARY TESTS AND DIFFERENTIAL DIAGNOSIS

After completing the anamnesis, a colposcopic examination was performed. Macroscopically, the following were observed: eutrophic external genitalia, and at the level of the internal gluteal

FIGURE 1. Condyloma in the gluteal region

FIGURE 2. Colposcopy image with iodine staining, an iodine negative lesion can be seen in the anterior lip.

surface a verrucous formation, centimetric, compatible with condyloma [Figure 1]. The patient reported having undergone local topical treatments with liquid nitrogen, podophyllotoxin and imiquimod, with recurrence of lesions months after the end of treatment. On colposcopic examination and after the application of acetic acid and iodine, we observed a satisfactory colposcopy, with a type 1 transformation zone. A dense, iodine-negative, acetowhite, lesion was seen affecting 50% of the upper cervical lip. There was a zone of minor changes with fine stippling at 10 o'clock [Figure 2]. A directed biopsy was performed resulting in a grade 3 cervical dysplasia. A biopsy was also performed for molecular detection of HPV, with a negative result for subtypes 16 and 18 and positive for other high-risk subtypes (31, 33, 35, 39, 45, 45, 51, 52, 56, 58, 59, 66, 68).

TREATMENT AND EVOLUTION

After evaluation of these results, the patient was informed of the indication for cervical conization. Under local anaesthesia, the procedure was performed with a loop diathermy without complications. A definitive anatomopathological analysis of the specimen was found to be grade 3 cervical dysplasia, with the resection margins free of lesions. In addition to the local excision procedure, the patient was instructed to stop smoking and recommended to undergo HPV vaccination.

At the first control with co-testing 6 months after the conization, the cytology was reported as negative, while the patient was still positive for high-risk HPV. A new colposcopy was therefore indicated, in which no alteration or lesion suggestive of biopsy was visualised [Figure 3]. At that time, it was decided to initiate treatment with *Coriolus versicolor* gel daily for 21 days and then every other day for 6 months. At the next check-up a year after the ablasive technique, the patient tested negative for HPV and had a normal cytology. Additionally, external genitalia and gluteal region did not show any condylomatosis lesions. An appointment was made for a new co-test one year later, with negative results. Therefore, it was decided to discharge the patient from the Cervical Pathology Unit, indicating the inclusion in the cervical screening protocol for at least 25 years.

FIGURE 3. Cervix without any lesion or alterations suggestive of biopsy.

DISCUSSION

The diagnosis of squamous cell atypia (ASCH), which impedes the ruling out of high-grades lesions accounts for 0.29% (0.24% HPV-associated and 0.05% HPV-negative) of all Pap cytology smears, which accounts for less than 10% of all cytology smears with atypi[a](1). This result represents a higher risk of CIN 2 than ASCUS or LSIL cytology and lower than HSIL cytology. The risk of CIN 2-3 in these patients varies depending on the presence or absence of HPV infection. Thus, among HPV positive patients, the risk ranges from 26-50%, while in HPV-negative patients the risk is 3.4%. In this sense, the risk of cervical cancer follows a similar pattern, being 0.92% in the presence of infection compared to 0.69% in the absence of infection[2].

Among these patients, HPV positivity is very prevalent, affecting as many as up to 90% of women with ASCH. The combination of such a cytological result with HPV infection presents a cumulative risk of CIN 2 at 5 years of 52%. For CIN 3 the risk would be 28% and for cervical cancer 1.6%.

Therefore, the current recommendation, with a moderate level of evidence, is to refer patients with ASCH to a Cervical Pathology Unit for colposcopic examination. If this assessment shows a type 1 transformation zone and the presence of a lesion, as in this clinical case, the indication is to perform a guided biopsy[3].

Patients with fulfilled gestational desire and a biopsy compatible with CIN 3, should undergo excisional treatment. In a high percentage of cases this eliminates the lesion and the HPV infection. Thus, 70% of patients are HPV-negative in the first 6-12 months after conisation. The persistence of a positive HPV test at the first post-treatment check-up is the main predictor of lesion persistence. In case of HPV positivity at the first post-treatment check-up, as in our case, the risk of lesion persistence/recurrence is 91%. Therefore, a new colposcopy was indicated[2].

In this profile of patient with HPV infection, studies have been published evaluating the use of gels with *Coriolus versicolor*.

The PALOMA study analysed the results of employing the *Coriolus versicolor*-based vaginal gel in patients with low-grade alterations. The study found that a higher rate of HPV clearance was observed among those who had treatment for 6 months (59.6%), compared to those who did not receive treatment (41.9%). This difference is accentuated if high-risk subtypes are assessed, finding HPV clearance rates of 62.5% after the use of the gel compared to 40% without treatment[4].

In this regard, Criscuolo et al. show results of high-risk virus negativization in 67% of patients in treatment group compared to 37% of those in the control group. Similar differences were observed for colposcopic (76.1% vs. 40.8%) and cytological findings (78.5% vs. 37.7%), with 78.5% of the patients treated with the *Coriolus versicolor*-based gel achieving cytological remission[5].

Therefore, if these studies support a better rate of viral clearance in patients with persistent infection, which as mentioned above, worsens the prognosis, and is directly related to the recurrence of lesions, the use of *Coriolus versicolor*-based gels could be

considered as an adjuvant treatment, as it could improve clearance and healing rates. Randomised clinical studies are needed to assess this effect.

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HPV Associated Lesions and Co-Existence with other Sexually Transmitted Infections in a Patient Younger than 30 years old

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Summary

With this clinical case it is highlighted the importance of HPV as the world's most common sexually transmitted infection (STI) and its association with other STIs.

Although, low-grade cervical lesions in patients under 30 years of age are usually transient and resolve within about 1 year essential, screenings are an essential part of the medical strategy.

Keywords: HPV; Low-grade lesions; LSIL; Sexually transmitted infections; Trichomoniasis.

MEDICAL HISTORY

- Family history: no onco-gynecological history of interest.
- Personal history: no known drug allergies, no toxic habits, no diseases, mammoplasty. Correctly vaccinated, including HPV in adolescence.
- Gynaeco-obstetric history: M10 Menstrual Formula Irregular. G0. Family Planning Method (FPM): barrier (started 3 months ago), previously oral hormonal contraception (OHC). Cervical cancer screening: yes, cytology 1 year ago, normal. Stable couple for several years.
- Reason for consultation: 27-year-old patient, attends for an annual gynaecological check-up. She mentioned a micturition syndrome with recurrent dysuria and vulvovaginitis for several months (last episode a week ago). Amenorrhoeic episode since leaving OHC, with negative pregnancy test.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Normal weight. Normal external genitalia with 2 known stable nevi located in the lower third of the right labium vulvae. Slightly erythematous vagina, macroscopically healthy cervix, with non-specific leucorrhoea, yellowish, not malodorous. Bimanual touch non-painful.

TV Ultrasound: normal uterus, triple lined endometrium, para-uterine zones without abnormal findings, both ovaries normal, with functional image in left ovary, no free fluid in Douglas.

A sample is taken for cytology (triple sampling).

DIFERENTIAL DIAGNOSIS

- Genitourinary syndromes: recurrent lower urinary tract infection, interstitial cystitis, non-infectious cystitis, urethritis.

TABLE 1. Differential diagnosis in Vulvovaginitis

Type of vulvovaginitis	Mytotic vulvovaginitis	Bacterial vaginosis	*Trichomonas* vulvovaginitis
Aetiological agent	*Candida albicans*	*Gardnerella vaginalis*	*Trichomona vaginalis*
STI	No Associated Factors	No Associated Factors	Yes
Clinical manifestation	Itching, irritation, erythema, dispareunia	Malodorous leucorrhoea	Pruritus, itching, disuria, malodorous lecorrhoea
Leucorrhoea appearance	White	White-grayish dense	Yellow-greenish foamy
Vaginal pH	4-4.5	> 4.5	5-6
Microscopy	Hyphae ("bamboo canes")	Clue cells or key cells ("enembryonic")	Ovoid protozoan with flagella
Diagnosis	Culture	Gram stain Amsel's criteria	NAAT/PCR Culture
Treatment	Vaginal Clotrimazole 500 mg Oral Fluconazole 150 mg for 3 days	Metronidazole 500 mg every 12 h 7 days Vaginal Clindamycin 100 mg for 3 days	Oral Metronidazole 2g single dose
Main feature	"Cottage cheese-like" discharge	"Fishy odour"	Strawberry cervix

- Vulvovaginal syndromes: contact dermatitis, mycotic vulvovaginitis, vaginosis, trichomoniasis or other causal agents of STI with symptomatic clinical affectation at this level.

