PAPILOCARE®

CLINICAL CASES

LESIONS CAUSED BY **HUMAN PAPILLOMAVIRUS**

CERVICAL PATHOLOGY EXPERTS COMMITTEE

Dr. F. Javier de Santiago García

Dr. Andrés Carlos López

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Dr. Javier Cortés Bordoy

FIRST PRIZE DR. EDUARDO VILAPLANA

Procare Health

Naturally woman

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SUMMARY

PRESENTATION

Last January we received the sad news that our friend, colleague and teacher Dr. Eduardo Vilaplana had passed away. All of us who had the pleasure to meet him know what a great loss this is for the world of Gynecology in general and Cervical Pathology in particular. Dr. Vilaplana was one of the best and most innovative specialists of our time, a pioneer in his work and in his line of research. His work, always focused on the care of women's health throughout his professional career, earned him the title of Honorary Member of the Spanish Society of Gynecology and Obstetrics (SEGO), of the Spanish Association of Cervical and Colposcopy and of the Mexican Association for UNESCO.

We, his followers, have wished to honor his memory and for this purpose we have developed the Dr. Eduardo Vilaplana clinical case program, which we present in this monograph. This program has collected the clinical experience of fellow gynecologists in the field of cervical pathology, showing their experience in the management of HPV-positive human papillomavirus patients. Here we show the 42 cases presented in the first edition, of which the Scientific Evaluation Committee (SEC) has selected nine finalists and one winner.

The ten best cases selected by the Evaluation Committee (ECC) - to whose members I am very grateful for their valuable work - have already been presented in two virtual workshops to expand the knowledge and experience among our colleagues, which can be viewed again by clicking here, and which will be published in a prestigious international scientific journal. In addition, Dr. Zuramis Estrada, winner of this first edition, will have the opportunity to present her clinical case as a speaker in the next congress of the Section of Oncological Gynecology and Breast Pathology of the SEGO, which she will attend with a registration grant included in the Dr. Eduardo Vilaplana award.

The members of the CCoE are delighted with the quality of all the clinical cases presented, evidence which has been really difficult for us to select.

Therefore, and with the invaluable and strong support of Procare Health, we have come to the decision to extend the program and the award to a second edition, which is currently open: new cases can be submitted by using the access link to the platform.

Thank you so much to everyone for the trust placed in this group and in this project. The memory and tribute to Eduardo Vilaplana deserve this and much more.

Dr. Javier Cortes Bordoy
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SUMMARY

SUMMARY

VULVAR CONDYLOMAS. NEW LOCAL SYNERGISTIC TREATMENTS

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ABSTRACT

Condyloma acuminata or genital warts are the clinical expression of infection from certain types of human papillomavirus (HPV) that are considered to have low oncogenic risk (No. 6 and No.11). They are currently considered one of the most commonly sexually transmitted diseases with incidence increasing among most populations[1].

The lesions present and extend in numerous forms (from very localized forms and limited disease to very extensive forms with multi-focal involvement of the anogenital tract).

Sometimes, the lack of a single effective treatment for all patients mean that we have to choose from the different available procedures (excisional, destructive, topical, etc.).

Let's not forget the high post-treatment relapse rate, as new lesions appear in treated or untreated areas[2].

Genital infection by HPV is one of the most common sexually transmitted infections. However, condyloma acuminata are not included in surveillance systems in most countries, so worldwide epidemiological data is limited.

According to systematic reviews, the incidence of new cases (among men and women) ranges between 118 and 205 per 100,000 inhabitants.

The highest incidence rate is observed from 20 to 24 years old for women, and 25 to 29 years old for men[2,3].

CLINICAL CASE

A 26-year-old patient visiting our office in CIMEG MADRID (Vithas La Milagrosa) in August 2020 due to presenting multiple vulvar condyloma lesions that had already been evaluated and treated in a dermatology center using local cryotherapy and sinecatechins (Veregen) ointment twice a day at home. The patient mentions experiencing intense stinging when applying the ointment, as well as continuous symptoms of local itching and discomfort, so in the absence of visual improvement, she decided to seek out another medical opinion.

- Ethnicity: Latin American.
- Personal disease history: no chronic diseases of interest.
- Smoker. Yes (3-5 cigarettes a day).
- First sexual relations: 16 years old.
- No. of sexual partners stated: 4
- Long-term sexual partner: not presently (but she had one until the lesions appeared).
- Pregnancies: No.
- Contraceptive method: No
- Family disease history: none of interest

PHYSICAL EXAMINATION

In the standard lithotomy position (for gynecology), a thorough vulvar examination was performed (vulvoscopy) using a colposcope and staining with acetic acid at 2% across the entire vulvar area in order to detect other smaller-sized lesions in the affected area. We observed

ZOOM IN

FIGURES 1 TO 3. 1) 1st laser session. 2) 2nd laser session. 3) 6th month.

protruding condylomas on an extensive plaque base, some of which were reddish and others with more pigmentation, almost brown (due to the evolution time and aforementioned treatment). Other smaller lesions approximately 1 mm in size were detected on the clitoris hood, the external zone of the lower lips, and the vaginal vestibule.

A vaginoscopy and colposcopy were also performed, ruling out the presence of condylomas (inside the vaginal channel and the cervix).

Perianal condylomas on the patient are ruled out, despite mentioning a lack of anal coitus and symptoms of anal itching or rectorrhagia.

The physical examination is the "gold standard" when diagnosing this disease.

Biopsies on the lesions is not standard procedure; they are only performed if the treatment response is not as expected, the lesions are suspicious, or the patient is a girl (due to suspected sexual aggression)[4].

There are dissimilar differential diagnoses for these lesions that we could mention. I found this clinical case very clear, as can be seen in the attached photos. However, I propose some pathologies or lesions that could cause confusion and should be differentiated.

DIFFERENTIAL DIAGNOSIS

Vestibular papillomatosis: finger-like proliferations of mucosa centered around a connective-vascular axis. They are located on the internal face of the lower lips, sometimes extending throughout the vestibule. Not HPV-related. It is a benign condition with no pathological correlation.

Fordyce spots: these are heterotopic sebaceous glands. They present in the form of white-yellowish pimple-like structures 1-3 mm in diameter, either isolated or grouped into plaques, mainly on lower lips and the internal face of upper lips.

Other infection-derived lesions:

Molluscum contagiosum: a viral lesion (poxvirus), specifically *Molluscum contagiosum* virus. It presents as pink or skin-colored pimple-like structures, with a smooth surface and with a characteristic central thread.

Malignant tumors: they should be suspected if there are any exophytic, hard, ulcerative lesions with fleshy borders and a bleeding surface.

TREATMENT

Prior to starting a treatment plan, a suitable explanation needs to be provided to ensure that the patient understands: the evolution of

the process, the purpose of the treatment, the potential adverse effects that may appear, and the healing and relapse percentages.

For this patient, we started the first session by using a laser on the vulvar region (with condylomas), type Er:YAG with a wavelength of 2940 nm.

This laser enables us to perform accurate ablation without heating the surrounding tissue. Water - the chromophore representing the main objective with skin treatments - absorbs Er:YAG energy very well, thus allowing skin vaporization with micrometer-guided precision and very little heat conduction[11].

We then prescribed a home co-adjuvant treatment for the region treated for condylomas to be administered for 42 nights (apart from during the period). The Papilocare® vulvar gel helps to re-epithelialize and hydrate that zone due to its composition:

- Hyaluronic acid niosome, providing hydration and elasticity.
- Antioxidant β-glucan niosome to maintain a suitable skin and mucosa structure.
- Healing and repairing *Centella asiatica* phytosomes.
- Bioecolia. Balances the genital region flora.
- Aloe vera: hydrates and re-epithelializes.
- *Coriolus versicolor:* re-epithelializes genital lesions.
- Neem extract: moisturizer, relieving itching and redness.

This gel does not contain parabens or scents, and has a pH of 5[10].

At the end of the 6th week (42 days), a second local vulvar laser session is performed, and vulvar gel co-adjuvant treatment is indicated again (21 nights each month) for a total of 6 months.

She is re-evaluated clinically after the 2nd session and 42 days of treatment, with fewer lesions observed and the patient asymptomatic.

We explain to the patient that the final evaluation would take place at the 6th month since the treatment protocol started.

She visits in March 2021 (6th month check-up) for evaluation: Another vulvoscopy with acetic acid to 2% was performed, as no lesions are observed macroscopically.

Vulvoscopy with no lesions.

We observed a complete lack of lesions and scars as shown in the photo.

The patient is currently asymptomatic, not on treatment, with healed lesions.

She is encouraged and recommended to do the following as part of her treatment:

- Give up smoking.
- Start HPV vaccination.
- Always use a barrier method.
- Visit for check-up at 12 months since starting the treatment.

HPV is the causal agent for condyloma acuminata. Genotypes 6 and 11 are responsible for 95% of condyloma acuminata. Other genotypes involved less often are: 8, 13, 30, 32, 42, 43, 44, 54, 55 and 70. Up to 20-30% of cases present co-infection by high-risk oncogenic types of HPV[4].

The incubation period ranges between 3 weeks and 8 months, and the average time for lesions to appear after infection is 2 months, making condyloma acuminata the first clinical marker of sub(acute) infection by HPV18[4].

Sexual contact is the main route of transmission. The main risk factors are the number of sexual partners and the early onset of sexual relationships. It is a very common disease among immunocompromised patients.

If left untreated, condyloma acuminata can resolve unaided, remain unchanged, or increase in number and/or size. Physiological immunosuppression states, such as pregnancy, favor condyloma progression[5-7].

There is no scientific evidence to show one treatment is clearly superior to another.

Treatment must always be personalized, as there isn't one that is more suitable for all patients and all types of condyloma acuminata.

Multiple variables need considering when choosing the most suitable treatment, such as:

the number and size of lesions, the area of the lesions, whether or not keratosis is present, the doctor or therapist's personal experience, the potential for treatment adherence, toxicity, side effects, prices, etc.[6-8]

For this clinical case, the combination or synergy of laser therapy with the locally administered vulvar Papilocare® gel turned out to be suitable for this patient with a satisfactory evolution, the complete elimination of lesions, and no relapses 6 months after treatment.

Vaccines containing viral genotypes 6 and 11 (tetravalent and nonavalent) are currently the most effective primary prevention method for condyloma acuminata, with efficaciousness highest when administered before the first sexual relationship[7,8].

The nature of the disease and the fact that it is linked to sexual transmission causes a major physical, emotional, and psychosexual impact among affected patients, so we should insist that the adolescent population is fully vaccinated.

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VAIN AFTER HYSTERECTOMY DUE TO CANCER 21 YEARS AGO

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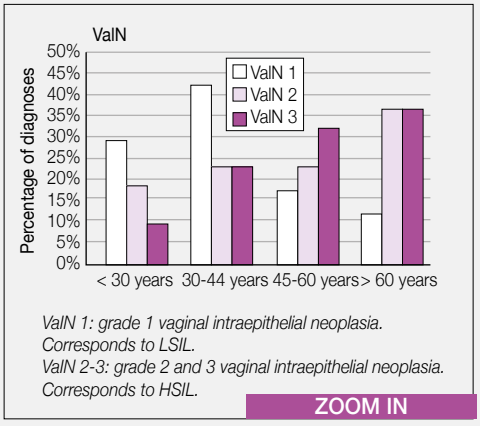
ABSTRACT

Vaginal intraepithelial neoplasia (VaIN) is a precursor legion for vaginal cancer. It is an uncommon and asymptomatic condition. Its diagnosis accounts for 0.4% of all premalignant lesions of the lower genital tract. VaIN lesions are classified based on the grade of involvement of epithelial maturation in high-grade intraepithelial lesions or HSIL (VaIN II or III) and low-grade intraepithelial lesions or LSIL (VaIN I)[1]. HSIL is considered the true precursor of vaginal cancer[2]. Vaginal cancer is a very uncommon neoplasia, accounting for 1-2 % of gynecological neoplasias[3]. Squamous cell vaginal carcinoma is the most common histological variant, accounting for 65-95% of all vaginal cancers[4,5]. Given the low prevalence of this neoplasia, there are few works in the literature from which to gain an in-depth knowledge of the disease's etiology and natural history.

A multicenter study in Spain on 5,665 women seen by 385 gynecologists, showed that VaIN accounts for 2% of all HPV[6] -associated lower genital tract diseases.

HPV infection is causally implicated in up to 90% of VaIN cases. This justifies that VaIN lesions are associated with multifocal lesions of the anogenital tract, such as cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), or anal intraepithelial neoplasia (AIN)[8].



VaIN 1: grade 1 vaginal intraepithelial neoplasia. Corresponds to LSIL.
VaIN 2-3: grade 2 and 3 vaginal intraepithelial neoplasia. Corresponds to HSIL.

ZOOM IN

Percentage of diagnoses of the different grades of VaIN according to the age of the patients (Taken from Cortés J et al. ref. nº 6).

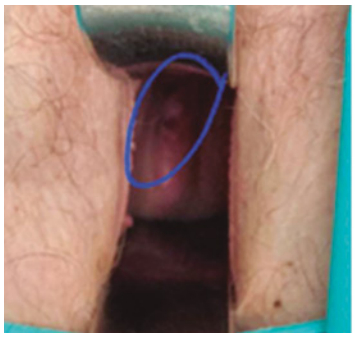
There is no evidence of which therapeutic approach is most suitable for all VaIN cases. However, excisional treatments such as colpectomy, used traditionally, present significant morbidity, so recent years have seen destructive treatments used more frequently, with fewer adverse effects and acceptable healing results.

Local treatments are currently being developed based on phytotherapy components, such as hyaluronic acid, aloe vera and *Coriolus versicolor,* in order to re-epithelialize the cervix and vaginal mucosa. Their integrity plays a key role in the form of the first epithelial barrier, which along with the balance of the vaginal microbiota, helps prevent HPV integration[8].

Treating patients with VaIN is a challenge for gynecologists due to low frequency, the difficulty of diagnosis, the limited knowledge of its natural history, and the lack of evidence and guidelines to support defined treatment and follow-up.

KEY WORDS: VaIN. HPV. Vaginal integrity. Screening. *Coriolus versicolor.*

SUMMARY



ZOOM IN

FIGURES 1 TO 3.

MEDICAL HISTORY

A 56-year-old woman, voluntarily visiting for check-up after being given the all clear by her hospital's oncology department a year ago. She also refers to experiencing a non-foul smelling yellowish discharge in recent weeks.

Regarding her personal history, in 2000 she had endometrial cancer that spread to the ovaries, i.e. stage IIIA, resulting in complete cytoreductive surgery, followed by chemotherapy treatment with cisplatin, carboplatin and paclitaxel, along with radiotherapy and brachytherapy. No HPV-induced disease described by anatomical pathology.

The patient is a regular smoker, of high socioeconomic status, and had two children via a normal birth. Menopause began iatrogenically at the age of 35 years old after surgery for cancer.

Her long-term partner died in 2019 and the patient has only had one new partner since 2020.

PHYSICAL EXAMINATION

On the first visit, the examination shows vaginal dryness, a hypotrophic vagina, which is in good condition after having received brachytherapy, the hood is suspended correctly without apparent macroscopic lesions. The bimanual exam did not palpate any tumors, the hood is loose, and no cysts were palpated. The transvaginal ultrasound does not show evidence of internal female sexual organs or masses or collections. A hood cytology is requested, along with a mammogram, densitometry, and a blood test with tumor markers. The cytology result indicates: H SIL, the rest of the tests are normal and in line with her age.

As soon as the cytology result was available, we met with the patient, discussed the H SIL finding, which was likely to be high-risk VaIN, and we performed a vaginoscopy with acetic acid at 5% and Lugol's solution, which showed an acetowhite, dense mosaic lesion on the right rectovaginal pouch (Fig. 1) and on the superior vaginal third at 2 o'clock (Fig. 2), on which biopsies were performed. Additionally, multiple vestibular papillomatosis is observed in the introitus (Fig. 3).

The differential diagnosis with other vaginal pathologies could be established by atrophy, post-radiotherapy changes, vaginal papillomatosis (which the patient has but is not HPV-related), lichen planus, vaginal adenosis or inflammation from a vaginal infection. However, lesions that appear after stains with acetic acid at 5% and Lugol's solution are a potent diagnostic tool for HPV-induced epithelial changes, so biopsies are performed on both lesions.

TREATMENT AND EVOLUTION

On the day of the vaginoscopy, the patient is explained hygienic measures, such as stopping smoking and using a condom, as well as being recommended that both she and her partner have a nonavalent HPV vaccine. Treatment is initiated

with re-epithelializing vaginal gel for the cervical transformation zone to prevent HPV-induced lesions. The gel contains natural moisturizers and *Coriolus versicolor.*

The biopsies report VIN 2, and the culture is HPV positive for the high-risk 16 variant.

Again, we spoke with the patient and agreed on excisional treatment. In the operating room, the vaginal lesions are resected with an electric scalpel, i.e. a partial colpectomy and excision of the proximal lesion, with extensive coagulation of the entire surgical site, sedation, and post-vaginoscopy, with the same previously described lesions observed macroscopically.