TREATMENT AND EVOLUTION

Pending cytology results and microbiological assessment, local symptomatic treatment is prescribed with intimate gel and soothing cream.

Cytological result: ASCUS. *Trichomonas vaginalis*. A co-testing is recommended after treatment for the STI.

The result is reported, and a STI screening is requested. The patient is informed about the possibility of concomitant STIs, a verbal request for HIV serology is done, and an assessment of her partner by a specialist in dermatology and venereology is indicated.

Aetiological antibiotic treatment is established with metronidazole 2 g oral single dose, for her and her partner. Abstinence from alcohol during treatment and from sexual intercourse for a week after treatment, as well as a 3-month follow-up is indicated.

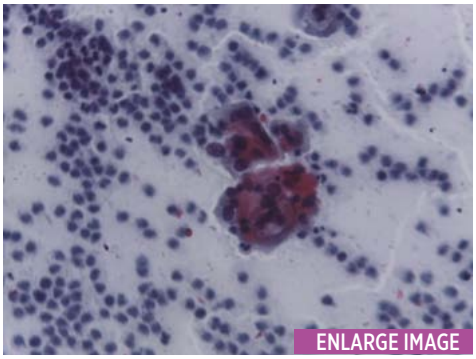

FIGURE 1. ASCUS *(courtesy of Dr. Ramos Guillén)*.

At the 3-month follow-up, the patient is asymptomatic (no micturition symptoms or further episodes of vulvovaginitis), her partner was treated by a dermatologist for another STI that she cannot specify. The serologies of both performed at 2 months have been negative for other STIs. She continues to use condoms as her preferred contraceptive method, despite having restarted ACHo. A co-test was

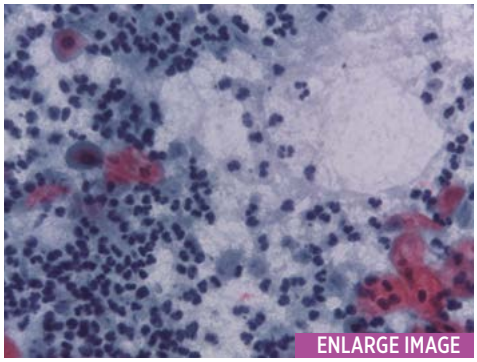

FIGURE 2. *Trichomonas vaginalis* found in the cytology test *(courtesy of Dr. Ramos Guillén)*.

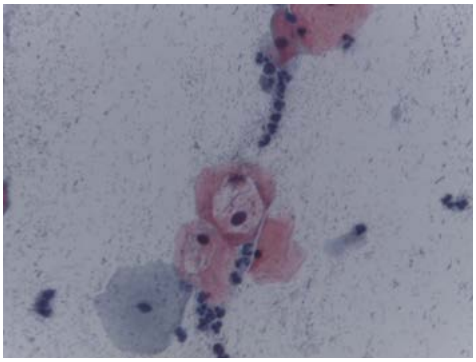

FIGURE 3. LSIL cytology *(courtesy of Dr. Ramos Guillén).*

performed after finding a normal genital examination, non-specific non-foaming leucorrhoea, with no alterations in odour, colour or texture. Cervix does not present macroscopic alterations compatible with Trichomoniasis (not "strawberry cervix").

Co-test result: LSIL, cytology with normal microbiological evaluation, HR HPV not 16/18.

The results and actions to be taken are explain to the patient: A new co-test in 1 year and depending on the results, possible colposcopy. For 6 months we recommend local treatment with a *Coriolus versicolor*-based Vaginal Gel 3 weeks daily for the first month, then resting for 1 week during the period and every other day for the following 5 months. The patient acknowledges the follow-up and the conservative treatment, and is informed that this type of lesion does not require surgical treatment but rather a follow-up in a specific unit.

At the one-year control co-test, the patient suffers atypical parakeratosis, LSIL and HR HPV not 16/18. Treatment with the *Coriolus versicolor*-based vaginal for 6 months following the same posology is indicated once again plus an appointment for colposcopy.

The patient went abroad and did not follow-up. After 6 months she returns to the consultation. She claims to have undergone the proposed local treatment. Asymptomatic. She continues with the same partner and uses condoms as method to prevent STIs as well as pregnancy prevention (no longer using Hormonal Anticeptives). Gynaecological examination and ultrasound scan without findings of interest. Gynaecological examination and ultrasound scan without findings of interest.

The colposcopy is performed according to IFCPC 2011 Rio de Janeiro after signing the informed consent form: colposcopy was adequate colposcopy, Type 1 TZ, no acetic changes, Schiller lugol test negative in the entire TZ (non-specific change). No biopsies taken, but new cytology and endocervical study reported as negative. A follow-up appointment is scheduled in 1 year.

FINAL DIAGNOSIS

Cytological LSIL concomitant with other STIs in patient under 30 years of age.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HPV is the most common sexually transmitted infection in the world, and as other STI (ex. trichomoniasis) can act as a co-factor for the development of other STIs, including HIV infection.

Trichomoniasis is caused by the anaerobic protozoan parasite *Trichomonas vaginalis* and is the most common non-viral STI. It is associated with HPV infections and cytological abnormalities and may even act as a facilitator for HIV infection and other STIs. It is characterised by micturition with dysuria, and vulvovaginal symptoms with pruritus, and some characteristic signs such as foamy, foul-smelling leucorrhoea and "strawberry cervix" (due to cervical capillary dilatation and punctiform haemorrhages

which gives the characteristic appearance), as well as being visualised at colposcopy following application of iodine staining with a homogeneous and widespread mottling throughout over the entire cervical area. It is diagnosed by molecular testing or culture preferably. However, it can also be visualised by microscopy or cytological analysis. It is treated with imidazole (oral metronidazole or tinidazole) and the treatment must also be prescribed to the partner to reduce complications and sequels in the mid or long-term.

In patients under 30-year-old, low-grade HPV-associated lesions are mostly caused by transient HPV infections (that do not persist over time beyond 12-24 months). They can sometimes recur and are not amenable to more active or interventional therapeutic strategy, as they usually do not progress to more severe lesions.

The inherent immunity of young patients, as well as acquired immunity through primary and/or secondary prevention with the HPV vaccine, avoidance or cessation of smoking and local treatment with therapies such as *Coriolus versicolor* are essential to accelerate the resolution or promote non-progression of HPV-associated lesions.

On the other hand, in day-to-day clinical practice, patients increasingly demand some treatment to help to negativize or decrease HPV viral load, and these products such as a *Coriolus versicolor*-based vaginal gel can be a valuable tool for a conservative management in the case of low-grade lesions.

The importance of a good, oriented anamnesis is fundamental to establish a diagnosis of suspected STIs, so the **"5 P's"** rule might be useful in this context: clinical anamnesis about sexual habits in the Inferior Genital Tract Pathology Unit: 1) Number of sexual **P**artners in the last few months, 2) What method of STI **P**rotection if used, 3) Existence of **P**revious STIs, 4) Type of sexual **P**ractices, 5) Method of **P**reventing Pregnancy.

Condoms remain the best strategy along with information, dissemination, education, and promotion of sexual health to fight against STIs.

Identification of groups at risk of STIs, correct anamnesis and detailed physical examination will facilitate the treatment of the patient (and the partner if necessary). Employment of a mono-dose treatment if possible, as well as ruling out other STI and subsequent follow ups are key factors to avoid future sequels and health complications that can affect the reproductive and sexual life of patients.

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Combined use of Papilocare® Vaginal Gel, External Genital Gel and Immunocaps: A Case Report

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Summary

A 32-year-old patient with LSIL and vulvo-perineal condyloma acuminata treated with green tea extract cream and imiquimod 5% cream without achieving complete remission. Finally, the lesions were treated with laser and co-adjuvant treatment with Papilocare® External Gel and Papilocare® Immunocaps®, achieving remission of the warts. Papilocare® Vaginal Gel was also used and cervical HPV infection was cleared after 6 months.

Keywords: LSIL; Condyloma acuminata; HPV; Laser; Papilocare®.

MEDICAL HISTORY

A 32-year-old female patient is referred to the Cervical Pathology Unit from Primary Care for a LSIL cytology result with HPV+ types 35 (HR) and 6 (LR) and for several vulvoperineal warts that have been treated with green tea leaf extract cream without response to treatment.

The patient is nulliparous, has no regular partner and uses condoms, although not in all relations. She smokes 6 cigarettes a day.

PHYSICAL EXAMINATION AND COMPLIMENTARY TESTS

Several condyloma acuminata (CA) are observed on the vulva, perineum and perianal region.