The patient requests that we do not inform her relatives of her diagnosis, as the precancerous disease represents a high emotional burden for her given her history, and the human papillomavirus-caused pathology being obtained via sexual transmission.

At the time of surgery, the patient informed us that she had initiated HPV vaccination, as well as the local treatment using vaginal gel with *Coriolus versicolor,* but was still smoking and not using a condom. She promised to carry out these recommendations at that time, along with continuing treatment.

FINAL DIAGNOSIS

The histological description of the surgical piece of the hood lesion is VaIN 3 with clear margins, and the most proximal lesion is VaIN 1 with an involved margin.

The next check-up will be at 6 months after surgery, using a co-test, with any action taken based on the result. Meanwhile the patient is being vaccinated and continues using the re-epithelializing vaginal gel with *Coriolus versicolor* for at least 6 months and in accordance with medical indication.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Several aspects are discussed with this case:

- The main aspect is to rethink the follow-up of patients that have had a hysterectomy and are sexually active, as there is a risk of HPV transmission with every sexual exposure, with the age range becoming more extended, due to a cultural shift in society's sexuality.
- Furthermore, it is worth noting that we currently have new local treatment options that can be an opportunity for treating HPV-induced cervico-vaginal pathology. This may be to help eliminate the virus among carrier patients without cervical pathology, help the re-epithelialization and subsequent repair of low grade lesions, help prevent HPV-induced disease progression over the period of time from diagnosis to excisional treatment for cases with high-grade lesions, and/or post-excisional treatment for the re-epithelialization of the involved margins and the surgical site. These new treatments are not as abrasive as other traditional treatments that involve a high rate of treatment abandonment due to local adverse effects or difficulty with their administration.
- When it comes to the importance of the patient eliminating the main risk factors to prevent the disease from progressing, like the patient attempting to stop smoking, as well as reducing exposure to HPV by using a condom, modifying these risk factors is more important in order to improve the patient's local immunity than all the established treatments for eliminating the virus' persistence and its viral load.
- Human papillomavirus-induced disease continues to be stigmatized, meaning doctors treating the pathology have to invest more effort into earning the patient's trust so that they follow the recommendations..

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ADJUVANT THERAPY FOR VIN USING EXTERNAL PAPILOCARE® GEL. A CASE STUDY

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ABSTRACT

Usual VIN is a precancerous lesion, which almost always involves oncogenic high-risk human papillomavirus (HR-HPV)1. As such, treating both the lesion and helping to eliminate the virus using a complementary treatment would be a good approach. This clinical case shows the example of using an adjuvant treatment on a patient with VIN lesions after receiving LASER vaporization treatment.

KEY WORDS: VIN. Vaporization. HPV. *Coriolus versicolor.*

MEDICAL HISTORY

This is a 45-year-old patient, who had 2 normal births, smokes 3 cigarettes/day, is not vaccinated against HPV, with no personal history of interest, who consults due to several itchy lesions on the external genitals that don't improve with topical corticosteroid use. She doesn't have a long-term partner at present and it's been 5 years since her last cervical screening.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Vulvoscopy. 2 heterogeneous plaque-like lesions with well-defined edges are observed, which protrude to some extent and are highlighted using acetic acid 5%, with erythematous and pigmented areas. Each one is approximately up to 3 centimeters in diameter and located on the internal face of the lower right lip and to the right and rear of the introitus (Fig. 1).

Given the lesions' characteristics and no recent screening, a biopsy was carried out on both lesions with a 4 mm punch, completing the study of the lower genital tract, with the following results:

- Cervical liquid-based cytology: Satisfactory, no malignancy.
- Cervical HR-HPV genotyping: Negative.
- Colposcopy: Type 2 transformation zone, typical re-epithelialization around the orifice that enters the canal, observed using maneuvers.
- Vaginoscopy: Normal with acetic acid and Lugol's solution.

The outcome of the 2 vulvar lesion biopsies was: Usual VIN, HPV 16.

Given this outcome and the higher frequency of extracervical lesions among immunosuppressed patients[2], the study was completed with a HIV serology study, which was negative.

DIFFERENTIAL DIAGNOSIS

According to the International Society for the Vulvovaginal Disease (ISSVD) clinical classification[3], a differential diagnosis is required with infectious disorders (vaginal yeast) or irritating inflammatory disorders such as dermatitis, but these don't tend to be so focal in nature with such defined edges, as well as having a more erosive and eczematous component.

There is also a need to differentiate from lichenification lesions (lichen planus, lichen sclerosus) or psoriasis, for which we can use a biopsy.

ZOOM IN

FIGURE 1. Lesions at the time of diagnosis

The finding of more than one lesion, along with her age, makes us decant for a usual VIN diagnosis for the lesion, which is more closely associated with HR-HPV.

TREATMENT AND EVOLUTION

Vaporization is performed on the lesions using a CO_2 LASER in continuous wave (CW) mode, using coloscopy vision and 30-watt scanner, which went as normal (Fig. 2).

The patient was then informed about the daily care regimen, consisting of frequently cleaning (2-3 times/day) the vaporized location using a gauze and saline solution, removing any fibrin buildup, before administering external Papilocare® gel.

The healing evolved favorably, with full epithelialization at 6 weeks. She is indicated to continue applying gel externally every day. A vulvoscopy is performed at 3 months with no signs of residual lesion (Fig. 3). She continues to apply the gel every two days until 6 months of treatment are completed.

Check-ups at 6 and 12 months completed the evaluation, when she remained disease-free.

Annual check-ups in the Lower Genital Tract Unit using vulvoscopy continue.

FINAL DIAGNOSIS

Usual VIN, HPV 16 treated with CO_2 LASER vaporization + adjuvant *Coriolus versicolor* gel. Complete remission.

ZOOM IN

FIGURE 2. Lesions undergoing healing at 2 weeks.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Papillomavirus infection is an infection that involves the entire anogenital area. Precancerous and cancerous lesions from this infection occur most often on the cervix, but they can occur in other locations, as in this clinical case.

Vulvar lesions usually present in young people with multiple foci and often as relapses,

FIGURE 3. Vulvoscopy at 3 months of treatment.

particularly with immunosuppression. The aesthetic repercussions of repeated treatments on this organ can significantly affect women psychologically.

Surgery or CO_2 LASER appear to be effective treatments at eliminating the lesion. However, it would also be desirable to act on the cause to reduce the incidence of relapses, i.e. HR-HPV infection, for which few effective treatments exist at present.

Mycotherapy has been known for many years, which includes *Coriolus versicolor,* a significant stimulant of immunity against several viral agents[4]. Recent studies are providing evidence for the effectiveness of *Coriolus versicolor* extract in aiding HPV elimination and normalizing cervical lesions[5,6].

Neem has also been evaluated as a treatment for eliminating HPV when applied inside the vagina, with a positive outcome[7].

Furthermore, aloe vera is known to have antiseptic and epithelializing properties. *Centella asiatica* and hyaluronic acid will prove an important complement for repairing and hydrating the vaporized mucosa, as will *Coriolus versicolor* itself[8].

Papilocare® gel contains all these components, and as such, despite requiring prospective studies with a suitable sample size, the adjuvant treatment of HPV-induced precancerous vulvar lesions with this product appears suitable, both in terms of helping to heal the lesions and probably stimulating HPV elimination from the genital mucosa.

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THE AESTHETIC OUTCOME OF APPLYING *CORIOLUS VERSICOLOR*-BASED GEL AS AN ADJUVANT FOR EPITHELIALIZATION AFTER SIMPLE VULVECTOMY FOR VIN

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ABSTRACT

Vulvar intraepithelial neoplasia (VIN) is a precursor lesion for vulvar squamous cell carcinoma, and is classified by VIN 1, 2 or 3 based on epithelial cell maturation changes. Clinically there are two types: usual VIN, condylomatous, HPV-related, and differentiated VIN, associated with dermatosis. It is an underdiagnosed condition, given that the lesions are asymptomatic in most cases, meaning patients don't request medical attention for it. It is caused by oncogenic high-risk HPV infection. Itching is the most common symptom, followed by pain or stinging. Recent years have seen the incidence rise, mainly among young women.

KEY WORDS: Vulvar intraepithelial neoplasia. Papillomavirus. Condyloma. Epithelialization

MEDICAL HISTORY AND ANAMNESIS

A 36-year-old patient visits, referred from Primary Care due to multiple condylomas.

She is a Romanian national and has lived in Spain for the last 10 years. Her history of interest includes being overweight and having active chronic Hepatitis B. She has given birth more than once and smokes 15 cigarettes a day. She has never had cytology screening before. She has had the same partner for 4 years.

She refers to the genital lesions appearing 6 years ago and didn't consider them important until now, given that they have become itchy and large.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

There is a large condyloma conglomerate on the upper third of the bottom lips and clitoral hood, which is hard and whitish in appearance. There is another confluent condyloma plaque at the frenulum and around the anus. There is also an erythematous de-epithelialized region around the right anal margin, approximately 4 cm in size. (Fig. 1).

Among the differential diagnoses with this examination, we could consider skin diseases of the vulva, such as psoriasis, seborrheic keratosis, or lichen sclerosus.

A biopsy was performed around the clitoris and the anus, with a VIN 3 result (high-grade vulvar intraepithelial neoplasia).

A co-test and colposcopy are performed, showing a faint acetowhite lesion on the anterior cervical lip at 12-1 o'clock, from which a biopsy is taken.

The co-test results: L-SIL cytology and positive for HPV 18 and 59. The cervical biopsy finding is CIN I.

TREATMENT AND EVOLUTION

The CIN I was treated conservatively with *Coriolus versicolor*-based vaginal gel, administering 1 cannula per day during the first month, and then 1 cannula every other day until 6 months of treatment was completed. A colposcopy control was performed at one year, without pathological findings. She remained

FIGURE 1. The lesions' appearance on the first visit. Note the conglomerate on the clitoris and around the anus, as well as the lesion from external irritants.

FIGURE 2. First post-surgical check-up. Initiating treatment with *Coriolus versicolor* gel was chosen as an adjuvant for epithelialization.

positive for HPV 18. She was recommended to have a nonavalent vaccine.

Her Primary Care doctor initiated topical treatment for the vulvar lesions using green tea leaf extract, providing a very limited response and causing extensive local irritation.

She was initially referred to Dermatology, where she had 6 cryotherapy sessions without responding.

Once in our department, she was treated with Imiquimod at 3.75% without responding.

Given such extensive involvement and the very limited response to conventional medical treatments, serologies were performed to rule out HIV. An evaluation by Coloproctology using anoscopy was required, which ruled out endoanal involvement.

Given the medical treatment-refractory VIN 3 diagnosis, the patient was proposed for surgical treatment using partial vulvectomy, along with treatment for the lesions and diagnosis of a possible occult invasion.

The definitive anatomic pathology confirmed the high-grade vulvar intraepithelial neoplasia without invasion diagnosis.

During the post-surgical check-up (Fig. 2), she was offered adjuvant treatment for epithelialization with external *Coriolus versicolor* genital gel. This was applied twice a day once the surgical wounds had dried after healing using aqueous chlorhexidine.

Complete epithelialization was achieved at the surgical site and the iatrogenic ulcer in 45 days (Fig. 3).

FINAL DIAGNOSIS

This is a case of extensive genital condylomas in a patient with positive high-risk HPV, refractory to different medical treatments, with surgery required as a solution (partial vulvectomy). A *Coriolus versicolor*-based vaginal gel is used to improve the epithelialization of the area, given that it is a traumatic operation that affects the woman's self-image and any healing issues in this region may mean the patient experiences a worse quality of life.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Vulvar intraepithelial neoplasia is the precursor for vulvar squamous cell carcinoma. Early diagnosis

FIGURE 3. The healing process. Note the epithelialization compared to the previous image.

FIGURE 4. Current status, one year after surgery with a good aesthetic outcome.

and suitable treatment are vitally important to prevent the condition from developing. In our case, it is worth highlighting that the patient did not visit until the lesions were large and symptomatic (itching); an earlier diagnosis would likely have meant surgery could have been avoided. VIN presents clinically in very heterogeneous forms; in our case, it presents as hard, extensive hyperkeratotic lesions. This examination favors a usual VIN diagnosis, so a complete lower genital tract study was undertaken, given that a high percentage of cases are associated with other synchronous lesions (CIN I in our case). Regarding treatment, it was preferred to start with more conservative treatments in order to conserve a higher level of functionality for the patient. We had to consider that this case involves an immunocompromised patient (chronic active hepatitis B), so that the treatment of choice is excisional (multiple lesions, a high relapse rate, more progression to carcinoma). We performed a partial skin vulvectomy with primary closure. This is an effective treatment, but it strongly impacts on a patient's self-image, so the *Coriolus versicolor* gel was chosen as an adjuvant treatment, in order to achieve uniform epithelialization as quickly as possible. This allows the patient's self-esteem to improve, reducing the treatment's psychosocial impact.

Our patient currently receives annual check-ups, presenting a good aesthetic outcome (Fig. 4), and she is asymptomatic without vulvodynia or dyspareunia.

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EFECTIVENESS OF A MULTI-INGREDIENT *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL IN HPV+ AND HIV+ PATIENTS

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ABSTRACT

Infection by human papillomavirus (HPV) is the most common sexually transmitted disease among humans[1]. Potentially affecting up to 80% of sexually active people at least once during their lives, its course is usually favorable1. All the same, 10 to 15% of infected subjects find eliminating the virus difficult, leading to greater propensity for the infection to persist. This viral persistence over time is the main risk factor for developing lesions rather than the infection itself[1,2].

Although the factors that determine persistent genital HPV infection are still somewhat unclear, it can be reasonably argued that the essential factors for infection prognosis are the viral genotype, the host's immune system status, the vaginal microbiome, and the histological structure of the cervix[2].

Among the factors that predispose persistent genital HPV infection, immunosuppression due to infection by human immunodeficiency virus (HIV)[3,4] particularly stands out.

Compared to uninfected patients, HIV-positive patients are at greater risk of incident, persistent, or recurrent HPV infection, a lower clearance rate, a higher viral load, and a marked predisposition for being colonized by several serotypes; all leading to more frequent and severe HPV-dependent lesions[5]. In fact, HIV-positive women are six times more at risk of developing cervical cancer than women without HIV, and it is estimated that up to 5% of all cervical cancer cases worldwide can be attributed to HIV-derived immunosuppression[3-5].

KEY WORDS: Human papillomavirus. HIV. *Coriolus versicolor.* Vaginal gel.

Once infection by HPV is confirmed among HIV+ patients, the clinical approach targets diagnosing and treating potential dysplasias that can appear in the anogenital tract[2,5]. However, recently published results about a new topically administered treatment regimen have shown that it could both reverse mild HPV-derived cervical injuries and increase viral clearance rates among immunocompetent patients[6-8]. We don't have any information regarding its potential usefulness among HIV+ patients at present.

With this communication, we aim to provide evidence about the initial experience for the scientific community.

MATERIAL AND METHODS

A prospective observational study was developed to evaluate a series of 15 HIV-positive patients colonized by HPV in the endocervix region with an anomalous cervicovaginal cytology.

They were evaluated for the therapeutic effect of a vaginally administered gel comprised of nio-

somes that contain hyaluronic acid, βglucan, alpha-glucan oligosaccharide, *Coriolus versicolor*, *Asian centella, Azadirachta indica,* and Aloe vera.

Only marketed by Procare Health®, under the brand name Papilocare®, the gel comes in single dose cannulas for self-application, and was prescribed with the following posology:

1. Each dose consisted of inserting the contents of one cannula inside the vagina, prior to bedtime.
2. Treatment was started after the menstrual period, where applicable. 1 dose was administered every night for 21 consecutive days during the first month. After a 7-day rest period and other than on days during the menstrual period, administration during the subsequent 5 months consisted of 1 single dose cannula every other night.

No sexual activity related restrictions were advised during treatment, but intimate washes were contraindicated, as was any other activity that could affect the therapeutic gel's adhesion to the vaginocervical mucosa.

The cases were evaluated to obtain a baseline status prior to initiating treatment using a hybrid capture test for endocervical HPV, a vaginal culture for screening for Gardnerella vaginalis, and a colposcopy with a biopsy, where applicable.

The control observation was carried out during the 3-week period after the treatment ended. All cases had a cytology, a hybrid capture test for endocervical HPV, a vaginal culture for screening for Gardnerella vaginalis, and a colposcopy with a biopsy, where applicable. The exact same methodology was used to collect data both at baseline on inclusion to the study and this second data collection point at 6 months.

A colposcopy was used to evaluate the possible presence of cervix lesions caused by HPV, as well as the degree of epithelialization of the cervical mucosa.

The colposcopy findings were classified in accordance with the colposcopy terminology currently accepted by the International Federation of Cervical Pathology and Colposcopy. The degree of cervical epithelialization was established using the Likert scale, with scores ranging from 1 to 5, where 5 represents no ectopy, 4 represents mild ectopies (with less than 25% of the outer cervix orifice compromised), 3 represents moderate cases with 25% to 50% of the outer cervix orifice compromised, 2 represents severe ectopies that affected over half of the cervical orifice, and 1 represents cases of severe ectopy with bleeding.

In order to control the potential influence of HIV infection-derived immunological status on the results, the data was evaluated with respect to the viral load and the lymphocyte count, both at baseline and post-treatment. These parameters were determined with a maximum 2 weeks' difference compared to when the cervix observations were made.

The study was carried out in accordance with the best practice principles for biomedical investigation in the Declaration of Helsinki. The patients provided specific consent and didn't receive any different forms of care to those they had already received in the event of no longer wanting to participate in the project.

The investigation was approved, but it wasn't monitored by our center's Clinical Research Ethics Committee, "as it is the clinical evaluation of an approved therapy for cases such as those of the patients included in the study protocol and there are no indications of specific risk to patients with HIV in the summary of product characteristics nor in the literature available to date".

RESULTS

Table I summarizes the main clinical characteristics of the patients included in the series. Six of them fulfilled the criteria for AIDS.

In six cases, the cytological changes suggested a low-grade lesion (LSIL), while the cytological reports for the other cases described atypical squamous cells of undetermined significance (ASC-US).

Every case was evaluated using a colposcopy/biopsy, with no moderate, severe dysplasia or carcinoma (CIN II+) cases found.

TABLE I. Main clinical characteristics of the studied patient series

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Age	41	49	38	47	53	50	31	33	29	25	54	44	39	35	49
Anti-HIV therapy	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Inconstant	Inconstant	Yes	Yes	Yes	Yes	Yes
Smoking	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Hormone therapy	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No
CD4 lymphocytes/ml	1431	700	490	318	597	615	No	208	324	107	625	410	327	521	470
Viral load (copies/ml)	Undetectable	Undetectable	Undetectable	5,321	Undetectable	Undetectable	119	1210	110,000	420,466	Undetectable	Undetectable	Undetectable	Undetectable	Undetectable
Cytology	ASC-US	ASC-US	ASC-US	L-SIL	ASC-US	ASC-US	36575	ASC-US	L-SIL	ASC-US	ASC-US	L-SIL	L-SIL	ASC-US	L-SIL
Endocervical HPV	6,11,16,18	16,68	11,16,31	16,18,35	6,16,18	18,33	18.59	11.16	16,18,52	5,16,18, 31,45, 68	16,35	16,18	16,18,35	16,68	6,11,16
Chlamydia (current)	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

The blue text indicates the variables corresponding to cases with AIDS.

<< >>

SUMMARY

TABLE II. Baseline situation (prior to treatment) for the 15 cases included in the series

	Cytology	HPV	Condylomas	Colposcopy	Biopsy	Likert scale
Case 1	ASC-US	6,11,16,18	No	Normal		3
Case 2	ASC-US	16,68	No	Normal		4
Case 3	ASC-US	11,16,31	No	Grade 1 abnormal	CIN I	4
Case 4	L-SIL	16,18,35	No	Grade 1 abnormal	CIN I	3
Case 5	ASC-US	6,16,18	No	Normal		4
Case 6	ASC-US	18,33	No	Normal		5
Case 7	L-SIL	18,59	No	Grade 1 abnormal	CIN I	4
Case 8	ASC-US	11,16	No	Grade 1 abnormal	CIN I	4
Case 9	L-SIL	16,18,52	No	Grade 1 abnormal	CIN I	3
Case 10	ASC-US	5,16,18,31,45,68	Vulvar	Grade 1 abnormal	CIN I	2
Case 11	ASC-US	16,35	No	Grade 1 abnormal	CIN I	2
Case 12	L-SIL	16,18	No	Grade 1 abnormal	CIN I	3
Case 13	L-SIL	16,18,35	No	Grade 1 abnormal	CIN I	2
Case 14	ASC-US	16,68	NO	Normal		3
Case 15	L-SIL	6,11,16	NO	Normal		1

Table II summarizes the data relating to the examination performed on each case at baseline, prior to initiating the treatment, while table 3 compares the baseline and post-treatment statuses of each studied case.

The 15 patients showed suitable adherence with the recommended therapy, without any associated adverse effects, other than a case of an "excessive sensation of genital humidity" and another of "self-limiting mild vulvar pruritus during the first two weeks of treatment", neither of which prevented completion of the recommended treatment regimen.

The overall viral clearance and cytological rates were 73.33% and 80% respectively. Endocervical colonization by HPV also partially cleared among 13.33% of the series' cases.

When it comes to colposcopies with anomalies associated to HPV, 55.56% of them normalized during the observation period.

The qualitative re-epithelialization rate improved in 66.66% of cases, providing an average benefit of 1.5 points on the scores obtained for the 10 studied cases.

DISCUSSION

HIV-positive women show a higher risk of infection by HPV, a lower rate of viral clearance, and a notable increase in the risk of pre-malignant and malignant lesions associated to the virus compared to women not infected by HIV[5]. That predisposition can be explained by how HIV modifies HPV pathogenesis[2,5].

It is long established that both the risk of acquiring HPV and its clearance and reactivation closely depend on the HIV viral load and the CD4 lymphocyte count[9,10] among HIV+ patients. That explains that the "immunological restitution" derived from antiretroviral therapy notably reduces the risk of infection by HPV. However, its effect at preventing lesion progression is still very much in doubt[4].

As well as presenting a higher risk of infection, disease, and cancer compared to persons

TABLE III. A comparison of baseline and post-treatment statuses for each case from the series.

	HPV endocervical		Cytology		Colposcopy (IFCPC 2011)		Colposcopy-directed biopsy		Cervical epithelialization rate		CD 4 count (cells /ml)		Viral load (copies per milliliter)	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months
Case 1	6,11,16, 18,68	11,18	ASC-US	Negative	Normal	Normal			3	3	143	201	Undetectable	Undetectable
Case 2	16	-	ASC-US	Negative	Normal	Normal			4	5	700	601	Undetectable	Undetectable
Case 3	11,31,16	-	ASC-US	Negative	G1 abnormal	Normal	CIN I		4	5	490	440	Undetectable	Undetectable
Case 4	16,18,35	-	L-SIL	Negative	G1 abnormal	Normal	CIN I		3	4	318	497	5,321	4,827
Case 5	6,16,18	-	ASC-US	Negative	Normal	Normal	CIN I		4	4	597	600	Undetectable	Undetectable
Case 6	18,33	18,33	ASC-US	Negative	Normal	Normal	CIN I		5	5	615	794	Undetectable	Undetectable
Case 7	18,59	-	L-SIL	L-SIL	G1 abnormal	G1 abnormal	CIN I	CIN I	4	4	119	186	36,575	36,800
Case 8	11,16	-	ASC-US	Negative	G1 abnormal	G1 abnormal	CIN I	CIN I focal	4	5	208	111	1,210	1,348
Case 9	16,18,52	-	L-SIL	ASC_US	G1 abnormal	G1 abnormal	CIN I	CIN I	3	4	324	296	110,000	207,006
Case 10	5,16,18, 31,45,68	16,18,31, 68	ASC-US	ASC_US	G1 abnormal	G1 abnormal	CIN I	CIN I	2	4	107	91	420,466	517,200
Case 11	16,35	-	ASC-US	Negative	G1 abnormal	Normal	CIN I		2	3	625	575	Undetectable	Undetectable
Case 12	16,18	16,18	L-SIL	Negative	G1 abnormal	Normal	CIN I	CIN I	3	4	410	506	Undetectable	Undetectable
Case 13	16,18,35	-	L-SIL	Normal	G1 abnormal	Normal	CIN I		2	4	327	302	Undetectable	Undetectable
Case 14	16,68	-	ASC-US	Normal	Normal	Normal			3	3	521	412	Undetectable	Undetectable
Case 15	6,11,16	-	L-SIL	Negative	Normal	Normal			1	2	470	303	Undetectable	Undetectable

SUMMARY

without immunosuppression[5], HIV+ patients presented some suboptimal immune responses to vaccination against HPV[11]. This is why exploring possible therapies that mitigate the significant disease load represented by HPV for this particularly vulnerable population is urgent.

Although the precise factors that condition persistent genital HPV infection[2] are still somewhat unclear, it can be reasonably argued that the essential factors for infection prognosis are viral genotype, the host's immune system status, the vaginal microbiome, and the histological structure of the cervix.

Of the different HPV serotypes described, 16, 18, and 45 are particularly important among the population with HIV[12]. All the same, there don't appear to be any relevant differences in terms of the prevalence of serotypes between the HIV+ population and the general population.

When it comes to the immune situation, recent suggestions are that the risk of lesions by HPV could depend more on the proportion of CD4 lymphocytes rather than their overall count, but there isn't a consensus in that respect[13].

Mild immune changes were observed in the studied series in terms of viral load and CD4 lymphocyte count, so even when adopting a cautionary standpoint, we can suppose that the results largely depend on the initiated therapy. In any case, additional investigations need to be undertaken to clarify this aspect.

When it comes to the cervicovaginal microbiome, there are speculations that some of its characteristics could condition the potential HPV pathogen. The reduction in Lactobacillus, excessive microbial diversity, the presence of Gardnerella and a predominance of atypical anaerobic bacteria appear to predispose the appearance of moderate, severe dysplasias and carcinomas[14-17]. Several factors influence the weakening of the immune response of the vaginal mucosa, mainly the release of enzymes that degrade mucin, the change in pH balance, and a cytokine modulation that predisposes chronic inflammation[5,14,17].

As far as we know, no pre-clinical studies have been undertaken that investigate the vaginal microbiome in the context of HPV; probably because of the difficulty in simulating human microbiome conditions among animals. All the same, we have observational studies that attribute marked preventive effects against infection by HPV to microbiomes rich in *Lactobacillus* (particularly Lactobacillus gasseri, jenseni, and crispatus). On the other hand, some micro-organisms such as *Sneathia, Anaerococcus tetradius, Peptostreptococcus,* and *Fusobacterium,* as well as *Gardnerella vaginalis,* appear to be more frequently and severely associated with infection by HPV, increasing the host's susceptibility to dysplastic or neoplastic lesions[14-17].

Only information relative to Gardnerella was collected for our series, as it is the germ most strongly and constantly associated to persistent HPV infection. No patients were carriers at baseline nor during post-treatment control, and on reviewing the digital clinical history of the 15 participants, no notes relating to a potential infection by that germ during the treatment period were found.

When it comes to repairing cervical histological damage, considered a strongly predisposing factor for infection by HPV[19,20], the results obtained with our series were promising. In line with prior experiences regarding a non-immunosuppressed population[6-8], the proposed therapy achieved high rates of re-epithelialization in just 6 months.

Multiple therapies for improving cervix epithelialization have been tested among patients with ectropion and surgical damage[21]: medroxyprogesterone, alpha interferon, boric acid, deoxyribonucleic acid, Chitosan, autologous platelet-rich plasma, hyaluronic acid, and even applying amniotic membrane patches. Physical therapies like electrocauterization, cryotherapy, and coagulation with microwaves and lasers have also been tested. Overall, every technique offers a re-epithelial rate close to 92% at 6-12 months from the intervention[21].

The recommended therapy for the series of studied cases was based on administering a vaginal gel comprised of hyaluronic acid, β-glucan, alpha-glucan oligosaccharide, *Coriolus versicolor, Asian centella, Azadirachta indica,* and Aloe vera. Its composition treats four therapeutic objectives: to improve cervical re-epithelialization, to boost the immune system, to restore the vaginal micro-environment that conditions the microbiota, and to boost endogenous antitumor activity.

Results reported to date were from a non-immunosuppressed population[6-8]. The published viral clearance rates range from 60 to 70%, with cyto-colposcopy improvements among 70-80% of treated patients[6-8].

The limited sample size of our series means proposing comparative analyses against the results obtained by other authors isn't prudent, but it does mean that the therapeutic response of HIV+ patients can be assumed to be no lower than that observed among immunocompetent patients not infected by HIV[10,11]. In any case, it is convenient to consider that the reversion rate for mild dysplasias (CIN I) is 60% one year from the diagnosis without treatment[22].

In our view, this series' main contribution is to present the first experience described in the literature about the use of a new effective therapy for infection by HPV among a population group particularly vulnerable to infection[5,23]. Clearly its limitations need to be signaled: it is an observational study, with a limited sample size, with limited clinical follow up among a population that only presented infection by HPV or mild associated damage. This means that categorical conclusions cannot be extracted based on the results, but that a likely pattern of population behavior for the prescribed therapy can be inferred.

When it comes to the preparation administered as therapy, two elements of its composition deserve a specific mention, as they are closely linked with the cervical disease: β-glucan and Krestin or PSK, a polysaccharide derived from the *Coriolus versicolor* fungus.

There is evidence for beta glucan acting as an effective vaginal prebiotic with high re-epithelializing potency[8,24,25]. When it comes to Krestin, it is a widely studied substance in the scientific literature and known for potent antioxidating, neurodegenerative, liver protecting, and immunomodulating effects[26-30]. There is also evidence for antiviral activity against human immunodeficiency virus, as well as a marked cytotoxic effect on dysplastic and neoplastic cells[26]. Its target organs are dendritic cells[26] and although it is considered an effective therapeutic agent to support chemotherapy when treating certain cancers[26-30], its main contribution regarding the pathology that concerns us involves modifying human biological responses against viral infections, increasing competence[27-33]. Its main benefit is that it does not modify the effects of antiretroviral therapy nor the action of liver enzymes, so it can be used without restrictions among weak patients, such as those with AIDS and older people[31].

Lastly, it just remains to highlight the negative impact of vaccination against HPV on our series. Of the 15 participants, only one fulfilled the age criteria for being able to receive the vaccine funded through the Andalusian public health care system. All the same, the patient had already rejected it on repeated occasions, despite it being offered by the health care system. None of the other pregnant women had been vaccinated.

Treatment tolerability and adhesion among our series was good with 13.3% experiencing mild side effects that didn't lead to treatment discontinuation.

To sum up, our results suggest that the proposed therapy could be an effective and safe method for treating endocervical infection by HPV among HIV+ patients. We hope that our results prove a starting point to encourage future relevant investigations.

CONCLUSIONS

The promising results obtained for the limited series can be matched to those reported from prior experiences among patients without im-

munosuppression. All the same, new trials need to be started to confirm the current signs and establish the potential influence of other factors on the results, including the patient's immunological status.

The authors declare that they are not subject to any conflicts of interest, nor have they received any funding for carrying out the project, other than the funding provided by the institution where the work was undertaken (Complejo Hospitalario de Jaén, an entity belonging to the Spanish National Health System hospital network).

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CORIOLUS VERSICOLOR VAGINAL GEL USE FOR THE CONSERVATIVE TREATMENT OF CIN II

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ABSTRACT

HPV causes both cervical cancer and its precursor lesions.

Using systematic treatment on all women with HSIL/CIN II-III has been considered an unquestionable option in clinical guidelines in recent years.

Recent studies show that up to 40-74% of patients with a histological diagnosis of HSIL/CIN II can regress unaided during the two year period post-diagnosis[1]. The most commonly associated factors with regression are being aged under 25 years old, limited lesion spread, negativization for HPV and no HPV infection[2,3].

The AEPCC guideline for preventing cervical cancer defines a set of special situations for potentially choosing conservative treatment for HSIL/CIN II lesions. These include the possibility of following up the patient, and lesions affecting less than 50% of the cervix, which are fully visible and don't affect the endocervical channel.

KEY WORDS: HPV. Papilocare®. CIN II. Regression.

MEDICAL HISTORY AND ANAMNESIS

A 30-year-old patient wanting to fall pregnant, but yet to do so. No history of interest. Smoker. No prophylactic HPV vaccination. Began sexual relationships at 16-years-old, 6 sexual partners to date.

Referred by the midwife at her health center due to LSIL cytology.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient has an HPV test and colposcopy.

HPV culture positive for type 16 and other high-risk types.

Colposcopy satisfactory: TZ 1, mosaic with spotting on the anterior lip. Schiller's test positive. (Fig. 1).

Biopsy of the lesion taken, with an anatomo-pathological diagnosis of CIN II.

TREATMENT AND EVOLUTION

Given the HSIL/CIN II lesion diagnosis, affecting at least 50% of the cervix, fully visible, with no endocervical involvement, the patient is offered and accepts a conservative treatment.

A prophylactic HPV vaccination is prescribed and she is offered a co-adjuvant treatment with a *Coriolus versicolor*-based vaginal gel.

The patient visits for a check-up at 6 months. She completed treatment with Papilocare® for 6 months without any mention of adverse effects. A colposcopy was performed and samples were taken for control.

FINAL DIAGNOSIS

The colposcopy at 6 months shows clear improvement with no images suggestive of epithelial lesions, only areas of metaplasia. A sample is taken for cytology, confirming LSIL, a culture for

FIGURE 1. Colposcopy during the first visit.

HPV is negative, and a cervix biopsy confirms that there aren't any residual lesions, with an anatomopathological diagnosis of squamous metaplasia.