The colposcopy study is adequate, with a type 1 TZ (visible) and faint acetowhite epithelium in the anterior quadrant of geographical outline and slow onset and rapid disappearance, suggestive of minor change.

A serological study was requested, which was negative, and an anal co-test was performed resulting in LSIL cytology and positive for HR-HPV serotype 35, the patient was referred for a proctology consultation.

TREATMENT AND EVOLUTION

Treatment is started with Imiquimod 5% cream and after 6 weeks only a partial resolution of the condyloma acuminata is achieved, so it was decided to apply CO_2 laser vaporisation to the condylomatous lesions using Papilocare® external gel as a co-adjuvant. Regular use of condoms, smoking cessation, and Gardasil® nonavalent vaccine is recommended.

One month after this treatment, we confirmed that all the condyloma acuminata had been eliminated and that they had not recurred.

Additionally, we also recommend the use of Papilocare® Vaginal Gel for 21 days following with 7 days of rest in the first month and on alternate days with 7 days off every month for the following 5 months.

After 6 months, we called the patient in for a consultation who informed us that the condyloma acuminata had not recurred. A co-test was performed, which was negative, and a colposcopy, which was normal.

FINAL DIAGNOSIS

- Vulvoperineal condyloma acuminata with resolved with CO_2 laser vaporisation and co-adjuvant treatment with Papilocare® External Genital Gel.
- LSIL with clearance of HPV viral infection using Papilocare® Vaginal Gel and Immunocaps.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The impact of human papillomavirus (HPV) and cervical lesions is very important in today's society. Cervical cancer is a rare and preventable complication of a very common infection.

HPV infection is the most common STD in the world, with cervical cancer being the second most common cancer in women worldwide. More than 150 HPV subtypes are known, of which 40-50 can cause genital lesions. These viruses are classified into 2 groups: viruses with a low risk of developing cervical cancer (LR-HPV) and high-risk viruses (HR-HPV). The latter include genotypes 16, 18 and 31, which are the most directly related to persistence and cervical cancer.

In women under 30 years of age, there is a high prevalence of HPV and a high rate of HPV clearance. Nonetheless, the clearance of HR-HPV at 6 months and 18 months is 29% and 41% respectively, with clearance of HPV 16 being only 9% at 6 months and 19% at 18 months, much lower than for the other genotypes, which is consistent with the malignant potential of this genotype.

HPV infection is a necessary but not sufficient condition in the development of disease. The genotype responsible for the infection is not the only factor relevant in the course of disease, as other factors such as host immunity, the histological structure of the exo-cervix and the state of the vaginal transformation zone and vaginal microbiota also play an important role in the progression or regression of the infection.

Papilocare® Vaginal Gel is made up of ingredients that can have a favourable effect on these modifiable factors: improving epithelialisation of the cervix to make it more difficult for the virus to enter, improving the vaginal microbiota to move it towards a less favourable state for viral persistence, and creating conditions to boost natural immunity, responsible for viral clearance and lesion repair.

Lesion repair and viral clearance rates at 6 months in patients infected with HR-HPV, in addition to the reduction in stress levels and in the degree of treatment tolerability and satisfaction with the treatment, open the possibility of offering a treatment to HPV+ patients with low-risk cervical lesions (ASCUS and LSIL) as opposed to the classic "wait and see" approach.

Papilocare® External Genital Gel is an adjunctive treatment for external condyloma acuminata caused by HPV. It has an intensive moisturising formula that improves skin barrier function. It contains botanical extracts with repairing and antioxidant action. Its prebiotic and lactic acid balances the microbiota of the intimate area. The Aloe vera gives it moisturising, epithelializing and repairing properties for the external genital area. It is indicated for moisturising and repairing the genital mucous membranes when it needs special care, after certain medical-surgical treatments (e.g. laser treatment for the treatment of genital warts caused by HPV).

Papilocare® Inmunocaps is a dietary food supplement formulated with natural

ingredients such as Reishi extract, which is an immunopotentiator of the immune response and can be used as an adjuvant for the rapid clearance of HPV and normalization of HPV lesions. It has several benefits: it promotes the multiplication of healthy bacteria already present in the body, promotes normal function of the immune system and the protection of cells from oxidative stress, supports the process of cell division, contributes to normal macronutrients and to the normal function of the nervous system.

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Adjuvant Treatment with Papilocare® Vaginal Gel for HR-HPV Clearance

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Clínica SEPTEM

Summary
Human papillomavirus (HPV) is the most common sexually transmitted infection in the world. HPV is classified into low-risk viruses, responsible for the development of genital warts, and high-risk viruses, capable of developing precancerous lesions or cancer precursors of vulvar, vaginal, cervical, and anal cancer.
Approximately 8 out of 10 sexually active women have been in contact with HPV. However, more than 80% of these lesions resolve spontaneously within a few years after infection. Nonetheless, in about 10-15% of cases, HPV infection can persist over time without the body's defences being able to eliminate it. In the case of persistent infection, HPV can cause lesions which, over time, can eventually develop into cancer.
The cervix is the genital area most at risk for persistent HPV infection and therefore most at risk of developing cancer.

Keywords: HPV; HSIL; Conization.

MEDICAL HISTORY AND ANAMNESIS

A 41-year-old patient, non-smoker. Primiparous. Preferred contraceptive method: the pill.

Consultation for a second opinion, brings cytology showing cytological alterations compatible with ASCUS.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

EGO: GE without lesions, vagina epithelium of trophic characteristics without lesions, cervix with micropapillary trophic epithelium without lesions, cervix with macropapillary ectopia, periorificial bleeding easy to the touch. CCV and HPV genotype.

TV ECHO: uterus in AVF, normal shape and size, SML. 5.8 mm, adnexa normal, Douglas free. Ex. Breast: s/p.

The patient is indicated to undergo vaccination with Gardasil® 9, and apply Papilocare® Vaginal Gel, one vaginal application per night for 21 nights. Additionally, the patient is also advised condom use, discontinuation of the pill, in addition to hygienic-dietary advice.

CCV: Trophic smear. Atypical squamous cells suggestive of intraepithelial lesion (ASCH).

HPV (+) 33 AR.

Colposcopy III: periorificial micropapillary ectopia, type 1 TZ with extensive dense acetowhite area. A biopsy is taken at 11 A 3 and cauterized with Silver Nitrate. The material was sent to Pathological Anatomy resulting in HSIL/CIN 2.

DIAGNOSIS

HSIL.

TREATMENT

A conisation of the cervix is planned. Anatomical Pathology of conisation specimen: HSIL/CIN 2. Chronic cervicitis, resection margins intact. CSF: no lesions

EVOLUTION

Evolutionary control 6 months after the intervention CCV: normal and HPV (-).

The patient was given the three doses of Gardasil® 9 and Papilocare® Vaginal Gel every other day, completing the indicated dosage of 6 months of application.

Subsequent follow-up visits were normal.

DISCUSSION OF THE CASE

Complementing surgical treatment for a high-grade cervical lesion/ HR-HPV (+) with Papilocare® Vaginal Gel on the recommended 6-month regimen, seems to me to be an excellent therapeutic strategy, as it forms a protective film on the cervix which improves the elasticity and healing of the epithelium (re-epithelialization), hindering the viral cycle. It also balances the vaginal microbiota because it contains prebiotics favouring beneficial bacteria growth and reduces harmful bacteria proliferation, which prevents viral persistence.

Often the virus goes unnoticed by the immune system and Papilocare® Vaginal Gel boots the natural immune response. 63% of women with high-risk HPV are free of the virus within 6 months, as demonstrated by the clinical case above.

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Coriolus versicolor-based External Genital Gel in the treatment of VaIN Associated with Persistent HPV Infection after Surgical Treatment for Cervical Cancer: A Case Report

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Summary

The clinical case presents a 49-year-old patient, with a clinical history of cervical carcinoma, who was diagnosed with a high-grade intraepithelial lesion at the vaginal level (VaIN) associated with HPV genotype 53. The lesion is treated with an extended excisional biopsy, plus treatment with Papilocare® Vaginal Gel, a *Coriolus versicolor*-based gel for 6 months, to boost HPV clearance. After treatment completion, HPV remission was achieved, although the VaIN was not completely cured. The prognosis significantly improved with the elimination of the virus.

Keywords: Human papilomavirus (HPV); VaIN; Papilocare® Vaginal Gel.

INTRODUCTION

Human papillomavirus (HPV) infection is the most frequently sexually transmitted disease in developed countries[1]. Although the incidence depends on geographic location, it is estimated that 80% of sexually active women will have contact with HPV at some point in their lives[2]. Infection with high-risk human papillomavirus (HR-HPV) genotypes has been linked to malignant precursor lesions at the cervical, uterine, vaginal and vulvar level, due to their high oncogenic potential which is also dependent on other individual factors such as age or patient's immune system status, between others. Given the fact that there are no available therapies nowadays that can achieve a direct viral elimination, all measures that support the immune system to clear the virus could have a potential interest.