Given the regression of the CIN II intraepithelial lesion and HPV clearance, the patient is indicated to continue receiving check-ups.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Despite the high level of unaided remissions with CIN II, there isn't an effective non-invasive treatment for such high-grade lesions.

Avoiding unnecessary surgical treatment, particularly among young women, also indirectly avoids morbidity from those treatments affecting the patient's reproductive ability[4].

A range of studies already support the beneficial effect of Papilocare® vaginal gel on low-grade ASCUS and LSIL lesions, as well as on patients who are high-risk HPV positive, with virus clearance observed at 6 months[5-7].

Through its action on the vaginal microbiota, the re-epithelialization of the cervix, and improvement in local immunity, the *Coriolus versicolor* vaginal gel could promote the regression of high-grade cervical intraepithelial lesions/CIN II and/or HPV clearance.

Given the positive result, more experience using Papilocare® vaginal gel to treat high-grade lesions that meet conservative treatment criteria is required.

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HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS ON THE CERVIX TREATED WITH PAPILOCARE®: EVOLUTION AND PROGNOSIS

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection around the world, affecting 90% of the sexually active population. This means that women will come into contact with the virus at some point during their life, which can resolve asymptomatically to remain infection-free, or it can become a chronic component in their body. HPV's persistence is definitively linked with the appearance of squamous intraepithelial lesions (SIL) in the cervix. As such, eradicating the infection is important when it comes to preventing or treating lesions caused by said infection.

This is a report on a case of HSIL, with Papilocare® the chosen treatment and it documents their evolution.

KEY WORDS: HPV. HSIL. Conization. CIN.

MEDICAL HISTORY

- 35-year-old patient.
- No known adverse reactions to medication, no CVRFs, no personal history of interest, no chronic treatment.
- Surgical interventions: meniscectomy.
- Occasional smoker.
- Balanced basal diet.
- Daily physical exercise.
- Reproductive and gynecological history: No prior disease.
- First menstruation aged 11 years old. Date of last menstruation: 6/11/19. OH: G1A1(abortion). MH: 28/3. Age of first sexual relationship: 16 years old. Number of sexual partners: 3.
- Oral contraceptive treatment: for 10 years. Not taking it at present.
- Does not use barrier methods.
- Has not had the HPV vaccine.
- Not recorded as an HPV carrier.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient visits the office for cervical disease having been referred by her PCP after the cervicovaginal cytology result of LSIL/ CIN I (10/12/2018), with cytology changes suggestive of human papillomavirus (HPV) infection.

Colposcopy indication: suitable, as she is over 21 years old and has LSIL.

Type 1 transformation zone present (in the ectocervix and fully visible).

Major changes are observed, such as faint acidophilia and hypo-uptake of Lugol's solution. Vascularization normal.

It is decided to perform a punch biopsy and an HPV test (12/02/2019)

Treatment initiated with Papilocare® during 6 months and another check-up after treatment.

Nonavalent HPV vaccination initiated.

DIFFERENTIAL DIAGNOSIS

Given the main discrepancy between the results of the initial cervicovaginal cytology and the colposcopy undertaken in the office, the differential diagnosis is established between HPV-induced high-grade lesions (HSIL) and low-grade lesions (LSIL).

TREATMENT AND EVOLUTION

- Results from the cervix biopsy are obtained (18/02/2019): Cervix mucosa with high-grade SIL (moderate dysplasia, CIN II) with signs of HPV and chronic inflammation. Intense positive signal for p16 and Ki-67 overexpression in the material provided.
- Results from the HPV test are obtained (25/02/2019):
  - HPV DNA with a high oncogenic risk is detected (16, 31, 56, 58, 73).
  - HPV DNA with a probable high oncogenic risk is detected (66).
  - HPV DNA with a low oncogenic risk is detected (70).

Given the results from both tests (CIN II, high-risk oncogenic HPV), it was decided to perform conization (06/05/2019). The anatomopathological diagnosis reports that there are signs of HPV infection with hyperchromatic nuclei and clear perinuclear halos. An intense positive signal for p16 is observed. Epithelial dysplasia observed between 12 and 9 o'clock: moderate from 12 to 3, mild from 3 to 6; and moderate with glandular extension from 6 to 9. No neoplastic stromal infiltration observed at any point. The surgical margins are lesion-free.

After conization, it was decided to restart treatment with Papilocare® for 6 months, before a check-up with CVC and an HPV test:

- 1st post-conization visit (November 2019):
  - Nonavalent vaccination completed.
  - Smoking stopped.
  - CVC (15/11/2019): cytology negative for malignant cells. There is no evidence of trophic or inflammatory changes to suggest HPV persistence. No atypias identified.
  - HPV test (22/11/2019): Genotype 16 DNA/RNA detected.
- 2nd post-conization visit (July 2020):
  - Continues treatment with Papilocare®.
  - Evolution control with CVC
  - CVC (02/07/2020): cytology negative for malignant cells. No atypias identified.
- 3rd post-conization visit (January 2021):
  - Continues on treatment with Papilocare to date.
  - Evolution control with CVC and an HPV test:
    CVC (28/01/2021): cytology negative for malignant cells. No atypias.
    HPV test (28/01/2021): no HPV DNA/RNA detected.

Patient given the all clear by the cervical disease office

Currently, on annual follow-up with CVC for at least 20 years.

FINAL DIAGNOSIS

Mild and moderate epithelial dysplasia (CIN II) with HPV-induced cervicitis foci and glandular extension in the affected area.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

In this case, there is evidence of the importance of correlating the results of cervicovaginal cytologies with the clinical examination and specific tests in the cervical disease office. A cervicovaginal cytology is a quick, simple, and reproducible test that can provide a high level of sensitivity for detecting HPV infection. However, it should never be taken as a gold standard and should be correlated with the results of tests to define the disease being treated.

Given the result of the initial cytology, the first decision was to use watchful waiting for the case, applying Papilocare® for 6 months. The result of

the biopsy and the HPV test indicated suitability for conization, as such complementing Papilocare® treatment with the surgical intervention. The successful outcome of this case may have been established by combining the conization with treatment with Papilocare® in order to eliminate human papillomavirus, although more cases are needed to corroborate such association.

Treatment was undertaken with Papilocare® for a total of 18 months, achieving negativization for the different high-risk oncogenic HPV types. Currently and based on the above, it could be concluded that the cure is definitively achieved in full by the medical or surgical intervention, but the association of the host's immunological defense, the prescribed treatment, and conization led to the cure of the disease. This case opens up a discussion regarding determining the resolution/curing factor attributable to each element involved, given that this case is merely informative in nature.

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HIGH-GRADE CERVICAL LESION DURING PREGNANCY

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ABSTRACT

Human papillomavirus is one of the world's most widespread sexually transmitted infections. According to a study published in 2012, the virus affects two million women in Spain, 28.8% of which are aged 18 to 25 years old, with that percentage reducing with age.

Complications from human papillomavirus during pregnancy are uncommon.

A group of over one hundred different viruses represent what is known as human papillomavirus. 13 of these are considered carcinogenic for humans, i.e. they represent a high-risk of developing cancer. Among women, this virus is more common in the cervix-uterus (cervical cancer).

MEDICAL HISTORY AND ANAMNESIS

A 26-year-old patient visiting for a pregnancy check-up

PH: No diseases, no surgical operations, no allergies to medicinal products, not on any medication, vaccinated for HPV with Gardasil 4 under the Castilla y León Regional Council's vaccination program when 14 years old with two doses (0 and 6 months).

Reproductive and gynecological history: G1P0A0. 12 5/28. Pill used as a contraceptive method for 5 years. Pregnancy 6+3 weeks.

Cytology performed on first visit as the patient had never had one under the Social Security protocol.

On receiving the cytology result after 10 days, she is advised about the H-SIL anatomopathological result.

A HPV sample is taken using PCR, which was positive for serotypes 31, 39 and 45.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient also has a colposcopy, which shows an irregular white plaque on the anterior lip, around two centimeters in size, flame-shaped, and both acetowhite and Lugol's solution positive.

A biopsy was undertaken on the area and the AP diagnosis is a high-grade lesion with a detached basal lamina.

TREATMENT AND EVOLUTION

Given the early nature of the diagnosis and the inconvenience of intervention on the cervix during pregnancy, the decision was to treat with Papilocare®, 21 days in a row, resting 7, and then every 48 hours for 2 months more, resting 7 days.

At the third month of treatment, a colposcopy is performed with the plaque less than 0.5cm in size, acetowhite, but Lugol's solution negative. Cytology and guided biopsy performed with an anatomopathological result of L-SIL.

The same dose was then continued for a total of 6 months. A colposcopy is performed at the seventh month, but with the plaque practically undetectable a biopsy wasn't performed; however, a cytology gave a L-SIL result.

At the 9th month, now untreated, another cytology is performed with a L-SIL result.

The patient had a vaginal birth without incidents during week 40+5, giving birth to a healthy boy weighing 3250 grams.

At six months from the birth, the cytology continued to give a L-SIL result, and the HPV had negativized in two serotypes, with only 45 remaining.

FINAL DIAGNOSIS

Papilocare® was capable of regressing a high-grade lesion and reducing viral load during pregnancy, without requiring additional medical or surgical treatments.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Through this case we were able to show that we prevented a HSIL progressing to carcinoma using only Papilocare® gel, and that such a serious lesion during pregnancy, for which very few treatments are available, had virtually disappeared.

I find it innovative because there are no studies on pregnant patients, and I consider it significant progress among this patient group, as operating or prescribing aggressive treatments or administering vaccines are not an option.

Evidence for the innocuousness of said treatment during pregnancy has also been shown.

I believe it is a great medical achievement.

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CORIOLUS VERSICOLOR-BASED VAGINAL GEL USED TO TREAT LOW-GRADE CERVICAL DYSPLASIA AND HPV PERSISTENCE AFTER CERVICAL CONIZATION ON A HIV-POSITIVE WOMAN: A CLINICAL CASE

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and most significant etiological agent for cervical cancer. Several studies have provided evidence that HPV infection is significantly more common among women with human immunodeficiency virus infection (HIV)[1]. HIV leads to a higher risk of cervical dysplasia and cervical cancer. HIV-positive women also experience a higher incidence of lesion and viral persistence after excisional treatments[2].

KEY WORDS: HPH. HIV. Cervical dysplasia. Cervical conization. *Coriolus versicolor.*

MEDICAL HISTORY

A nulliparous 33-year-old HIV-positive woman (sexually transmitted 10 years ago, status A1, on antiretroviral treatment with good adherence and control, undetectable viral load), with no other history of interest. Vaccinated against HPV 2 years ago. Visits the Cervical Disease office for cytological HSIL, positive for a high-grade (HG) HPV (neither 16 nor 18).

Physical examination

External genitals and vagina normal. Nulliparous cervix, ectopic around the orifice. Digital vaginal examination: no pathological findings.

Complementary tests

- Colposcopy: type 2 transformation zone, typical vascularization, grade 2 changes (70% involvement of the cervix) (Fig. 1).
- Exocervical biopsies: cervical intraepithelial neoplasia (CIN)[2-3].
- Endocervical curettage: no dysplasia.
- Anal cytology: negative.
- Screening for other sexually transmitted infections: negative.

TREATMENT AND EVOLUTION

Given the diagnosis of high-grade dysplasia, loop diathermy cervical conization as an outpatient was indicated. The anatomical pathology of the surgical piece confirmed the lesion (CIN II) with involvement of the exocervical margin due to a low-grade lesion (CIN I).

During the first post-conization check-up, HG-HPV persisted with a low-grade lesion (cytological LSIL, colposcopy compatible with minor changes and exocervical biopsy CIN I). Treatment with Coriolus versicolor vaginal gel (Papilocare®) was proposed, with a check-up at 6 months. That check-up showed viral negativization and disappearance of intraepithelial lesion (cytology and colposcopy negative -Fig. 2-). Confirmed in both subsequent annual check-ups, which were negative. Currently continuing to receive annual check-ups in the Cervical Disease office.

FIGURE 1.

FIGURE 2.

FINAL DIAGNOSIS

High-grade dysplasia treated with cervical conization, with persistent low-grade dysplasia and HG-HPV post-conization. After treatment with Papilocare® vaginal gel for 6 months, the result was viral negativization and cervical dysplasia resolution.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

HPV infection and cervical dysplasia present more frequently among HIV-positive women, and they experience HPV persistence and dysplasias more often too[3].

In this case, it is worth noting that treatment with Papilocare® vaginal gel led to viral negativization and resolution of the low-grade cervical dysplasia that persisted during the first cervical post-conization check-up of a seropositive woman.

Treatment with Papilocare® has provided evidence of a benefit compared to watch-and-wait approach among women with HG-HPV and associated cervical dysplasia[4-6]. Given the good evolution with this treatment, more evidence needs to be obtained from HIV-positive women with cervical dysplasia.

Regardless of the immunological status and antiretroviral treatments, extensive and prolonged gynecological follow-up of HIV-infected women is still a requirement[7].

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POST-CONIZATION CERVICAL RE-EPITHELIALIZATION USING *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL

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ABSTRACT

Infection by human papillomavirus (HPV) is the most common sexually transmitted disease, but most cases involve temporary infection that revolves without requiring intervention.

In some women, the virus' persistence favors the development of squamous intraepithelial lesions of the cervix that may need treatment by a gynecologist. This may involve using cervical conization for example.

Using repairing *Coriolus versicolor*-based vaginal gel accelerates uterine mucosa epithelialization and reduces the risk of bleeding after the intervention..

KEY WORDS: HPV. Conization. *Coriolus versicolor.* Re-epithelialization.

MEDICAL HISTORY AND ANAMNESIS

A 39-year-old patient with HPV-16 infection being followed up for two years in accordance with Cervical Pathology Unit protocols.

Allergic to amoxicillin and the only personal history of interest is the surgical intervention for bilateral tubal ligation, meaning the patient does not use a barrier method as a rule.

Her gynecological history includes 2 normal births.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Her last check-up in the office showed a cytology compatible with H-SIL and persistent HPV-16 infection.

Colposcopy (Fig. 1): Type 2 TZ. Regions of acetowhite epithelium on the anterior lip located at 10-12 o'clock and on the posterior lip located at 6-8 o'clock, both appearing to creep towards the endocervix. A guided cervical biopsy is performed, resulting in a CIN III high grade squamous intraepithelial lesion diagnosis.

TREATMENT AND EVOLUTION

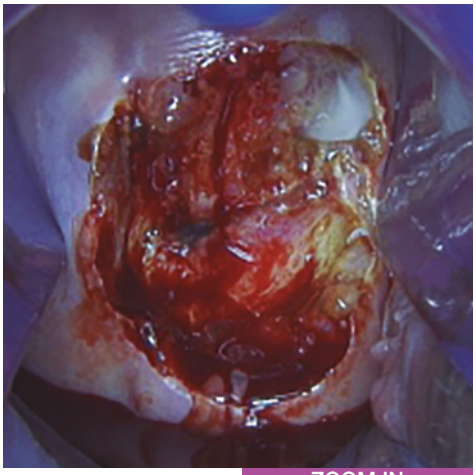
A "top hat" type cervical conization is selected, collecting more endocervical sample (Figures 2 and 3) under an outpatient regimen. The definitive anatomopathological diagnosis of the tissue provides evidence of a CIN III high grade squamous intraepithelial lesion, matching the earlier biopsy, and with clear resection margins. The endocervical cone does not present any histopathological changes.

Papilocare® vaginal gel is prescribed, 1 daily application before bed for three consecutive weeks, and the patient is asked to visit on days 7, 14, and 21 of the treatment to evaluate its effect on the re-epithelialization of the cervix mucosa (Figures 4, 5 and 6).

The aforementioned grade of re-epithelialization was confirmed using colposcopy

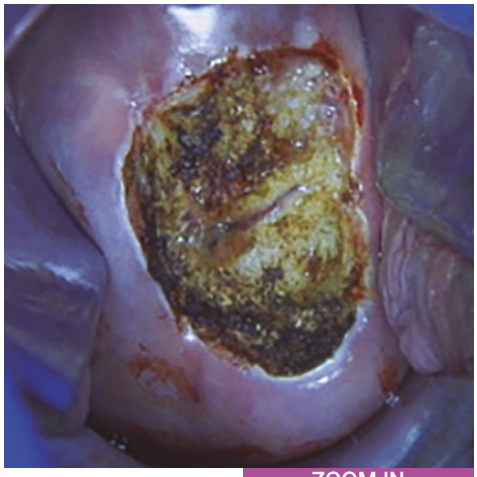
ZOOM IN

FIGURE 1.



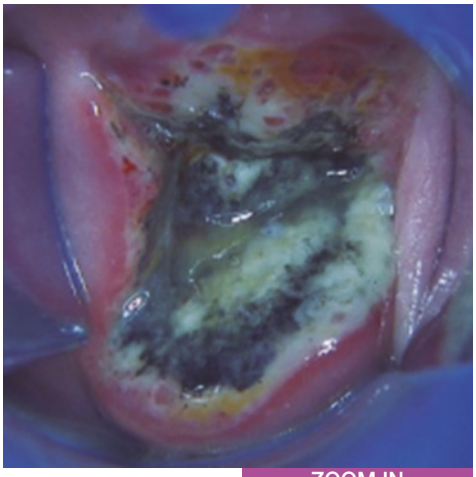
ZOOM IN

FIGURE 2.