Recently, the usage of *Coriolus versicolor* in oncology has begun given its direct toxicity over cancerous cells and its possible immunomodulatory effects. Given these facts, new applications for the aforementioned fungi can be considered to treat pre-cancerous lesions in the feminine genital tract, by potentiating HPV clearance due to its modulatory effects[3,4].

MEDICAL HISTORY AND ANAMNESIS

A 49-year-old woman, secundiparous with a personal history of squamous cell carcinoma of the cervix at 37 years old due to infection by HPV 16 and 18, treated with radical hysterectomy and lymphadenectomy, pelvic radiotherapy, brachytherapy and chemotherapy. Erratic post-procedure check-ups due to the patient's failure to keep her appointments.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

During a follow-up consultation a cytology of the vaginal vault was performed, resulting in high-grade squamous intraepithelial lesion (HSIL) associated with HPV genotype 53 infection. After that, the patient attended the cervical pathology clinic for a vaginoscopy, where an approximately 0.5 cm acetowhite positive, lugol negative lesion was found on the anterior face of the vaginal vault (at 11 o'clock in the lithotomy position), which also showed atypical vascularisation. Considering the vaginal lesion, the main differential diagnose that was stablished was the possibility of being changes associated with the brachytherapy and radiotherapy received by the patient in the past. Cytology with a diagnosis of HSIL ruled out these possibilities, establishing the suspicion of VaIN (high-grade intraepithelial lesion at the vaginal level).

A biopsy of the lesion was performed for histological study which revealed fragments of subepithelial chorion with fibrous chronic inflammation, in addition to a few detached epithelial fragments with cytological atypia and atrophy

TREATMENT AND EVOLUTION

Given these findings, despite the apparent lack of malignancy in the biopsy, the previous cytological results did not completely rule out a VaIN. As a consequence, a wider excisional biopsy of the lesion was performed under local anaesthesia. After the procedure, Papilocare® External Gel was used to accelerate the clearance of HPV 53, preventing the development of lesions that could be malignant precursors.

After completing a 6-month treatment regimen, following the recommended posology found in the data sheet, the patient came to a consultation for a medical check-up and cytology. During the vaginal examination we could not find lesions and the cytology resulted in LSIL in the absence of HPV.

FINAL DIAGNOSIS

Following the therapeutic biopsy of the lesion on the vaginal mucosa and application of Papilocare® Vaginal Gel, remission of HPV was achieved. However, the intraepithelial lesion was not completely cured. Nonetheless, the prognosis was markedly improved after viral clearance.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HPV infection is behind of 90% of VaIN cases. It is estimated that 30% of patients diagnosed with VaIN were previously treated for cervical cancer[5].

This clinical case shows a patient with a medical history of cervical cancer that was previously treated by hysterectomy, infected with HPV with a potentially malignant vaginal lesion (VaIN). The interest of this case is that its management is not clearly described in the malignant gynaecological pathology guidelines[5]. Therefore, the treatment must be individualised, using effective tools for similar conditions with a compassionate use in these atypical cases. The application of a *Coriolus versicolor*-based vaginal gel, after excision of the lesion, could help to prevent lesion's recurrence and aid in HPV clearance. However, further studies are needed to confirm the effectiveness of this approach in these types of patients. Based on a limited experience, it can be said that the use of Papilocare® Vaginal Gel to achieve HPV clearance was successful in this case.

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Post-Conization Residual CIN 3 in a Primigestive Woman: Conservative Management with Papilocare® Vaginal Gel

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Summary

Women with HSIL/CIN 3 biopsy have a high probability of developing cervical cancer (CC) of 12-31% as opposed to CIN 2 which has a variable progression, dependent on other risk factors and is 0.4%. Treatment of CIN 3 and a CIN 2 subgroup has shown a decrease in cervical cancer progression and is therefore currently considered as the most effective treatment for cervical cancer as the first therapeutic option in these cases. However, although CIN 3 has lower regression rates than CIN 2, this regression is not impossible. So, in young patients a conservative management can be taken, as long as it is aligned with the recommended criteria and under strict cyto-colposcopic control.

The main reason to follow up HSIL/CIN 2-3 lesions is to avoid overtreatment of lesions with a potential for regression and to avoid the obstetric morbidity associated with such treatments[1].

Keywords: Residual CIN 3; Post-conization; Positive Margins.

MEDICAL HISTORY AND ANAMNESIS

25-year-old woman, E 0-0-2-0.

Began sexual relations at the age of 15, smoker and user of oral contraceptives.

She was referred in 2019 to the Cervical Pathology Unit of our hospital for a HSIL.

COLPOSCOPIC EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The colposcopy shows an area covering the two anterior quadrants with coarse mosaic and fine stippling. Multiple biopsies showed CIN 3. The differential diagnosis was CIN 2.

TREATMENT AND EVOLUTION

A diathermic loop conization is performed under local anaesthesia in 2 fragments.

The anatomopathological analysis of the extracted cone showed CIN 2 with non-assessable margins. Due to the COVID-19 situation, the patient in did not attend consultations during the pandemic and returns 2 years after the conization. The Papanicolaou smear showed HSIL.

A colposcopy was performed showing a type 2 CSU, with an anterior and posterior AB lesion with coarse mosaic and gross stippling on both lips. Biopsies were taken confirming a CIN 3 lesion.

Given the patients profile a controlled watchful approach is decided, micronutrients and Papilocare® Vaginal Gel were prescribed and after 4 months, lesion regression is observed which is confirmed by biopsies showing alterations compatible with CIN 1. Hence, the next follow-up consultation is scheduled in 6 months.

DISCUSSION

In this clinical case, given the patient's youth, the fact that she is nuligest and the possibility to control the lesion's evolution by colposcopy[2], a strict wait-and-see approach was taken. This was combined with treatments to stimulate the local and systemic immunity which had a good response in a < 30-year-old women with reproductive desire.

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Resolution of Low-Grade Lesions and Clearance of Persistent HR-HPV Infection using a *Coriolus versicolor* Vaginal Gel

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Summary

Here are present three different clinical cases of patients aged 41–45-year-old, who attend the clinic for infection with HR HPV for one year. All three patients had cytological findings of low-grade lesion (LSIL) and persistence of HR HPV. They were treated with Papilocare® Vaginal Gel based on *Coriolus versicolor* and a foam wash for 6 months. At the six-month check-up, all three cytologies were negative for malignant lesions; however, all three remained positive for the same HPV genotypes, so treatment was extended for another 6 months. At the end of 12 months, all three patients were able to clear HR HPV.

Keywords: High Risk Human Papillomavirus (HR-HPV); Low-Grade Lesion (LSIL); *Coriolus versicolor*-based Vaginal Gel.

INTRODUCTION

Human papillomavirus (HPV) is a large family of viruses that can affect skin and mucous membranes of both women and men. HPV infection is very common and results in a wide variety of clinical conditions ranging from benign lesions (warts or condylomas), pre-cancerous lesions and some types of cancer such as cervical, anal, vaginal, vulvar, penile and oropharyngeal cancers[1].

Although HPV infection can be asymptomatic and not cause any lesions, different types of clinical approaches can be used accordingly to the types of alterations caused by HPV.

Patients with low-grade lesions (LSIL) or HPV-positive patients without lesions can be closely monitored to prevent the development of high-grade lesions (HSIL). To contribute to LSIL resolution and viral clearance, there are currently different systemic and local treatments available that can be used as adjuvants.

MEDICAL HISTORY AND ANAMNESIS

Here, the clinical cases of three patients between the ages of 41-45 are presented. All of them with at least one euthecological delivery, without known drug allergies or intolerances, and are asymptomatic. All three are ex-smokers for at least one year and all of them took combined oral contraceptives for less than 10 years (all of them have not used them for at least three years or more).

ENLARGE IMAGE

FIGURE 1 .

They attend the lower genital tract medical check-up for HR-HPV infection (all of them with at least one HR-HPV genotype other than 16 or 18) known for approximately one year. In this medical check-up, cytology, HPV testing and colposcopy were performed. All three patients have received at least three doses of the HPV nonavalent vaccine (Gardasil®) and all continue to avoid smoking and the use of combined oral contraceptives.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

esults from colposcopies were adequate and satisfactory, with two of them showing no atypia. One of the colposcopies showed minor changes with a faint acetowhite periorificial epithelium, which was more prominent at 6 o'clock [Figure 1]. This area was biopsied and found to be negative for cervical lesion. However, HPV tests were persistently positive for the same HR-HPV genotypes found one year earlier. In addition, the Pap smears showed a low-grade lesion (LSIL).