ZOOM IN

FIGURE 3.



ZOOM IN

FIGURE 4.

in the office, observing evidence for an excellent response to the treatment throughout the successive weeks.

A co-test is performed at 6 months from the conization with a cytology showing no signs of malignancy and negative for HPV.

FINAL DIAGNOSIS

Papilocare® vaginal gel is prescribed for 3 consecutive weeks after a conization for high grade cervical lesion, resulting in significant improvement and rapid epithelialization of the cervix from the treatment.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Infection by Human Papillomavirus is the most prevalent sexually transmitted disease in humans, affecting almost all sexually active women at some point in their lives. In most cases, the infections

FIGURE 5.

FIGURE 6.

are temporary and resolve without requiring intervention.

However, the persistence of this infection can sometimes lead to the development of cervical intraepithelial lesions, which may or may not require immediate treatment depending on their severity. This is the case for our patient, who with a CIN III diagnosis and persistent HPV-16, is a candidate for cervical conization.

Numerous studies have shown that using *Coriolus versicolor*-based gel has been widely effective at normalizing HPV-derived lesions, both as a vaginal presentation for cervical lesions and an external gel for the co-adjuvant treatment of both external lesions and condylomas after laser vaporization.

Furthermore, another of its indications relates to post-conization co-adjuvant treatment, whereby this mucosa repairing gel accelerates the normal epithelialization process and reduces the risk of bleeding among these patients.

Similarly, there appears to be increasing evidence that the vaginal microbiome plays a significant role in the contagion and persistence of HPV in the cervix. There is evidence that the composition is both different and more diverse among HPV-positive women compared to HPV-negative women. Numerous clinical trials are being undertaken in this respect in order to identify the species that can offer greater protection, and as such, enable the development of therapeutic agents that prevent HPV infection, favor its elimination among infected women, and nullify the potential risk of developing cervical dysplasia.

That is precisely how treatment with Papilocare® vaginal gel provided evidence for modifying the vaginal microbiome's composition, reducing bacterial diversity.

Therefore, and to conclude this clinical case, using *Coriolus versicolor*-based vaginal gel seems to be a safe treatment option for patients that undergo conization, with two well-established objectives. The first involves accelerating the cervical re-epithelialization process and the second involves favoring a balance between the different species comprising the vaginal microbiome. This would create a more hostile environment for HPV, favoring its elimination.

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THE USEFULNESS OF PAPILOCARE® AS AN ADJUVANT TREATMENT FOR CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA IN AN IMMUNOSUPPRESSED PATIENT

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ABSTRACT

An immunosuppressed patient with cervical and vaginal intraepithelial neoplasia subjected to multiple sequential treatments, with high risk HPV persistence and vaginal cytology and histology changes for many years, achieving clearance after treatment with Papilocare®.

KEY WORDS: HPV. Excisional treatment. Total hysterectomy. Laser vaporization. Papilocare®.

MEDICAL HISTORY

Age: 64 years old.

Family history. Nothing of interest.

Personal history. No allergies to medicinal products. Dermatomyositis. Atrial fibrillation. Surgical interventions: Appendectomy. Cardiac ablation.

Regular treatments. Methotrexate. Prednisone. Bisoprolol. Flecainide. Sintrom.

No toxic habits.

Gynecological and obstetric history. First menstruation: 15. Menopause: 51 years old. G4P3A1. Prior cytology screening normal.

First visit to the Cervical Disease Unit in our center for cytology check-ups with an ASCUS result (April 2013). Asymptomatic from a gynecological point of view.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

External genitals atrophic. Vaginal atrophy. Cervix normal.

Digital vaginal examination: no findings.

Colposcopy (May 2013) and exocervical and endocervical biopsies with a HSIL/CIN III result.

DIAGNOSIS

Exocervical and endocervical HSIL/CIN III.

TREATMENT AND EVOLUTION

- Excisional treatment in September 2013. AP: CIN II-III, free margins.
- 1º post-conization check-up: Cytology HSIL. Colposcopy and exocervical biopsies with a HSIL/CIN II result. Significant atrophy with complete destruction of rectovaginal pouches during this check-up. Practically impossible to identify the external orifice of the cervix. As such, total hysterectomy proposed, as another excisional treatment is not possible.
- Total hysterectomy in June 2014. AP: HSIL/CIN II-III.
- 1st post-hysterectomy check-up: Vaginal cytology: ASCUS. HPV 18 (HR), 42 (LR) and 67 (LR). Vaginoscopy normal.
- 2nd post-hysterectomy check-up: Vaginal cytology: LSIL. HPV 18 (HR), 42 (LR) and 67 (LR). Vaginoscopy with vagina biopsies with a HSIL/VAIN 3 result. As such, laser vaporization proposed.
- 1st laser vaporization in October 2015.

- 1st post-vaporization check-up: Vaginal cytology: HSIL. HPV 18 (HR), 44 (LR) and 55 (LR). Vaginoscopy with vaginal biopsies with a HSIL/VAIN 2 result. As such, another laser vaporization proposed.
- 2nd laser vaporization in June 2016.
- 1st check-up after 2nd vaporization: Vaginal cytology: HSIL. HPV 18 (HR), 44 (LR) and 55 (LR). Vaginoscopy with vagina biopsies with a LSIL/VAIN 1 result.
- 2nd check-up after 2nd vaporization: Vaginal cytology: ASC-H. HPV 44 (LR) and 55 (LR). Vaginoscopy with vagina biopsies with a LSIL/VAIN 1 result. Starts using Papilocare® (August 2017).
- 1st check-up after initiating Papilocare® (November 2017): Vaginal cytology negative. Vaginoscopy with negative vaginal biopsies.
- 2nd check-up after initiating Papilocare® (September 2018): Vaginal cytology negative. Vaginoscopy normal.
- 3rd check-up after initiating Papilocare® (January 2020): Vaginal cytology negative. HPV negative.

FINAL DIAGNOSIS

Clearance of persistent HPV and resolution of vaginal intraepithelial neoplasia after multiple sequential treatments and Papilocare® use.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

The importance of immunosuppression in the evolution of cervical and vaginal intraepithelial neoplasia and HPV persistence.

This case study provides evidence for the potential usefulness of Papilocare® in adjuvancy with other sequential treatments, whether excisional or destructive.

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THE ROLE OF *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL IN CURING INFECTION BY HIGH-RISK HUMAN PAPILLOMAVIRUS (HR-HPV): A CASE STUDY

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ABSTRACT
Infection by human papillomavirus (HPV) is the most common sexually transmitted infection (STI). Most infected people will present an indolent course, before it cures unaided in less than two years. However, in some people, the infection can persist and cause symptoms (for example, vaginal bleeding during sexual intercourse), and it can even evolve towards cervical cancer, among other conditions.

KEY WORDS: Cytology. Coitalbleeding. HPV. Cervical cancer prevention.

MEDICAL HISTORY AND ANAMNESIS

A 43-year-old female with two pregnancies and two vaginal births. Non-smoker. Operated on for inguinal herniorrhaphy and hemorrhoidectomy. Regular cervical cancer screening undertaken in the Autonomous Community of Galicia (cytology every 3 years, no HPV determination), which was negative. Referred to the cervical disease office due to presenting bleeding during sexual intercourse (coital bleeding) with 2 years' evolution.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

- External genitals normal. Vagina and cervix well-epithelialized. No ectropion.
- Colposcopy: Suitable and satisfactory. Type 2 transformation zone. After applying acetic acid and performing Schiller's test, cervical biopsy taken on the compatible zone with minor changes at 12 o'clock.
- Cervical cytology and HPV determination performed.
- Vaginal cultures undertaken.

DIFFERENTIAL DIAGNOSIS

Cervical dysplasia vs. Sexually transmitted infection vs. Bacterial vaginosis.

TREATMENT AND EVOLUTION

Empirical treatment with vaginal ovules of *Centella asiatica,* Metronidazole, Miconazole nitrate, Neomycin sulfate and Polymyxin B sulfate (Blastoestimulina®) to see the results.

On the next visit, given the results: Cultures compatible with bacterial vaginosis and high risk HPV infection (33, 68) with cytology and cervical biopsy negative, watch-and-wait approach and evolution control at one year decided.

At one year of treatment for bacterial vaginosis, patient no longer presents coital

bleeding and a cytology check-up performed with a new HPV determination.

HR-HPV infection persistence confirmed and treatment with *Coriolus versicolor*-based vaginal gel (Papilocare®) prescribed for 6 months: One daily application for the first 21 days and then every other day, when not menstruating, until 6 months completed.

During the first check-up after treatment with *Coriolus versicolor*-based vaginal gel, the patient had already cleared the HR-HPV infection. Discharged from the office after findings confirmed (Cytology + HPV both negative) the following year.

FINAL DIAGNOSIS

- Coital bleeding probably related to bacterial vaginosis with good response to empirical topical treatment.
- Sexually transmitted infection (HR-HPV) that eliminates after a cycle of 6 months of treatment with *Coriolus versicolor*-based vaginal gel.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Human papillomavirus (HPV) is the most common sexually transmitted infection. Estimations are that over 80% of sexually active people will contract HPV infection at least once in their life[1].

40 different types of HPV capable of infecting genital and anal mucosa in both genders have been identified.

These HPVs are divided into:

- High risk or oncogenic viruses (HR-HPV) given their capacity for developing premalignant lesions and cancer.
- Low risk viruses (LR-HPV), which cause benign lesions (genital warts).

Infection by high-risk HPV is asymptomatic in most cases, representing temporary infections that disappear unaided[2]. However, the signs/symptoms that can help with the early diagnosis of cervical cancer need to be monitored. These include abnormal uterine bleeding, bleeding during sexual intercourse, pain...

Cervical cancer is known to be a serious yet extremely uncommon complication of a relatively common phenomenon like HPV infection. For example, there are estimated to be 18 million sexually active women in Spain aged over 18 years old, of which around 2 million are HPV carriers and approximately 400,000 present cytology changes. Around 1,942 cervical cancers are diagnosed annually in our country, and they are the cause of death for around 825 women[3].

Prophylactic vaccines against HPV have been acknowledged as the most effective intervention for controlling cervical cancer and other HPV-related diseases.

Cervical cancer prevention programs (cytologies and/or regular HPV tests) can detect and enable early treatment of premalignant cervical lesions, helping to considerably reduce the number of cases and mortality from this cancer type.

Furthermore, in addition to primary prevention measures (HPV vaccination) and secondary prevention (cervical cancer screening), specific treatments targeting curing the HPV infection are gaining relevance. A notable example for our case (HR-HPV infection clearance) is *Coriolus versicolor*-based vaginal gel (Papilocare®), for which the Paloma[4] clinical trial provided evidence for increasing the virus clearance rate by 57% compared to the control group.

Papilocare® is the first and only treatment indicated in Europe for preventing and treating low-grade HPV-caused lesions[5].

The post-treatment lesion repair and the viral clearance rates, along with the reduction in stress level[6] and the evidence for a good level of satisfaction and tolerability with the treatment, open up the possibility of HPV carrier patients using a treatment for low risk cervical lesions as opposed to the option of continuing everyday clinical practice based on "watch-and-wait" type check-ups.

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TREATMENT WITH *CORIOLUS VERSICOLOR.* A CASE STUDY

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ABSTRACT
Cervical cancer (CC) is the 3rd most common cancer among women worldwide. Suitable and sustained screening of healthy women using cervical cytology has managed to reduce the incidence and mortality from CC by 80-90%.
HPV is the causal agent of practically all cervical neoplasia and their precursor lesions.
Women aged over 30 years old present a lower prevalence of HPV infection, but a higher percentage of resistance, deriving in a higher risk and incidence of precursor lesions from this age onwards.

KEY WORDS: Screening. HPV. Precursor lesions. Cytology.

ANAMNESIS

A 31-year-old patient visiting for a routine gynecological check-up. Asymptomatic.

Personal history. Nothing of interest. Non-smoker. SH: Inguinal hernia.

Gynecological history: MM: 12 years old MD 4-5/28-30. TPAL 3003 (3 normal births). CM: Oral contraceptives. Last cytology performed in 2014. Diagnosis: negative for intraepithelial lesion or malignancy. Hormonal pattern compatible with age and history.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Physical examination: External genitals and vagina normal. Multiparous cervix. Uterus in anteversion, normal sized. Ligaments not touching.

Complementary tests:

- Transvaginal ultrasound: Uterus in anteversion, regular, 45x85x48 mm. EL 8.5 mm. Right ovary 22x19 mm. Left ovary 25x20 mm. No free fluid observed in pouch of Douglas.
- Patient has a cytology check-up. Diagnosis: intraepithelial squamosus lesion of low grade (LSIL) that undestands HPV/low displasia/ CIN I. Hormonal pattern compatible with age and history of the patient.
- Patient referred to the HUAV Cervical Disease Unit for the following in 6 months:
  - Cytology. Diagnosis: reactive celular changes asociated with inflamation. Negative to malignant cells. Changes in the microbiota because the bacterial vaginosis: Gardenella. moderate componenet inflamatory. Note: marking is observed defect of fixation/preservation of the sample.
  - Colposcopy: Suitable and satisfactory. TZ II. No acetowhite or Lugol's solution negative zones, a small zone with minor change at 1 o'clock (Fig. 1).
  - HPV. Molecular Biology: detection of human papillomavirus. Cervical sample: positive result LRU/CO=81,7.
    Comment: qualitative presence of high

FIGURE 1.

grade carcinogenic HPV (types 16/18/3 1/33/35/39/45/51/52/56/58/68) with the Hybrid Capture 2 tecnology. The numeric result correspond with arbitrary units.

TREATMENT AND EVOLUTION

- Patient recommended to use the barrier method with a condom, vaccination, and medical recommendations not to smoke. Prescribed treatment with *Coriolus versicolor* as follows:
  - 1 cannula/24 hours for 1 month (except during menstruation).
  - 1 cannula/48 hours for 6 months (except during menstruation).
- Check-up at one year.
- Does not smoke. Contraceptive method: oral contraceptives. Not vaccinated. Refers to treatment with *Coriolus versicolor* for 6 months.
- On examination presents: EG and vagina normal. Cervix with normal appearance. Colposcopy: TZ: type I suitable. Normal Acetic acid: fine mosaic at 12 o'clock. (minor changes). Schiller's test: positive (Fig. 2).
- Patient receives:
  - Cervical cytology: Negative diagnostic for the intrahepitelial lesions or malignancy. Presence of inflamation. Hormonal pattern compatible with age and history.
  - Cervical biopsy with location at 12 o'clock. Macroscopic description: 0.6 cm fragment. IT. JBC. Diagnostic: uterine cervix in 2 hours. Biopsy: mild dysplasia (CIN I, LSIL).
  - HPV - Cobas 4800. Diagnosis: detection of papilomavirus human of high risc with Cobas 4800 system. Results: negative. genotype: HPV16 negative; HPV18 negative; others HPV high risc (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) negative. Analytic sensibility: the limit of the detection of HPV is the 600 copys/ml, the HPV 18 is the 600 copys/ml and the other high risc HPV is between 80 and 2400 copys/ml according to genotype.

FINAL DIAGNOSIS

- After evaluating the tests, patient recommended to use the barrier method during sexual intercourse and is prescribed the Gardasil 9 vaccine.
- Patient requested for a check-up in one year to see the evolution.
- Said check-up currently pending.

FIGURE 2.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

In this case, it is worth noting that despite not following medical recommendation for vaccination against HPV, treatment using *Coriolus versicolor* for 6 months suitably manages to negativize the HPV.

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RESISTANT HPV 53 THAT DISAPPEARS AFTER TREATMENT WITH PAPILOCARE®

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ABSTRACT
Persistent HPV 51 infection disappearance after administering Papilocare® for 6 months.

KEY WORDS: Cytology. colposcopy. HPV, Papilocare®.

INTRODUCTION

A 46-year-old female diagnosed with a LSIL, HPV + 51 (high risk) 5 years ago. Cervical biopsy CIN I (low grade). After a watch-and-wait approach for one year, the cytology changes have disappeared, but HPV 51 persists. After several regular check-ups, vaccination, and stopping smoking, HPV + 51 persists. The infection disappears after treatment with Papilocare® for 6 months (pending confirmation by PCR in one year).

MEDICAL HISTORY

Sept 2015: A 41-year-old female referred from primary care for LSIL cytology, HPV + 51 (HR).

Personal history. Asthma on treatment with Symbicort. Smoker. Nothing else of interest

No known allergies to medicinal products

No family gynecological history of interest.

Gynecological and obstetric history: G.3 A.1 P.2 (one cesarean due to risk to fetal well-being, vacuum-assisted). Last menstruation date: two weeks ago. MT regular. CM: Ethinylestradiol/drospirenone for years. Does not recall the last cytology (years ago).

Gynecological examination and speculoscopy without significant findings.

Colposcopy: satisfactory, type 1 TZ. Acetic acid (3%) used to visualize a small fine mosaic zone from 7 to 9 o'clock, biopsy taken. Otherwise no findings.

Transvaginal ultrasound. uterus in anteversion regular, no findings. Endometrium 6 mm regular. Both ovaries viewed normal, no free fluid.

ANATOMOPATHOLOGICAL DIAGNOSIS: CIN I

Watch-and-wait approach and check-up at one year decided. Recommended to stop smoking.

Oct 2016: Cytology negative, HPV + 51 (HR). Has stopped smoking. Oct 2017: Cytology negative, HPV + 51 (HR).

Nov 2018: Cytology negative, HPV + 51 (HR). Nonavalent vaccination proposed due to the patient's concerns. Will think about it given the vaccine's high cost.

Vaccination with nonavalent Gardasil. (3 doses)

Jan 2020: Cytology negative, HPV + 5. Proposed Papilocare® for 6 months.

Dec 2020: Cytology negative, HPV negative. Pending confirmation in one year.

DISCUSSION

HPV is an infection that sometimes persists over time. It does not need to be a cause for concern if not associated with cytology damage,

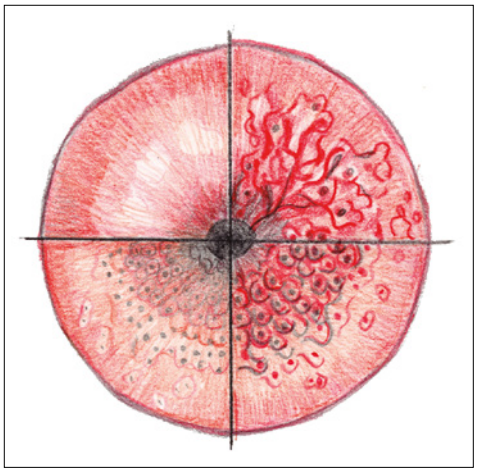

FIGURE 1.

ZOOM IN

however. Despite that, the virus' persistence over time, often for very long periods, causes many patients to feel anxious.

Coriolus versicolor (Papilocare®), can be a therapeutic option for patients in whom the virus does not clear unaided.

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INTERNAL *CORIOLUS VERSICOLOR*-BASED GENITAL GEL AS A TREATMENT FOR CONTROLLING AND HELPING TO REVITALIZE THE CERVICAL TRANSFORMATION ZONE TO PREVENT THE RISK OF HPV-CAUSED LESIONS (ASCUS/LSIL): A CASE STUDY

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection around the world, affecting up to 90% of sexually active people. Despite the infection eliminating unaided in most patients, viral persistence is related to the appearance of lesions, such as on cervical transformation zones (ASCUS/LSIL).

Other studies indicate that HPV persistence is more likely among people with an altered microbiota. Guo Y-l et al showed that women with HPV persistence had a bacterial vaginosis prevalence of 11% compared to only 5% of women who had eliminated the virus. Similarly, King et al observed that women with bacterial vaginosis presented later viral clearance (hazard ratio: adjusted 0.84, CI 95%: 0.72-0.97).

MEDICAL HISTORY AND ANAMNESIS

A 45-year-old patient with no history of interest, visiting for an asymptomatic check-up.

PHYSICAL EXAMINATION AND DIFFERENTIAL

The patient visits for her annual gynecology check-up in the office, the patient doesn't present external symptoms, external genitals normal.

Speculoscopy: cervix with mild erosion, discharge suggestive of ovulation, cytology performed and sent to Anatomic Pathology. Patient will visit the office again after 30 days to collect results

Patient called after 15 days to visit the office due to pathological results:

- Cytology with (LSIL/CIN I).
- Referred for colposcopy and PCR for HPV.
- The patient visits the office after 20 days for results.
- Colposcopy agrees with cytology.
- PCR positive for 51 (High Risk).
- Treatment with Papilocare® prescribed for HPV, check-up in 6 months
- Patient visits after six months of treatment, cytology, PCR and colposcopy performed

Results: Cytology negative. Colposcopy negative. PCR negative

TREATMENT AND EVOLUTION

Six months' treatment with Papilocare® vaginal gel started.

HPV clearance diagnosed after six months of treatment and specific tests

FINAL DIAGNOSIS

After six months of treatment, lesions confirmed to have disappeared, patient discharged.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

In this case, it is worth noting the clearance of high risk HPV 51 after only six months of treatment with Papilocare®, with cervical lesions returning to normal.

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TREATMENT WITH *CORIOLUS VERSICOLOR* GEL DUE TO HPV 16 PERSISTENCE AFTER CERVICAL CONIZATION: A CASE STUDY

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ABSTRACT
Excisional treatment is chosen for most high grade cervical lesions. Despite the high rate of success with that treatment, 5 to 25% of patients present a post-treatment lesion in the subsequent two years.
Two hundred conizations are performed each year in our center with a high rate of negativization for HPV tests at the 6 and 12 month check-ups.
The presented case is a patient subjected to a cervical conization for HSIL and HPV 16 in 2018, with viral persistence during post-treatment follow up.

KEY WORDS: HPV. Persistence. Conization.

MEDICAL HISTORY AND ANAMNESIS

A 37-year-old female, nulligravid. Combination hormone-based contraceptive user for several years. Not HPV vaccinated and a non-smoker.

Referred to the LGTPU for cytology change consistent with ASC-H and HPV 16.

EXAMINATIONS PERFORMED

Colposcopy: Unsatisfactory. Type 3 TZ, ECL only visible on the anterior lip. Small spotting area at 11 o'clock. Negative endocervical study. Cervical biopsy: CIN II.

TREATMENT AND EVOLUTION

Excisional treatment performed on the lesion using loop diathermy conization, obtaining a conization piece with the following anatomopathological result:

- With a thermal artefact and presence of an artefact fragment that expresses p16, which could correspond to a squamous lesion zone.
- Free margins
- Curettage without lesions.

First check-up at 4 months given that the margins weren't considered evaluable. The result was a normal TZ1 colposcopy, a normal cytology, and positive for HPV 16.

The second check-up showed identical results, so Papilocare® vaginal gel use added and a third check-up scheduled.

The patient had an HPV vaccination in her health center with 3 vaccine doses during this follow-up.

FINAL DIAGNOSIS

After 6 months of treatment (first dose daily and every other day during the subsequent 5 months), cytology and HPV test performed, both negative.

The patient did not have tolerability issues with Papilocare® vaginal gel, with no side effects presenting during use.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

There is sufficient evidence to show that high risk HPV persistence is an important factor

regarding the development of post-treatment lesions.

Complete elimination of the lesion negativizes HPV in 70% of cases at 6 and 12 month check-ups.

This case forms part of the viral persistence percentage after excisional treatment of the lesion.

Every cytology was normal after the conization, suggesting complete excision of the lesion. However, HPV 16 remained positive at 6 and 12 month check-ups.

Using *Coriolus versicolor* gel on this patient, based on relevant published evidence, appears to have contributed to HPV 16 clearance during the 3rd check-up on completing the 6 month regimen. This enabled referral to the standard Primary Care screening program, as such avoiding unnecessary check-ups in the LGTPU.

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LSIL-CIN I TREATED WITH *CORIOLUS VERSICOLOR* VAGINAL GEL (PAPILOCARE®)

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ABSTRACT
Treatment of LSIL- CIN I with Papilocare® vaginal gel

KEY WORDS: LSIL. HPV. Colposcopy- biopsy. Papilocare®. Viral clearance and resolution.

MEDICAL HISTORY

A 35-year-old female, nulligravid, visiting the Cervical Disease Unit for the first time due to a LSIL cytology with an HPV test of HR + (31 and 45), performed at her health center. She smokes 10 cigarettes a day, has had a stable partner for 2 years, having had 4 previous sexual partners. She uses condoms from time to time, is not vaccinated against HPV and does not have any surgical or family history of interest. The patient would like to fall pregnant in the medium-term and is very concerned about the possibility of malignant disease, and what this could mean regarding her reproductive future and relationship with her partner.

PHYSICAL EXAMINATION AND COLPOSCOPY

he external genitals are normal. Colposcopy examination performed, observing a type 1 TZ, a thin acetowhite epithelium with geographical margins, a regular mosaic and fine spotting, minor changes that cover the anterior quadrant. Decided to take a biopsy of that cervical lesion, reported as a low-grade squamous epithelial lesion - CIN I, so indicated to return for another check-up in 6 months. Recommended to stop smoking and regularly use a condom, prescribing her nonavalent HPV vaccine.

She had another cytology at 6 months, with LSIL persisting, and the colposcopy examination is similar to the previous one.

TREATMENT AND EVOLUTION

Given these results and the patient's concern, decision taken to treat with Papilocare® vaginal gel for 6 months and to evaluate her again afterwards. Another co-test performed, which was negative, and the colposcopy examination is normal.

The patient expresses great relief and satisfaction, wanting to fall pregnant from that moment onwards, managing to do so after 4 months. Currently following a normal course of birth in her 28th week.

FINAL DIAGNOSIS

LSIL- CIN I of 1 year evolution treated with *Coriolus versicolor* vaginal gel (Papilocare®).

DISCUSSION AND THE CASE'S IMPORTANCE

Human papillomavirus is a virus that infects the skin and mucosa. 200 types have been identified and 40 can infect the genital and anal mucosa (mucosal HPVs). They are divided into high risk or oncogenic HPV (16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59) and low risk - not associated with cancer, but can cause genital warts or condylomas. It is a

sexually transmitted virus, with most likelihood of contagion occurring during the early years of sex life. 20-30% of women aged under 30 years old are HR-HPV carriers and this percentage reduces with age to below 10% among women aged over 50 years old. Over 80% of HPV infections are temporary in nature and resolve within the 3 years period after infection[1].

However, in a small percentage of cases (15%), HPV infection persists over time without the immune system being able to eliminate it. This persistence over time is the main risk factor for developing premalignant lesions. In the case of persistent infection, HPV can cause cell changes that derive in the development of premalignant lesions that can evolve into cancer over time.

The risk factors contributing to persistent infection are HPV type, smoking, immunosuppression, and taking hormone-based contraceptives for an extended period.

The genial area at most risk from persistent HPV infections is the cervix, and specifically the transformation zone. The cervix' histological structure is somewhat unstable with 2 epitheliums opposing each other: the multi-stratified squamous vaginal and the columnar or glandular endocervical. The reserve cells are located under the glandular epithelium, which conserve the capacity to grow and differentiate towards mature squamous epithelium cells (most commonly) or glandular cells. This process is called metaplasia and creates a more or less extensive area in the cervix known as the transformation zone, which is very susceptible to infection by HPV.

HPV needs cells in mitotic activity to integrate and the reserve cells are in metaplastic reepithelialization process, meaning they are targets for HPV anchoring[2].

Premalignant lesions are classified as low grade lesions (LSIL – CIN I) or high grade lesions (HSIL – CIN II-III). Most low grade lesions resolve unaided without any treatment. However, high grade lesions tend to be persistent with a low likelihood of unaided resolution and a significant risk of malignant transformation[3].

In the presented case, the LSIL had evolved for 1 year and the patient is concerned, because she fears cancer and also that it will affect her reproductive future. As such, a WATCH & WAIT approach is abandoned, with an attempt to reduce the infection persistence time and slow down its progression, so we think that using Papilocare® vaginal gel for 6 months could achieve that[4].

Papilocare® is a health product in the form of vaginally applied gel based on *Coriolus versicolor* and other phytotherapeutic ingredients, such as hyaluronic acid, *Centella asiatica,* aloe vera and *Azadirachta indica* (neem), some of which contain nyosomes and phytosomes that enable its use as vaginal mucosa moisturizer and repairer[2].

Coriolus versicolor is a fungus from China that contains β glucan polysaccharides with known immunostimulating properties, and antimicrobial and antitumor activity. This fungus acts as an immunomodulator and its β glucans can cause selective apoptosis on cancerous cells without affecting healthy cells. In humans, there is evidence for its enhancing effect on cell immunity, achieving anti-tumor activity among patients with different types of solid cancers. Among patients with HPV infection, a regression effect has been observed in low-grade squamous cervical intraepithelial lesions, as well as viral clearance.

Azadirachta indica (Neem) is an evergreen tree from India providing therapeutic activity through its components, with include azadirachtin, and they have pharmacological effects via significant antioxidant activity.

Several studies have provided evidence for the efficacy of applying Neem in the vagina compared to placebo, eliminating HPV from HPV 16+ women with or without LSIL in 80% of cases compared to 10% with placebo, providing evidence for the efficacy of the intravaginal use of Neem.

The PALOMA clinical trial managed to show the normalization of the HPV-caused ASCUS/LSIL lesions (normal cytology and concordant colposcopy) at 6 months of treatment among 85

% of women treated with Papilocare® vaginal gel compared to 65% in the control group.

The PALOMA trial also managed to show viral clearance at 6 months of treatment in 63% of women with high risk HPV compared to 40% in the control group[5].

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TREATING GENITAL WARTS ON MEN WITH EXTERNAL PAPILOCARE® GEL: A CLINICAL CASE

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ABSTRACT
Anogenital warts caused by Human papillomavirus (HPV) represent one of the world's most common sexually transmitted diseases. There isn't a specific curative treatment for them, although there are many therapies that target their destruction, anti-proliferation, or immunomodulation, in addition to other complementary options[1].

KEY WORDS: Condyloma. HPV. Male.

MEDICAL HISTORY

A 33-year-old male patient consulting due to warty lesions appearing in recent weeks.

No notable medical-surgical history of interest, although he states that he is lactose-intolerant. Does not refer to any toxic habits or family history of note. Varied and healthy diet.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The physical examination shows 2 x 5mm lesions above the pubic area and 3 x 2-3mm lesions on the shaft of the penis (the right margin), all suggestive of condylomas. The patient provides serologies for sexually transmitted diseases, with negative results.

DIFFERENTIAL DIAGNOSIS

Different conditions need considering regarding the differential diagnosis of condyloma lesions among men. Some are variants from the norm, like pearly penile papules, preputial exocrine glands, vestibular papillae or sebaceous cysts. There is also the need to rule out infections or inflammatory conditions, such as syphilis, *molluscum contagiosum,* lichen planus, or psoriasis. Lastly, it is worth evaluating for possible benign or malignant tumors, such as carcinomas, seborrheic dermatitis, Bowen's disease, or lymphangioma[2].

TREATMENT AND EVOLUTIONN

Undertaking initial medical treatment and evaluating the need for subsequent ablative therapies was agreed with the patient. Imiquimod 50mg/g cream was indicated for application on the external genitals three times a week, alternating with the use of Papilocare® external gel twice a day. At 15 days, a new physical examination was performed, observing a clear reduction in the size of the condylomas. Cryotherapy was applied to the residual lesions and maintenance treatment with e xternal Papilocare® gel was indicated. A final clinical check-up at 15 days showed complete remission of the warty lesions, which were absent during the examination.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

HPV (particularly subtypes 6 and 11) is one of the main causal agents of genital warts, with

prevalence having increased in recent years [3]. Although most studies focus on their presence among women, condyloma acuminata are common among men, so detecting and treating them is important.

As indicated in the clinical guidelines, the initial management of patients consulting due to the appearance of genital warts, consists of a detailed anamnesis (with particular emphasis on the HPV-related risk factors: smoking, immunosuppression, risky sexual behaviors…), and a thorough physical examination, in order to obtain a suitable differential diagnosis. It is important to personalize each patient's treatment, adapting it to the number, size, morphology, and location of genital warts. Therapeutic options include ablative treatment (cryotherapy, CO_2 or Nd:YAG laser, electrocautery, surgical resection, or trichloroacetic acid), immunomodulatory therapies (imiquimod or sinecatechins) and other topical treatments (podophyllotoxin or zinc nitrate)[2].

Using complementary treatments, such as Papilocare® (Procare Health), based on a *Coriolus versicolor* gel, has provided evidence of beneficial effects on HPV-related cervical lesions and an association of greater viral clearance among HPV-positive patients[4,5].

The patient described in this review presented multiple small-sized condylomas, so the decision was to initiate treatment with immunomodulators, and external Papilocare® gel as a complementary treatment, in order to reduce the volume of the lesions and enable more conservative use of ablative techniques. The evolution was favorable, observing complete remission within 4 weeks.

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CORIOLUS VERSICOLOR-BASED VAGINAL GEL FOR TREATING PERSISTENT HPV IN THE CERVIX WITHOUT ASSOCIATED CERVICAL DYSPLASIA. A CASE STUDY

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection around the world, affecting up to 90% of sexually active people. Despite the infection clearing unaided in most patients, viral persistence is related to the appearance of lesions, such as condylomas, and low-grade (LSIL) and high-grade (HSIL) cervical intraepithelial lesions. Cervical intraepithelial lesions regress over a period of about 2 years in over 80% of cases, particularly in the case of lower risk viruses[1]. However, other cases can evolve towards high-grade cervical intraepithelial lesions (HSIL) that can require excisional treatment[2].