TREATMENT AND EVOLUTION

In all these three cases, a treatment with *Coriolus versicolor*-based vaginal gel and foam wash was prescribed and the patients were appointed for a consultation in 6-months' time[2–5]. The posology with the *Coriolus versicolor*-based vaginal gel for these 6 months was 1 application daily (preferably at night) for 21 days, with a 10-day break, and then 1 application every other day for the remaining 5 months (resting on during the menstruation days). The foam wash was used daily.

At the six-month check-up, a new colposcopy, and cytology were performed. HPV testing was also performed at patients' requests. The colposcopies from all three patients were adequate and satisfactory, without atypia. Including the patient that in the previous consultation had a minor epithelial acetowhite change at 11 h. All three cytologies resulted negative, showing no lesion. However, the HPV tests were still positive for the same genotypes found in the initial consultation for all three patients.

Hence, the patients accepted the recommendation of maintaining the treatment with Papilocare® Vaginal Gel for another 6 months using the vaginal gel every other day plus the external foam wash every day.

After this extension, all three patients came back for a follow-up check-up. As in the previous consultations, colposcopies and cytologies were negative, but importantly all three HPV tests resulted negative in this occasion.

FINAL DIAGNOSIS

Resolution of low-grade lesion (LSIL) on cytology after 6 months of treatment with *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal Gel) and external foam wash as well as resolution of minor colposcopic changes found by colposcopy in one of the patients).

HR-HPV clearance (genotypes other than 16 and 18) after 12 months of treatment with *Coriolus versicolor*-based vaginal gel and foam wash.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The current posology associated with the *Coriolus versicolor*-based vaginal gel is 6 months. Nevertheless, when it was applied for 12 months in our three cases, it resulted in the clearance of the

HR-HPV infections which had been persistent for more than a year in all cases.

It is worth noting that after 6 months of treatment with the *Coriolus versicolor*-based vaginal gel, we achieved the resolution of a minor changes in the colposcopy of one of the cases and the and regression of low-grade lesions (LSIL) on cytology in all three cases.

It should be noted that none of the patients changed partner during our follow-up. This could open an option for the use of the *Coriolus versicolor*-based gel for more than 6 months in individual cases.

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High Grade Lesion with Persistent HPV Infection. Importance of the Restoration of the Immune System and the Vaginal Microbiota in the Clearance of HPV after 2 Excisional Treatments

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Summary

In this clinical case we describe a patient with persistent HPV infection with HSIL who underwent two surgical treatments. Subsequently, a treatment with Papilocare® Vaginal Gel was prescribed. With this case, we aim to evaluate the effects of the local therapy with Papilocare® Vaginal Gel on cervical epithelialization and vaginal microbiota in patients with persistent HPV infection and HSIL, instead of applying the product just for the recommended use in low-grade cervical lesions (LSIL). Its evolution and resolution are described in this clinical case.

Keywords: HPV; HSIL; Conization; CIN.

MEDICAL HISTORY

36-year-old patient. No RAMc, no FRCV. No chronic treatments.

Anatomopathological exploration: recurrent urinary tract infections and pyelonephritis.

Surgical Interventions: laparoscopic myomectomy.

No toxic habits.

Ob/GYN History: hemorrhagic follicles, surgery for symptomatic intramural myoma (10 cm).

Menarche at the age of 13. Date of last Period: 07/10/18. OF: G1A1. MF: 28/6. Age of first sexual encounter: 19. Number of sexual partners: 6. Does not use barrier-methods.

Treatment with Hormonal Contraceptives: for 7 years. Not currently taking them.

Vaccinated against HPV with Gardasil® 9 (2 doses). Carrier for genotypes 16, 31, 33, 58, 66 (April 2018).

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient attended the cervical pathology consultation on July 19th 2018 referred from another hospital after conization (on 18th April 2018), with a post-surgical diagnosis of HSIL (CIN 2-3) with an affected margin at 6 hours. The result of the cervical biopsy which indicated the conization was as follows: "Mild and moderate focal dysplasia (CIN 1-2) with marked coilocytic atypia on chronic endo-cervicitis with immature squamous metaplasia, contacting resection margins". After the first conisation, a re-conization was performed on June 21st, 2018, as the resection margins were again found to be affected.

She attended for a post re-conization follow-up. The patient reports no gynaecological symptoms after the operation.

Speculoscopy was performed and showed a macroscopically healthy cervix, with expected post-surgical changes. A new evolutionary control is scheduled with CCV and HPV in 6 months without treatment.

DIFFERENTIAL DIAGNOSIS

High-grade cervical lesions, HSIL (CIN 2-3). The diagnosis established by the hospital that referred the case to our unit is assumed.

TREATMENT AND EVOLUTION

1st Post Re-Conization Visit (October 10th, 2018)

Vaccinated with nonvalent Gardasil® (2 doses).

A colposcopy is performed which is unsatisfactory, due to the presence of an endocervical polyp, abundant leucorrhea, and a nonvisible transformation zone. It is noted that the conization ring has been large.

Vaginal exudate is extracted, a cytology was taken as well as HPV testing. A polypectomy by devolvement was performed and sent for pathological analysis.

- Cytology (October 26, 2018): ASCUS (squamous atypia of uncertain significance). Marked inflammation with signs of repair and parakeratosis suggestive of being caused by HPV.
- HPV test (October 31, 2018): DNA/RNA of genotypes 16, 31 and 66 is detected.
- Vaginal exudate (October 22, 2018): Trichomonas vaginalis is not observed. Vulvo-vaginal flora.
- Polyp biopsy (October 24, 2018): endocervical polyp with ulceration of epithelium and intense acute and chronic lymphoplasmacytic inflammatory infiltrates. Stroma with abundant vascularisation.

In view of the findings, a new medical check-up with cytology and HPV testing is scheduled in 6 months. Blastoestimulina® and Papilocare® Vaginal Gel are prescribed.

2nd Post Re-Conization Visit (April 3rd, 2019)

She has completed the treatment with Papilocare®. Fully vaccinated with nonvalent vaccine.

In routine gynecological check-up an asymptomatic intramural myoma of 42x48 mm is observed. Patient put on wait list for treatment with radiofrequency.

A colposcopy is performed which results satisfactory, with expected post-surgical changes and a type 1 transformation zone.

A cytology and HPV testing is performed.

- Cytology (April 4th, 2019): squamous metaplasia with lesion compatible with low grade dysplasia (LSIL).
- HPV test (April 15th, 2019): DNA/RNA of genotypes 16, 31, and 66 is detected.

Treatment with Papilocare® is re-started and follow up with colposcopy is scheduled in one month's time.

2nd Post- Conization Visit (biopsy) (April 30th, 2019)

She has completed the treatment with Papilocare®. Fully vaccinated with nonvalent vaccine.

Colposcopy and biopsy are performed at 12 h in the anterior lip and at 5 h in the posterior lip, these being the most suggestive areas of abnormal macroscopic findings. In the 5 h zone, it appears to be a condyloma.

- Biopsy cervix posterior lip 5h (3/05/2019): Histological appearance compatible with condyloma acuminatum. No dysplasia.
- Biopsy cervix anterior lip 12H (3/05/2019): Exocervical mucosa with epithelial hyperplasia with no evidence of dysplasia. No coilocytic changes (P16-).

It was decided to continue treatment with Papilocare®. Given these results the patient is appointed for a new check-up in 6 months' time.

3rd Post-Conization Visit (October 31st, 2019)

Treatment with Papilocare® is continued. Nonvalent vaccination is complete.

Transvaginal ultrasound scan shows 2 asymptomatic intramural myomas, 17 mm and 28 mm in size. Colposcopy was satisfactory, with normal squamous epithelium in the ectocervix and a type 1 transformation zone. Cytology and HPV testing are performed.

- Cytology (28/11/2019): negative for malignant cells. Metaplasia, parakeratosis, and small LSIL affected areas. Signs of HPV infection.
- HPV test (8/11/2019): a HPV-16 and HPV-18. detects high-risk genotypes other than 16 and 18.

Therefore, it is decided to continue treatment with Papilocare®. Follow-up is scheduled in 6 months' time.

4th Post Conization Visit (May 26th, 2020)

Continued treatment with Papilocare®. Nonvalent vaccination is complete.

A colposcopy is performed which results satisfactory with normal squamous epithelium in the ectocervix and a type 1 transformation zone. Cytology and HPV testing are performed.

- Cytology (27/05/2020): negative for malignant cells. Metaplasia, parakeratosis, and small LSIL affected areas. Signs of HPV infection.
- HPV test (29/05/2020): DNA/RNA of HPV genotypes are not detectable.

Treatment with Papilocare® is continued. A new control is scheduled in 6 months' time.

5th Post Conization Visit (November 4th, 2020)

Continued treatment with Papilocare®. Nonvalent vaccination is complete.

A colposcopy is performed which results satisfactory with normal squamous epithelium in the ectocervix and a type 1 transformation zone. Cytology and HPV testing are performed.

- Cytology (6/11/2020): negative for malignant cells. Inflammation and reactive atypia. No signs of HPV infection.
- HPV test (6/11/2020): DNA/RNA of HPV genotypes are not detectable.

Papilocare® treatment is concluded. The patient is scheduled for a checkup in 12 months' time.

6th Post Conization Visit (November 9th, 2021)

No treatment.

Yearly check-up after cytological normalization and HPV clearance.

The patient has had a birth via caesarean (failed induction with prolonged pregnancy) on July 19th, 2021.

A colposcopy is performed which results satisfactory with normal squamous epithelium in the ectocervix and a type 1 transformation zone. Cytology and HPV testing are performed.

- Cytology (11/11/2021): negative for malignant cells. Morphologic appearance with absence of atypia, mild inflammation, and repair. No signs of HPV infection.
- HPV test (18/11/2021): DNA/RNA of HPV genotypes are not detectable.

The patient is discharged from the cervical pathology consultation unit. She is currently undergoing annual follow-up with cytology for at least 20 years.

FINAL DIAGNOSIS

High-grade epithelial dysplasia (HSIL, CIN 2-3) that resolves after local surgical treatment and immunotherapy plus treatment with Papilocare® Vaginal Gel.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, affecting up to 90% of the sexually active population. The persistence of HPV is closely related to the development of squamous intraepithelial lesions (SIL) in the cervix, which defines the importance of eradicating the infection when preventing or treating lesions caused by HPV. Factors that determine the persistence of infection include the integrity of the cervicovaginal mucosa, the immune system, and the local microbiota[1]. The presence of high-risk HPV types (HR HPV) is associated with the development of high-grade cervical intraepithelial lesions (HSIL).

The natural course of HSIL depends on a multitude of viral, clinical, and immunological factors. The recovery of the "natural barriers" is essential for the cure of the disease, so that adequate vaginal and cervical trophism is indispensable for re-epithelialization of lesions caused by infection[2].

Local immunity is crucial in the pathogenesis and progression of the disease, either towards regression or progression of cervical dysplasia. The immune microenvironment favouring HSIL is characterised absence of intraepithelial infiltrates of CD3+, CD4+, CD4+, CD8+ T cells and Langerhans cells compared to normal epithelium and by an increased number of CD25+FoxP3+ regulatory T cells (Tregs) and CD163+ M2 macrophages. Therefore, a 'hot' immune microenvironment with low numbers of Tregs, CD8+ intraepithelial CD8+ intraepithelial T lymphocytes and a high

proportion of CD8+ T lymphocytes and CD4+/CD25+ T-lymphocytes appears to be essential for the regression of HSIL[3].

Closely related to the immune system, the vaginal microbiota plays an important role modulating feminine' immune system genital tract. *Lactobacillus crispatus* and *Lactobacillus rhamosus*, among other lactobacilli, appear to dominate the vaginal flora of most healthy women[4,5]. Scientific evidence supports that dysregulation of the vaginal microbiota favours HPV persistence and, affecting balance of the vaginal microbiota ensures a better response against HPV.

In this clinical case, the importance of correlating the results of cervicovaginal cytology with the clinical examination and specific cervical pathology tests is illustrated. Cervicovaginal cytology is a rapid, simple and reproducible test with a high sensitivity in the detection of HPV infection. However, it cannot be taken the gold-standard and must correlate with the results obtained from specific cervical pathology tests, such as HPV tests[6].

Initially, a conservative management was implemented with a 6 month treatment with Papilocare® Vaginal Gel, taking into account the Pap smear results. Considering the results of the initial cytology, the biopsy and the HPV test and following the current guidelines, a surgical excision was performed. After the intervention, the patient continued the treatment with Papilocare® Vaginal Gel. During the follow-up consultations, the patient had a successful outcome. The combination the conization with the Papilocare® Vaginal Gel treatment was successful normalising the HPV-lesions and clearing the papillomavirus virus, although more cases are needed to corroborate this association.

Clearance of different HPV serotypes with high oncogenic risk was achieved after 18 months of treatment with Papilocare® Vaginal Gel. Although the current guidelines recommend the excisional treatment, and the resolution of the HPV infection should be attributed to the conization, here we illustrate how Papilocare® Vaginal gel could be potentially used as a coadjutant treatment that can help to boost immune system and prevent from viral re-infection[7,8]. This clinical case provides new preliminary evidence about this coadjutant treatment that should be confirmed by new clinical studies that explore the utility of the treatment in this type of patients.

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Use of Papilocare® Vaginal Gel as a Treatment for Exocervical CIN 2 in a Patient Under 30

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CAE Arona-El Mojón

Summary

Treatment of CIN 2 and CIN 3 by local cervical excision has been shown to be effective. However, it is known that in women treated by cervical conization, there is an increased risk of preterm delivery.

Due to the high rates of regression of CIN 2 described in some studies, as well as the morbidity associated with excisional treatment, has led to the adoption of alternative conservative management strategies in young patients without fulfilled genetic desire.

Keywords: Papilocare®; CIN 2; Conization; Conservative Management .

MEDICAL HISTORY

A 26-year-old patient without any relevant medical or surgical history. Nuligest.

PHYSICAL EXAMINATION, COMPLEMENTARY TESTS AND DIFFERENTIAL DIAGNOSIS

The patient was referred to our cervical pathology clinic for ASCH cytology and HPV 33.

Physical examination revealed normal external genitalia, normal vagina, and a healthy cervix, with ectopia.

Colposcopy: adequate, type 1 TZ, well-defined thick mosaic area at 12 and 2 o'clock, compatible with G2 changes, totally visible, which do not appear to enter the canal.

TREATMENT AND EVOLUTION

Both exocervical lesions are biopsied and an endocervical curettage is performed. The anatomopathological analysis results of both lesions resulted in a diagnosis of CIN 2. The pathological analysis (PA) of the endocervical curettage was negative.

Given the age of the patient and the lesions' locations, a conservative treatment with Papilocare® vaginal gel was indicated for 6 months following the recommended posology instead of excisional treatment. The patient agreed to the suggested treatment.

After 3 months, a new colposcopy is performed which showed a clear improvement in the lesion,

although with persistency. The colposcopy was adequate, showing a type 1 TZ, fine mosaic at 12 and 2 o'clock, both lesions compatible with G1 changes.

6 months after treatment begun, no lesions were observed in a follow-up colposcopy. Cytology and HPV testing were performed, both resulting negative.

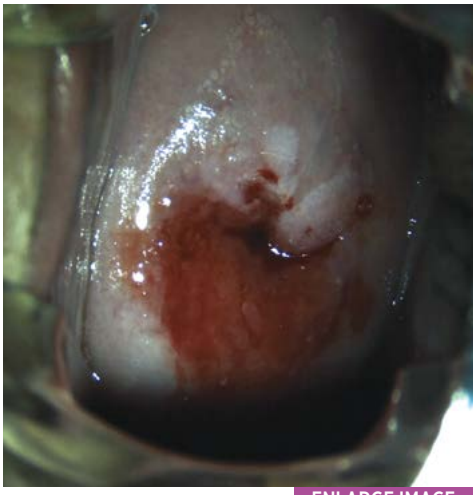
FINAL DIAGNOSIS

Use of Papilocare® Vaginal Gel as an alternative to excisional treatment in patients under 30 years old with a diagnosis of CIN 2, fully visible lesions, and the possibility of follow-up.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

With this clinical case, we can discuss the conservative management of exocervical HSIL/CIN 2 lesions in patients under 30 years old using Papilocare® Vaginal Gel as a treatment.

In our case we saw a clear improvement with only 3 months of treatment and a complete resolution after 6 months.



ENLARGE IMAGE

FIGURE 1 .

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Human Papillomavirus Infection. A Case Report

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Summary

Cervical cancer is the second most common cancer in women after breast cancer, with approximately 500,000 new cases per year worldwide, and it is the fifth most common of all cancers. Although previously the incidence was similar between countries, now-a-days it differs greatly, being a lot more frequent in less developed and poorer countries compared to more developed ones. This is mainly due to early diagnosis campaigns have played an essential role in reducing the incidence of this tumour in developed countries. Most cases are diagnosed before the age of 35.