Viral persistence is the most relevant marker for the lesion, and the biggest predictor of evolution to HSIL[3].

Of the 15 risk-type HPVs that affect the cervix, five (16,18, 33, 31 and 45) are associated with higher cancerous potential, with subtypes 16 and 18 causing 60% of grade 3 cervical intraepithelial lesions (CIN III) and 70% of cervical cancers[4].

KEY WORDS: HPV. Cervical conization. Cervical intraepithelial lesions. Surgical treatment.

MEDICAL HISTORY AND ANAMNESIS

A 56-year-old patient, with a clinical history of malaria in 2011 (which required hospitalization) and chondromalacia patellae since 2020. No surgical history of interest. Nulligravid. No known allergies to medicinal products. States no toxic habits.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Patient visits the ASSiR (primary care gynecological office) cervical disease office for low-grade cervical dysplasia (LSIL) presenting during the three times a year cervical cytology performed within the context of opportunistic population screening[5]. Referred to the office for a colposcopy. Said colposcopy examination does not show lesions requiring biopsy and requested to visit for a check-up in six months.

TREATMENT AND EVOLUTION

Six monthly follow-up of the patient initiated in the ASSiR cervical disease office, with a HSIL result in the cervical cytology, confirmed by cervical biopsy during 08/2015. Referred to the tertiary level hospital cervical disease unit for evaluation of excisional treatment of said lesion. Type III cervical conization and fractionated biopsy

curettage performed during 03/2016. The surgical piece results in anatomical pathology classification as CIN III, with free resection margins.

Post-surgical cytology check-ups and HPV determination are initially negative, meaning the patient is discharged from the hospital's cervical disease unit and referred again to the tertiary level ASSiR, when during the check-up of 10/2017, the cervical cytology is negative, but HPV detection is positive again for high risk HPV, RLU/CO:37.62. The patient does not want to receive vaccination for HPV. Requested to visit again for annual check-up.

During the co-test check-up of 10/2018, the cervical cytology results negative, but the HPV detection shows high risk HPV persistence, RLU/CO:11.97.

During 01/2019, initiating treatment with *Coriolus versicolor*-based vaginal gel for 3 to 6 months proposed to the patient, who accepts. During 05/2019, case evaluated again with a co-test, with a negative cervical cytology result and undetectable HPV.

The patient is discharged from the ASSIR cervical disease office and informed that she must continue the screening controls for cervical cancer based on the current protocol (cervical cytology three times a year)[6].

FINAL DIAGNOSIS

High grade cervical intraepithelial neoplasia: CIN III.

Persistent HPV infection.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

In this case, it is worth noting that after excisional treatment of high grade cervical intraepithelial lesion and subsequent confirmation of the disappearance of the lesion and undetectability of HPV, HPV was detected again in a cervical sample at 19 months from the operation. No cytology lesion detected and evidence of negativization of HPV after 4 months of treatment with *Coriolus versicolor*-based vaginal gel.

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DISAPPEARANCE OF PERSISTENT LOW GRADE INTRAEPITHELIAL LESIONS ASSOCIATED WITH HPV 18 VIRUS AFTER THREE MONTHS TREATMENT WITH *CORIOLUS VERSICOLOR* VAGINAL GEL

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ABSTRACT

Most clinical centers continue to include surgery, such as performing conizations or other types of major or minor surgical interventions, for patients that present a low-grade lesion (LSIL) associated with a positive test for risk HPV, and which persist over time, longer than two years of follow-up. Although indefinite follow up can be an option for reliable patients, patient weariness or fear, or even from the doctor him/herself, can necessitate the decision to perform a surgical treatment, which 'frees" the patient from the problem.

Despite encouraging results in recent studies, treatment with *Coriolus versicolor* vaginal gel is still not an option in most clinics, although it could represent an alternative to surgery when the situation extends over time.

We present a case here for whom medical treatment managed to, on the one hand, avoid unwanted surgery, and on the other, extended the follow-up that was a source of stress for the patent. The peculiarity of this case is that the satisfactory result was achieved with just three months of treatment.

KEY WORDS: *Coriolus versicolor.* LSIL.

MEDICAL HISTORY AND ANAMNESIS

A 35-year-old patient visiting the Gynecology office of Llevant hospital (Mallorca) in December 2019 for the first time.

No medical history of interest, only worth noting that she smokes 10 cigarettes a day.

When it comes to gynecological and obstetric history, she had an abortion at the age of 20 years old and she used oral hormone-based contraceptives up to six months ago, as she would now like to fall pregnant.

In June 2016 she had a routine cytology by her area midwife. This was the patient's first ever cytology, obtaining an ASCUS result.

The patient was referred to her tertiary level public hospital, where she was seen in August of that year in the Cervical Disease Unit.

Colposcopy performed during that visit describing a spotted zone on the upper lip, not enhanced by Lugol's solution, so guided biopsy performed along with an HPV test sample taken.

Requested to visit again two months later. According to the reports, the biopsy result is Low grade Squamous Intraepithelial Lesion (LSIL/CIN-I) and the HPV test was positive for HPV 18.

Six-monthly follow up proposed to the patient. At each of those six-monthly check-ups, colposcopy and cytology performed with a result

of LSIL every time, and a biopsy at one year of the diagnosis with another HPV test with the same result, LSIL and HPV 18 positive.

Given the persistence of the lesion, the gynecologist proposed conization in October 2019, which the patient rejects as she is hoping to fall pregnant and thinks that the intervention could place her reproductive ability at risk. Furthermore, she request therapeutic action as she is tired of visiting for check-ups with samples taken but no treatment offered.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

After two years of cytology and colposcopy follow-up, the patient decides to visit our office in December 2019. She is concerned because she thinks that both the lesion and surgical treatment she was offered may compromise her reproductive future.

After a detailed anamnesis and clarifying queries and misunderstandings, her current status is explained, she is recommended to stop smoking, and she is offered diagnostic tests again in order to confirm the diagnosis.

She has a complete gynecological examination, including vaginal ultrasound, which only highlights extensive erythroplakia around the orifice and thick discharge.

Vaginal culture, cytology, endocervical brushing, an HPV test, and colposcopy all performed.

Colposcopy shows a type 1 transformation zone on the upper lip with a guided biopsy taken.

Patient requested to visit for the results.

The cytology shows an ASCUS, the brushing shows no dysplasia, the guided biopsy gives a LSIL result, the HPV test remains positive for HPV 18 and the culture shows vaginal flora. This means the final diagnosis is HPV 18-related LSIL, ruling out other potential causes of cytology changes or infections.

TREATMENT AND EVOLUTION

Patient proposed treatment with *Coriolus versicolor* vaginal gel[1,2] daily for three months, apart from during the menstruation, and reevaluation after those three months.

Completing this treatment period, the patient visits for a check-up, with the physical examination noting the disappearance of the erythroplakia and that the discharge looks better.

Cytology, another HPV test, and colposcopy performed.

Colposcopy does not show any evidence of change this time, so no biopsy taken.

Patient requested to visit for the results, which are negative for dysplasia. HPV test also negative.

Decided to repeat the colposcopy and take a multiple biopsy from the upper lip despite no lesion observed. The biopsy result is also negative for dysplasia, only describing squamous metaplasia.

Patient asked to visit again 6 months later for a check-up after not taking treatment. Colposcopy performed during this last visit (negative) and cytology taken, with the result negative for dysplasia again.

Patient's next scheduled visit is for a routine check-up.

DISCUSSION

The case's importance comes partly from these situations that extend over time causing concern for the patient and a lack of confidence in the doctor[2,3], given that despite our explanations, and the validity of active surveillance, many patients infer that we aren't doing "anything" to resolve their problem.

Furthermore, although treatment with *Coriolus versicolor* vaginal gel[4] has already been available in the market for years, many doctors don't use it due to inertia, given that medical treatment wasn't possible for many decades, rather only surgical or destructive treatments.

More and more studies ate supporting the benefits to cervical reepithelialization when using *Coriolus versicolor* and its positive influence on eliminating the virus or cells it affects.

Furthermore, no significant side effects with this therapy have been described, meaning it could be offered for every case of mild

intraepithelial dysplasia associated with a positive risk HPV test at the time of diagnosis.

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VULVAR HSIL (USUAL TYPE VIN) RELAPSING DURING PREGNANCY

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ABSTRACT

Treatment and subsequent follow-up of a 44-year-old patient with a prior history of lower genital tract disease and a usual VIN relapse during pregnancy.

KEY WORDS: Usual type VIN. Pregnancy. Human papillomavirus. Vaccination.

HISTORY

No family history of gynecological and breast cancers.

Personal history. No allergies to medicinal products. Ex-smoker. No medical diseases of interest. Endometriosis operated on twice (laparotomy in 2002 and laparoscopy in 2018), conization in 2017.

Gynecology and obstetrics history. M11 MD3-4/28 with AMB. G1 (currently pregnant ART IVF-Ovodón). Date of last menstruation: 01/07/21. Probable due date: 10/13/21

LOWER GENITAL TRACT DISEASE HISTORY

- April 2015: LSIL cytology.
- July 2015: Colposcopy LSIL histological.
- July 2016: Co-test LSIL. HR-HPV no 16-18.
- October 2016: Colposcopy HSIL histological. p16 positive dual-staining.
- January 2017: Conization free margins. Suspicious upper right vulvar lesion, punch biopsy VIN1. Treatment with Imiquimod cream.
- May 2017: Upper right lip vulvar lesion, punch biopsy negative.
- November 2017: Colposcopy negative. HPV vaccination completed in 2018.
- January 2018: cytology negative.
- February 2019: cytology negative. Suspected upper right lip vulvar lesion, punch biopsy VIN3.
- May 2019: Excisional biopsy of a 2-3 cm vulvar lesion. VIN3, Carcinoma epidermoide in situ with skull base involvement margin.
- May 2019: Amplification of the lesion's upper margin. No histological lesion.

Treatment with specific dietary supplement and external *Coriolus versicolor*-based gel.

CASE PRESENTATION

A 44-year-old patient, visits the Lower Genital Tract Disease office for a check-up in March 2020, 8 weeks pregnant, asymptomatic, no vulvar symptoms, vulvoscopy without findings, no lesion on examination. Co-test with negative cytology, HR-HPV 16 positive. Another study postpartum proposed.

DIFFERENTIAL DIAGNOSIS OF HPV-ASSOCIATED AND NON-HPV-ASSOCIATED PREMALIGNANT VULVAR LESIONS

Table I.

TREATMENT AND EVOLUTION

During a virtual consultation during the COVID-19 pandemic, the patient refers to the reappearance of a vulvar lesion in a previously

TABLE I.

HPV-ASSOCIATED	NON-HPV-ASSOCIATED
HSIL. Usual type VIN	Differentiated type VIN
More common Multi-focal	Less common Single lesion
Generally involved HPV 16, 33, 18 Associated with: dysplasia in other LGT locations and condylomas, smoking, and immunosuppression	Associated with: chronic inflammation or skin diseases, and vulvar dermatitis (e.g.: Vulvar Lichen Sclerosus; Lichen Simplex Chronicus)
IHQ: p16(+); p53(-)	IHQ: p16(-); p53 overexpression
Risk of progression to squamous cancer: 6%	Risk of progression to squamous cancer: 33%
Young patients (20-40 years old)	Older patients (>60 years old)
Better prognosis	Worse prognosis

operated area. Requested to visit for a vulvoscopy and biopsy if required (2nd trimester of pregnancy), which is positive, with another punch biopsy on the lower right lip, reported as VIN3.

Specific treatment of this patient discussed by the Department's Committee and a watch-and-wait approach decided, with regular clinical check-ups, and to defer excisional treatment to postpartum.

Pregnancy check-ups in High Risk Obstetrics due to insulin-dependent gestational diabetes, and in the cervical disease office, with the vulvar lesion stable, no visible changes on examination.

In October 2020, birth induced due to insulin-dependent gestational diabetes, and emergency Cesarean due to lack of progression of the birth, with a female born weighing 3550g, Apgar 9-10, no incidents.

Visits the Lower Genital Tract disease office for postpartum check-up in November 2020, finding evidence of a 2cm vulvar erosive lesion in the right interlabial sulci. Cytology performed, negative.

Incisional vulvar punch biopsy performed in November 2020 under local anesthetic, reported as squamous cell carcinoma in situ.

Vulvar lesion excision with margins and depth performed under locoregional anesthesia in the operating room in February 2021, with the AP reporting extensive VIN3 that touches the internal lateral margin. Margin amplification surgery performed during the same month (without being able to amplify by depth due to contact with the vagina), with the anatomopathological report stating focal VIN3 with no surgical margin involvement.

FINAL DIAGNOSIS

VIN3/ squamous cell carcinoma *in situ* with no surgical margin involvement

Visits for post-surgery check-up in March 2021, asymptomatic and with correct healing after surgery, without lesions appearing to suggest relapse, and check-up scheduled in the specific Lower Genital Tract disease office for 3 months.

Virtual consultation in April 2021, patient asymptomatic and no lesions, pending evaluation in June 2021, which will include a vulvoscopy, another co-test and colposcopy.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Vulvar dysplasia or premalignant vulvar cancer lesions require an early diagnosis and suitable treatment in order to prevent progression to vulva cancer. There is no primary prevention or opportunistic or population screening, as this type of cancer is not highly prevalent.

VIN is very complex disease, with a high risk of recurrence after treatment and an optimal unique therapy doesn't exist, rather different alternatives.

HPV-associated lesions can appear both in the cervix and other lower genital tract locations, such as the vulva, the vagina, the perineum and the anus, and the oropharyngeal area, which are compulsory examination areas in the cervical disease or lower genital tract office. As such, a patient with a history of cervical disease can develop HPV-related disease in these related areas.

Topical and dietary co-adjuvant treatments with surgery on lower genital tract dysplasia, along with the importance of HPV vaccination and giving up smoking, are measures that help improve immunity against HPV, by far the main causal agent of these genital dysplasia.

As is the case for lower genital tract disease, sub-specialized gynecology units are required and needed to focus more specifically and suitably on these patients.

The importance of multidisciplinary treatment, expert committees with several specialties, joint approaches and the individualization of complex cases, mean better and quality medical care is possible.

The current SARS COVID-19 pandemic has caused us to change classic medical approaches, adapting to telehealth as a new very useful form of care and a suitable communication tool for patients, in order to remain in touch during complex situations that require regular follow up.

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RESOLUTION OF VAGINAL AND CERVICAL INVOLVEMENT DUE TO PERSISTENT HR-HPV AFTER TREATMENT WITH *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL: A CASE STUDY

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ABSTRACT

Squamous intraepithelial lesions (SIL) and cervical cancer represent a significant public health problem that requires priority intervention due to their high mortality and morbidity rates. With the implementation of tests to detect cervical cancer and its precursor lesions, morbidity and mortality has constantly decreased in recent decades. However, cervical cancer remains the third most common malignant disease[1] among women worldwide.

Data obtained from the numerous investigations undertaken to date provide evidence for a close relationship between the appearance of changes with a different grades of malignancy in the female genital tract, and the presence and persistence of high-risk human papillomavirus genotypes (HR-HPV)[2].

KEY WORDS: LSIL. HPV persistence. Vaginal microbiota.

MEDICAL HISTORY

A 38-year-old patient, Spanish, and university educated. Presents a family history of a maternal aunt with breast cancer. Patient with a personal history of dyspepsia, lactose and fructose intolerance. Underwent an adenoidectomy during childhood and no allergies to medicinal products. Does not take any regular treatment. Non-smoker or no other toxic habits stated.

First menstruation aged 12 years old with regular menstruation. Experienced a spontaneous abortion that did not require any evacuation treatment.

Does not have a stable partner at present. She had sexual intercourse for the first time aged 17 years old and has had 5 sexual partners. She uses condoms as a contraceptive method. She hasn't been vaccinated against HPV.

The patient visits having been referred the cervical disease office due to HPV 18 persistence for 3 years with normal cytologies and colposcopy (check-ups in private health care to date).

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Examination of the vulva and perineum does not show any abnormal finding. In the speculoscopy, the vagina presents numerous projections compatible with HPV infection. The cervix is nulliparous, presenting mild ectropion.

Co-test performed with liquid cytology.

Suitable colposcopy performed, showing a type one transformation zone. Fine acetowhite lesion observed at 1 o'clock and a one centimeter superficial mosaic (Grade 1). Biopsy of the lesion taken (Figs. 1 and 2).

In the vaginoscopy, signs of HPV infection with a condyloma appearance observed on the right lateral face (Figs. 3 and 4).

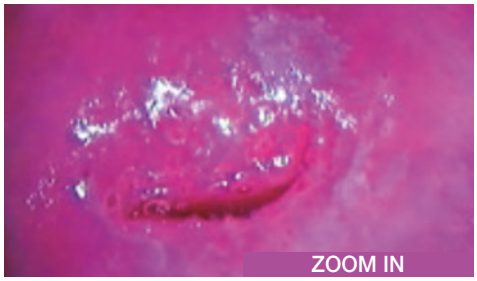

FIGURE 1. Colposcopy image: superficial acetowhite lesion at 1 o'clock.