In many developing countries, cervical cancer is the leading cause of cancer mortality among women, even ahead of breast cancer.

According to the AEPCC, about 2,100 new cases of cervical cancer are diagnosed each year in Spain, which represents 3.3% of female cancer.

Human papilloma virus (HPV), it is the most common sexually transmitted infection worldwide and is considered to be responsible for a very high percentage of cervical cancers.

Keywords: Human Papillomavirus (HPV); Cervical Cancer; Cytology.

MEDICAL HISTORY AND ANAMNESIS

22-year-old patient, no history of interest, no childbirths, no abortions, but a very active sexual life, and with frequent changes of partners.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Routine gynaecological examination

Cytology: Low-grade SIL HPV infection? Histological study of the cervix and HPV testing requested.

HPV-positive smear: 51, 66, 68, 82 high risk, low risk 62. Biopsy confirms LSIL.

TREATMENT AND EVOLUTION

Papilocare® Vaginal Gel 21 cannulas is prescribed for the first month.

Same treatment for the first 15 days of the following 3 months. Cytology and colposcopy control after treatment.

Cytology: negative for intraepithelial lesion and malignancy.

Colposcopy: limited ectopia OCE ZTT1.

Gynaecologic check-up in one year shows complete normalization of cytology and colposcopy results are like similar to those obtained one year ago.

The patient results positive for HPV serotypes 51 and 62. Giving the positive cytologic results obtained, rutinary gynaecological check-ups are decided. The patient declares that she maintains her previous sexual activity but is now using barrier methods, etc.

A new check-up on June 10th, 2020, the cytology results are indicative of HSIL. Given these results, a cervical conization is performed due to an anatomopathological diagnose of HSIL.

Since then, all the medical check-ups have been normal, and the patient remains negative to HPV.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

The patient had a very favourable response to treatment with Papilocare® Vaginal Gel, but her lifestyle and her relationships prevented the process from being successful; even with conization we have no guarantee that this will not happen again.

I have explained that we cannot afford a second conization due to her young age; for now, she seems to have taken the preventative measures seriously.

I have recommended the vaccine (Gardasil® 9) which she has already had (3 doses) as another form of prevention.

In this clinical case we can highlight the importance of gynaecological check-ups and the importance of cytology. Cytology, which forms part of the routine annual gynaecological check-up, can often alert us to a possible future cervical cancer, which allows us to take the necessary measures to prevent its evolution and harmful consequences.

FINAL DIAGNOSIS

Most high-risk HPV infections are asymptomatic and disappear spontaneously within 1-2 years and do not evolve to cancer. However, some HPV infections can persist for many years. Persistent infections with high-risk HPV serotypes can result in cellular changes that, if left untreated, can progress to cancer (NIH; National Cancer Institute).

HPV infections are the most common sexually transmitted infections in the United States. About 14 million new genital HPV infections occur each year. In fact, the Centers for Disease Control and Prevention (CDC) estimates that more than 90% and 80%, respectively, of sexually active men and women will be infected with at least one type of HPV at some time in their lives. Nearly half of these infections are from a high-risk type of HPV (NIH; National Cancer Institute).

Cervical Re-Permeabilization after Applying a *Coriolus versicolor*-based Vaginal Gel: A Case Report

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Summary

Here we present the clinical case of a 56-year-old patient who underwent cervical conization for HSIL and who, on follow-up, presented with an impassable cervical stenosis, with LSIL cytology and High Risk (HR) HPV serotypes 16 and 18.

Keywords: Conization; Cervical stenosis.

MEDICAL HISTORY

56-year-old patient. AP: morbid obesity (BMI:40.74). Ob/Gyn History: Menopause: at age 50. G3P3A0. Surgical history: Manchester operation in 1997 (cervical amputation), LTB, hysteroscopy, and polypectomy (hyperplastic polyp) in 2014. AE: Referred by the midwife for not being able to perform the cytology because she could not visualise the cervix correctly. Last cytology performed in 2017. Samples are taken for cytology and HR-HPV test with result of LSIL and positive for HR-HPV serotypes 16 and 18.

CLINICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient is referred to the Cervical Pathology Unit where the differential diagnosis between cervical and vaginal HSIL is established. A colposcopy was performed: adequate, type 3, with no pathological findings. Vaginoscopy: no pathological findings.

Following the AEPCC protocol[1], an endocervical sample was taken by endocervical curettage, with the result of HSIL.

TREATMENT AND EVOLUTION

Vaginal oestrogens were prescribed. Given that there were no factors for regression of the high-grade lesion[1], in April 2021 an excisional treatment was indicated by means of cervical conization with a diathermy loop. Due to the cervical stenosis present, endocervical curettage was not performed. AP of the cone: HSIL with glandular involvement in time zones 1 and 2. The lesion affects the endocervical and radial margin, with free exocervical margin. NOTE: from 3-12 hours only exocervical mucosa is observed, without representation of the endocervical epithelium transformation zone, so an insufficient excision was suspected. The case is discussed by the Cervical Pathology Unit, and due to the impossibility of an

adequate follow-up, the patients' age, and the AP findings of the cone, a total hysterectomy is decided.

Those patients who have undergone treatment for HSIL are considered as at risk of persistence/recurrence of the lesion and require adequate follow-up[2], which was not possible in this case. The patient appointment was delayed by 6 months because of difficulties of contacting her as well as COVID-19 situation. Therefore, she was re-scheduled for a new examination. Colposcopy (cervical stenosis, without visible pathological findings) and vaginoscopy (without pathological findings) were performed. The results of this visit were: LSIL, and HR-HPV positive for serotypes other than 16 or 18. HPV positivity 6 months after conization is the main predictor of lesion persistence-recurrence (with a risk of 91%, independent of other factors such being >50-years-old or affected margins). Sixty percent of patients with + margins have no lesion at subsequent follow-up, and it is not synonymous with residual lesion[3].

Total hysterectomy is proposed due to the impossibility of adequate follow-up, which the patient rejects due to the surgical risk of such an operation and her morbid obesity. The application of a *Coriolus versicolor*-based vaginal gel[4] was prescribed, with the following dosage: one application per day for one month, then every other day (resting one week per month during the period). Patient was also advised to improve the dietetic habits, to do exercise and was appointed in 4 months' time. A new colposcopy showed satisfactory results with a type 3 transformation zone (TZ), and lack of pathological findings. Hence, it was possible to perform cytology with endocervical sampling and endocervical curettage (not performed in the previous visit) "without any difficulty". The patient had only used Papilocare®. We are currently waiting for results.

FINAL DIAGNOSIS

Cervical stenosis after conization.

DISCUSSION AND DESCRIPTION OF THE SIGNIFICANCE OF THE CASE

Cervical stenosis after loop conization occurs in 4.3-7.7% of cases. Risk factors are the amount of tissue removed and postmenopausal status[5]. Various methods have been proposed to avoid this complication, such as the cervical device[6], or post-conization dilatations[7], but all of them having poor results.

Here we present a case in which a *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal Gel) was the only treatment administered to the patient after conization, which might contributed to the re-permeabilization of the cervix. The importance of the case lies in the fact that thanks to the permeabilization of the cervix it was possible to carry out an adequate study of the patient's cervical pathology, and therefore, a hysterectomy was not needed.

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Conservative Management of a High-Grade Cervical Lesion in a Young Patient

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Summary

A 32-year-old patient with previous history of low-grade cytological alterations (LSIL) and HPV persistency, comes for consultation due to grade 2 Cervical Intraepithelial Neoplasia (CIN 2). Due to patient's hesitancy to surgical treatment, excisional treatment is decided against, and a conservative management treated with a *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal gel) is prescribed instead. At the 6 months follow up consultation a cytology and PCR tests are performed, both testing negative.

Keywords: HPV; LSIL; *Coriolus versicolor*.

CLINICAL HISTORY

32-year-old patient with previous history of low-grade cytological alterations (LSIL) since 2017 and HPV persistency (not 16 nor 18). The patient comes for consultation due to a CIN 2 diagnosis in the endocervical channel made in a private centre.

PERSONAL HISTORY

- No known allergies.
- Tobacco smoker, about 7 cigarettes per day.
- No relevant medical history, no surgeries.
- Full HPV vaccination with Gardasil®.

OB/GYN HISTORY

- Menarche at age 14.
- TPAL: 0.0.0.0
- Date of Last Period: 7/10/2020
- MT: 2-3/28
- CM: Condoms

CERVICAL PATHOLOGY CHECK-UPS

HPV check-ups since 2016 due to LSIL. HPV+ (Not 16 nor 18).

- Cytology 06/20: LSIL
- Endocervical biopsy: CIN-1.
- Cervical biopsy: CIN-2.

PHYSICAL EXAMINATION

- External genitals are showing normal configuration without any signs of lesions.
- ESP: vagina and cervix showing normal macroscopic morphology.

COLPOSCOPY

Satisfactory colposcopy, with type 1 transformation zone. 2% acetic acid staining revealed a small-sized lesion with type 1 changes located at 1, with signs of penetration in the cervical channel, no type 2 changes are observed.

CASE ASSESSMENT

Given the colposcopy and biochemical results, an excisional surgical treatment is indicated. As the patient shows some reluctancy to the surgical treatment, a 6-month conservative treatment with a *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal gel) is prescribed. The patient is also advised to give up smoking.

During the 6 month follow up consultation a Co-test is performed resulting in negative for cytological alterations and negative for HPV PCR.

CONCLUSIONS

- The importance of reassessment of colposcopy in young women with low-grade lesions (LSIL/CIN1) due to high regression rate.
- In low grade lesions if correct controls are applied, conservative management of the HPV lesion can be done.
- Independently of the treatment, smoking cessation can favour the transformation zone renovation.
- Conservative treatment with a *Coriolus versicolor*-based vaginal gel (Papilocare® Vaginal gel) during at least a 6-month period could be an alternative for LSIL in young women.

Treatment of Cervical Condyloma with a *Coriolus versicolor*-based Vaginal Gel

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Summary

Condylomas are benign lesions caused by some types of human papillomavirus (HPV), the most common sexually transmitted infection in the world.

Keywords: Condyloma; HPV; Colposcopy.

MEDICAL HISTORY

26-year-old patient. Without any relevant medical background. AGO: G0P0A0.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient was referred for cervical pathology consultation due to a screening cytology result of LSIL+ HPV+ not 16 nor 18.

A satisfactory colposcopy was performed, ZT 1. Raised lesion with acetowhite epithelium. Lugol negative staining.

Lesion was biopsied and resulted in condyloma.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis made between condyloma lesion and grade 1 changes, suggestive of LSIL.

TREATMENT AND EVOLUTION

The patient is offered a topical treatment with the vaginal gel or CO_2 laser vaporization.

The patient chose the topical treatment, so the use of Papilocare® Vaginal gel is prescribed. After 6 months of treatment, a control colposcopy was performed, showing normalization of the LSIL lesion previously described.

FINAL DIAGNOSIS

In a young patient, as an alternative treatment to CO_2 vaporization of the condyloma, Papilocare® Vaginal gel is employed resulting in lesion resolution in 6 months' time.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

To consider the possibility of using Papilocare® Vaginal gel as an alternative to surgical treatment or CO_2 laser vaporisation in young patients (< 30-year-old) with low-grade LSIL lesions, condylomas, and even high-grade HSIL lesions that are fully visible and with the possibility of exhaustive follow-up.

ENLARGE IMAGE

FIGURE 1 .

ENLARGE IMAGE

FIGURE 2 .

In any case, more experience regarding the use of Papilocare® Vaginal gel and more studies covering this topic are needed.

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Adjuvant Treatment of CIN and VaIN with *Coriolus versicolor*-based Vaginal Gel

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Summary

The necessary agent of SIL/CIN and VaIN lesions is high-risk oncogenic HPV[1]. The following case report describes the outcomes of using a *Coriolus versicolor*-based vaginal gel as an adjuvant treatment in a patient with a history of multiple surgical treatments for SIL.

Keywords: SIL/CIN and VaIN; LLETZ; Vaporization; *Coriolus versicolor.*

MEDICAL HISTORY AND ANAMNESIS

44 year-old woman, under follow-up at the Lower Genital Tract Unit for persistent multicentric SIL lesions despite two LLETZ and a cervical vaporization with CO_2 for HSIL/CIN in 2007, 2009 and 2013, respectively; and a vaginal CO_2 vaporization by HSIL/VaIN in 2014. Ex-smoker, patient since 2018, nulliparous and under follow-up for endometriosis.

PHYSICAL EXAMINATION

The colposcopy findings from April 2013 to January 2015 are displayed in the figures below.

- Figure 1. Colposcopy/vaginoscopy in April 2013. Cervix with type 3 TZ. Major changes in cervix and posterior cul-de-sac, left lateral and anterior aspect of vagina. Previous cervical cytology: HSIL. Multiple cervical and vaginal biopsies with a diagnosis of HSIL/CIN and VaIN. Cervical and vaginal CO_2 vaporization is scheduled.
- Figures 2 & 3. Vaginoscopy in January 2014. Cul-de-sac disappeared. Major changes in the left lateral aspect vagina. Lugol´s negative coincident. Previous cervical cytology: ASCUS. HPV test (Cervista) positive.
  Vaginal biopsy with diagnosis of HSIL/VaIN. A new vaginal CO_2 vaporization is scheduled.
- Figure 4. Vaginoscopy in January 2015. No negative iodine lesions.

DIFFERENTIAL DIAGNOSIS

The main clinical suspicion was multicentric intraepithelial alterations secondary to persistent

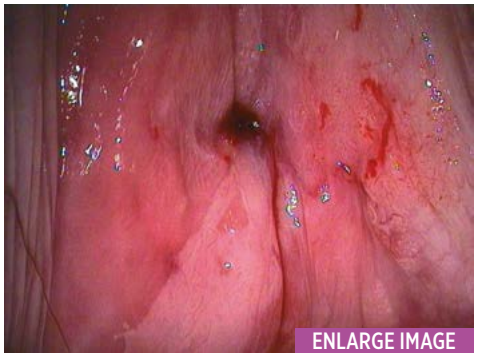
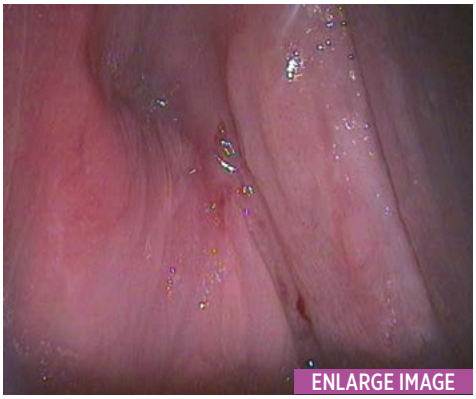


FIGURE 1. Colposcopy/vaginoscopy in April 2013.



FIGURES 2 & 3. Vaginoscopy in January 2014.

infection by an HPV with a high oncogenic potential. This suspicion should be confirmed by a biopsy guided by a high-resolution test[2].

Occasionally we may encounter condyloma areas that apparently simulate an HSIL lesion from the colposcopic point of view[3].

Finally, iodine-negative areas on vaginoscopy are frequent in women with vaginal atrophy or secondary to epithelial erosion due to manipulation of the speculum[4].

TREATMENT AND EVOLUTION

Follow-up with cervical cytology and colpo/vaginoscopy every 6 months, as well as annual HPV testing, following the AEPCC protocols[4].

After the surgical procedures and despite normalization of high-resolution tests, the patient presented results alternating between low-grade cytologic alterations and negative cytology while staying HPV positive (genotype 53) persistently throughout the September 2015 to November 2019 period.

In December 2019, an adjuvant treatment with a *Coriolus versicolor* based vaginal gel was prescribed for 6 months, following the posology on the technical data sheet. The co-test result after treatment was negative. Currently the patient has negative follow-up tests.

FINAL DIAGNOSIS

HSIL/CIN and VaIN, HPV 53. Treatment with LLETZ and multiple CO_2 laser vaporizations + adjuvant *Coriolus versicolor* based vaginal gel. Complete remission.

DISCUSSION AND DESCRIPTION OF THE IMPORTANCE OF THE CASE

HPV infection involves the entire anogenital area: it is a field infection. Although the cervix is the most frequently affected area, it can produce

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indicated in cases of cervical cytologic changes with normal colposcopy findings. This test is important in the follow-up of patients undergoing multiple therapeutic surgical procedures, as in the present case, when follow-up tests, HPV and cytology, remain altered[2].

LLETZ and CO_2 laser vaporization are both indicated techniques with proven efficacy for the removal and destruction of genital SILs[5].

In the case presented we had a patient with a persistent HPV-positive infection, which also alternated with low-grade altered cytology and without any HSIL lesions subsidiary to new surgical treatments.

Currently, there is limited evidence about medical treatments aimed at the elimination of HPV infection or normalization of cytologic LSIL alterations. We found promising results in the literature relating to the *Coriolus versicolor*-based vaginal gel for this purpose[6]. For this reason, we opted for the use of this compound as an adjuvant in the patient case, and a satisfactory result was obtained.

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