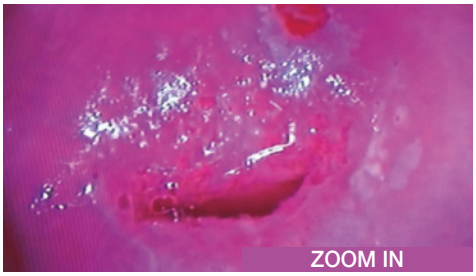

FIGURE 2. Cervix biopsy.

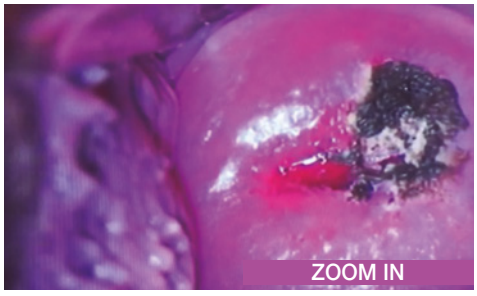

FIGURE 3. Vaginoscopy: right lateral face involvement of the vagina by HPV infection.

FIGURE 4. Amplification of the vaginal involvement zone.

RESULTS

Cytology reports LSIL, HPV 18 persists, and HPV 6 also presents. Cervix biopsy reports LSIL.

TREATMENT AND EVOLUTION

Check-up with co-test and colposcopy at one year recommended.

HPV vaccination recommended, along with treatment with Papilocare® vaginal gel for 6 months (applying the gel for 21 days during the first month and every other day during the subsequent months).

Cytology at one year is negative, both HPVs eliminated and colposcopy normal, no pathological findings.

FINAL DIAGNOSIS

HR-HPV clearance with regression of the LSIL cervix lesion and vaginal involvement.

One year of follow-up later, the patient did not present any changes, was discharged, and continues with population screening check-ups.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Squamous intraepithelial lesions in the cervix are the precursors of cervical cancer. They are classified as low-grade lesions (LSIL) and high-grade lesions (HSIL), depending on the level of epithelial involvement.

Millions of women throughout the world are diagnosed with these types of lesions, particularly LSILs, resulting in high care costs. This pathology involves numerous hospital visits, with cytologies, colposcopies with or without biopsies, treatment when necessary, and follow-up[3,4]. These women also often experience anxiety, a fear of cancer, sexual relationship difficulties, a lack of trust in their partners, they view their bodies differently, embarrassment, stress,…. To sum up, they can be perceived as a threat to both reproductive potential and life itself.

Many women diagnosed with LSIL are young, may or may not have had children, or are yet to complete their family, so conservative treatments

need to be used that don't compromise therapeutic efficacy, while also respecting the cervix's anatomy and function. Many changes have taken place when following up LSIL lesions. In the past, treatment of these lesions was offered to prevent progression to a cancer, but it is now known that many of these lesions regress unaided, so treatment is now more conservative.

In everyday practice, it would be very useful to use conservative treatments that help to eliminate HPV-caused lesions and clear the viral infection itself, given that the risk of the lesions progressing are HPV persistence-dependent.

The possibility of treating patients, helping them to eliminate the HPV infection would help reduce the health care cost, lengthening the follow-up intervals, and reducing the morbidity derived from invasive diagnostics and unnecessary treatments. This would also reduce anxiety among a significant number of patients.

Recent data shows a significant correlation between immunological status and the virus' persistence. The vaginal microbiota plays a significant role in modulating the immunological status of the female genital tract[5]. Vaginal microbiota composition is influenced by numerous factors: the level of the hormones estrogen and progesterone, menopausal status, use of contraceptive hormones, sexual interactions, hygiene measures, and infection[6]. There is a lot of evidence that correlates HPV persistence with the abnormal presence of vaginal lactobacillus and an abnormal microbiota. A balanced vaginal microbiota ensures a better response against HPV[7-9].

In the described case, the patient presented HR-HPV 18 persistence for 3 years. The final colposcopy check-up showed a low grade squamous intraepithelial lesion affecting the cervix, confirmed by biopsy and viral involvement of the vagina. In this case, the patient's immune system was not managing to eliminate the viral infection, so some form of intervention to help eliminate the persistent HPV infection was necessary. Suitably maintaining or improving the status of vaginal health and acting positively on the cervical epithelium and vaginal microbiota could be a new approach for preventing both the acquisition and persistence of HPV infection, and the progression of precancerous lesions.

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CERVICAL CONDYLOMA DURING PREGNANCY

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ABSTRACT
We present the case of a patient diagnosed and treated for cervical condyloma during the 1st trimester of pregnancy.
Genital warts are the most common clinical manifestation of HPV. 22,000 new cases are diagnosed among women each year in Spain, while approximately 8% of European women are estimated to have been diagnosed with this lesion at least once during their life.

KEY WORDS: Condylomas. HPV. Wart. Cervix. Pregnancy.

CLINIC CASE

A 33-year-old patient, asymptomatic, visiting to date the pregnancy.

No family or personal history of interest. As regards gynecological-obstetric history, she presents suitable CC screening; the last cytology was 3 years ago, so a new sample is taken.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The examination is insignificant other than warty lesions in the vaginal introitus. A vaginal speculum shows another warty lesion on the anterior cervical lip that looks like a cervical condyloma when examined macroscopically (Fig. 1). Early pregnancy developing normally at 6 weeks.

Cytology reports atypical squamous cells of undetermined significance (ASCUS) and flora suggestive of bacterial vaginosis. Reflex HPV test positive for other HR-HPVs. Colposcopy performed, suitable with a type 1 transformation zone, normal columnar epithelium, squamous metaplasia epithelium without lesions, vaginoscopy negative.

DIFFERENTIAL DIAGNOSIS

Condyloma acuminata (CA) are the clinical expression of infection from certain types of what are considered to be low oncogenic risk HPVs, mainly 6 and 11[1,2]. Condyloma acuminata is a common and highly infectious STD[3], which can cause psychological involvement among patients, given its tendency to relapse after treatment, cause malignancy, be transmitted to a sexual partner and from mother to child, and in the latter case, cause juvenile laryngeal papillomatosis[4].

The differential diagnosis should also be made with vestibular papillomatosis, a physiological finding different to CAs because their papules are not acetowhite, with each having a separate base, while CAs share a base and have a rooster comb-like surface. Other papules are molluscum contagiosum and seborrheic keratosis. Other differential diagnoses to consider are leukoplakia or hyperkeratosis (Fig. 2) and cervical adenocarcinoma (Fig. 3)[4].

Performing vulvar colposcopy after applying acetic acid is not recommended as a routine examination, but it can prove useful if an intraepithelial neoplasia or initially invasive cancer is suspected in the vulva and anal area. It helps to mark out the lesion and choose the site of the biopsy. However, it should be understood that an acetowhite epithelium in the vulva is a nonspecific finding.

SUMMARY

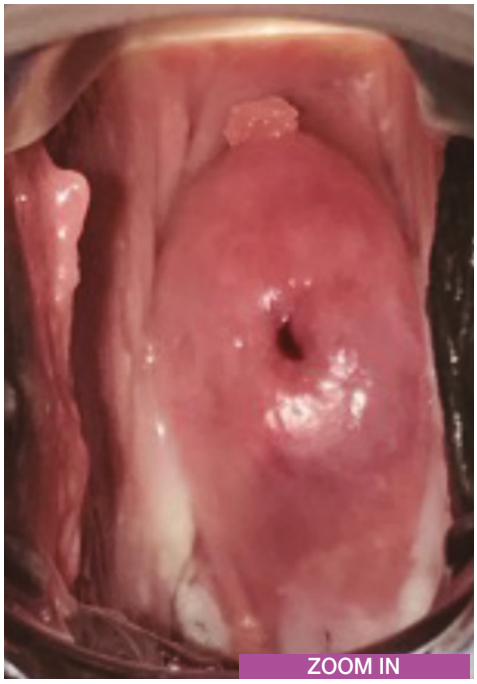

FIGURE 1. Condyloma on the anterior cervical lip.

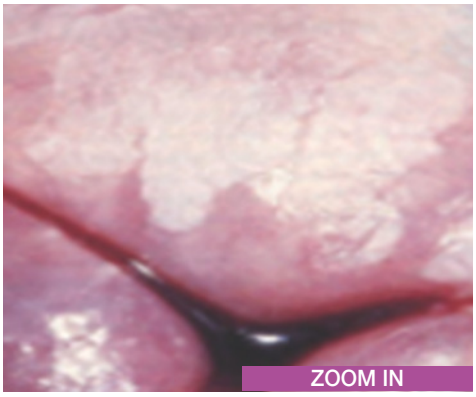

FIGURE 2. Keratosis or cervical leukoplakia.

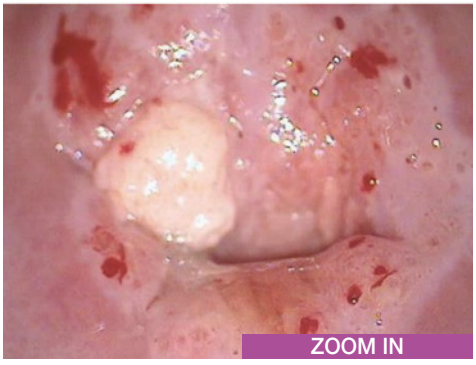

FIGURE 3. Adenocarcinoma on the anterior cervical lip.

TREATMENT AND EVOLUTION

Excision of the cervical condyloma performed using a punch biopsy with subsequent histological confirmation. Therapy mainly targets their elimination in order to reduce the emotional, psychosocial, and psychosexual impact, along with any local symptoms, and to reduce transmission, with eradicating the HPV infection unlikely[5].

Cryotherapy with liquid nitrogen, surgical excision, electrosurgery, CO_2 laser or bichloroacetic or trichloroacetic acid at 80-90% are all used, with the latter the first medical treatment option. All these options are suitable during pregnancy[5].

The patient is informed about the possibility of complementing treatment with *Coriolus versicolor* after the pregnancy, which she agrees to initiate after postpartum quarantine.

The pregnancy developed normally with a negative COTEST at the check-up one year later.

FINAL DIAGNOSIS

Cervical condyloma during pregnancy.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Condyloma acuminata are the mucocutaneous manifestation of HPV, generally subtypes 6 and 11, which are the least oncogenic. The cervix is a more uncommon location and often comes associated with condylomas in other locations. Most are sub-clinical and only visible after study with acetic acid, but as in our case, condyloma can be visible without a colposcopy, in the form of polypoidal finger-like lesions with a white pearl-like surface and their capillary loop. They are more common in the transformation zone, but they can extend towards the squamous epithelium and the endocervical canal[6].

Pregnancy alters the immune system leading to the condylomas appearing more often among HPV+ patients. These often resolve during the postpartum period6. Lesion size and relapses typically increase during pregnancy. CAs during birth are associated to a very small risk of transmission of juvenile-onset recurrent respiratory papillomatosis (JRRP) in around 1/400 births[8].

A conservative attitude regarding cervical condylomas is recommended given the high potential for spontaneous regression, particularly among immunocompetent young women. Irrespective of the routes of transmission, the virus infects both the oral and genital mucosa of newborns[7], causing conditions such as laryngeal papillomatosis, which despite some authors referring to the low risk, cases may be under-reported[6,8]. There is evidence that anti-HPV six antibodies are present in newborns from mothers carrying condylomas. These would have been acquired through the placenta[6,9].

There is a consensus among experts that infection during pregnancy should be treated before birth symptoms begin. The aim should be to eliminate the clinically visible lesion, although there isn't any evidence that this reduces viral transmission or transformation to malignancy[10]. However, this author considers that the factors favoring infection indicate that the fewer the lesions and relapses, the lower the risk of transmissibility, which would mean a maternal immunological status capable of counteracting the infectious process.

The aim of antenatal care should be to ensure that the mother and newborn have quality of life during the antenatal stage and in the future. As such, analyzing the behavior, transmissibility and treatment of HPV during pregnancy can help modify obstetric approaches among patients with the disease in order to fulfill that goal. Performing a basic gynecological examination in the office using speculoscopy after finding condylomas on external genitals is important.

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CORIOLUS VERSICOLOR FOR TREATING AND PREVENTING CONDYLOMAS AND CERVICAL INTRAEPITHELIAL LESIONS

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ABSTRACT
We present the case of a 34-year-old patient diagnosed with LSIL with condylomas in the vaginal introitus.

KEY WORDS: Conndylomas. HPV. Wart #intraepitheliallesion. Cervix.

CLINIC CASE

A 34-year-old patient visiting the office for genital warts with 5 months evolution. No family or personal history of interest. As regards gynecological-obstetric history, she presents suitable CC screening; the last cytology was 4 years ago and normal, so a new sample is taken.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The examination is insignificant other than warty lesions in the vaginal introitus that stain white with acetic acid. Cytology reports low-grade squamous intraepithelial lesion (LSIL) and flora suggestive of bacterial vaginosis. Reflex HPV test positive for other HR-HPVs. Colposcopy performed, suitable with a type 1 transformation zone, normal columnar epithelium, squamous metaplasia epithelium with a faint acetowhite lesion at the time reference where the punch biopsy is performed, vaginoscopy negative.

DIFFERENTIAL DIAGNOSIS

Condyloma acuminata (CA) are the clinical expression of infection from certain types of what are considered to be low oncogenic risk HPVs, mainly 6 and 11[1,2]. Condyloma acuminata is a common and highly infectious STD[3], which can cause psychological involvement among patients, given its tendency to relapse after treatment, cause malignancy, be transmitted to a sexual partner and from mother to child, and in the latter case, cause juvenile laryngeal papillomatosis[4].

The differential diagnosis should also be made with vestibular papillomatosis, a physiological finding different to CAs because their papules are not acetowhite, with each having a separate base, while CAs share a base and have a rooster comb-like surface. Other papules are molluscum contagiosum and seborrheic keratosis[4].

Performing vulvar colposcopy after applying acetic acid is not recommended as a routine examination, but it can prove useful if an intraepithelial neoplasia or initially invasive cancer is suspected in the vulva and anal area. It helps to mark out the lesion and choose the site of the biopsy. However, it should be understood that an acetowhite epithelium in the vulva is a nonspecific finding.

SUMMARY

TREATMENT AND EVOLUTION

Treatment with imiquimod at 5% indicated and after 4 weeks of treatment, two CAs persist in the right vaginal introitus, leading to alternative treatment initiated with Verrutop®, after which they finally disappeared.

Therapy mainly targets their elimination in order to reduce the emotional, psychosocial, and psychosexual impact, along with any local symptoms, and to reduce transmission, with eradicating the HPV infection unlikely[5].

The patient is informed about the possibility of complementing both vaginal and vulvar treatment with *Coriolus versicolor,* which they accept. Gel application initiated on both the vagina and the vulva using external Papilocare® gel.

The patient evolved suitably with a negative COTEST check-up at one year and the CAs have not relapsed to date.

FINAL DIAGNOSIS

Residual exophytic lesions treatment completed, vaginal and vulvar Papilocare® maintained for another 5 months, and lesions confirmed to have disappeared at one year by COTEST and physical examination.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Condyloma acuminata are the mucocutaneous manifestation of HPV, generally subtypes 6 and 11, which are the least oncogenic. The cervix is a more uncommon location and often comes associated with condylomas in other locations. Most are sub-clinical and only visible after study with acetic acid, but as in our case, condyloma can be visible without a colposcopy, in the form of polypoidal finger-like lesions with a white pearl-like surface and their capillary loop. They are more common in the transformation zone, but they can extend towards the squamous epithelium and the endocervical canal[6].

In this case, it is worth noting that after failure on treatment with imiquimod, Verrutop® is effective when applied and using *Coriolus versicolor*-based gel manages to prevent CA relapses and negativize the LSIL, alongside the other adopted measures.

After the result, there is a need to carry out new studies involving using external Papilocare® to eliminate vulvar condylomas, whether as a single therapy or to complement other traditionally used treatments.

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TREATMENT OF PERSISTENT CIN I

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INTRODUCTION

Human papillomavirus (HPV) is transmitted via skin or mucosa contact, with sexual interaction the main route of contagion. In fact, this infection represents the most common sexually transmitted infection (STI) worldwide. The infection generally courses asymptomatically and does not cause inflammatory storm activation, with viral clearance a determining factor for lesion regression.

Although HPV infection persistence is a necessary condition for developing Cervical Cancer (CC) among women, this variable isn't enough for this cancer to appear alone.

Several factors influence the risk of developing CC, also known as cofactors in cervical carcinogenesis. On the one hand, there are viral cofactors, notably including the viral genotype involved in the infection. On the other hand, there are host or behavioral cofactors, which include the status of the vaginal microbiota, which is arousing greater interest.

Viral cofactors

Viral genotype. among the HPV types involved in the carcinogenic process, genotype 16 is detected most frequently and is associated with faster progression of intraepithelial lesions and CC than other oncogenic types. It is found in 3.2% of patients with a normal cytology, and its prevalence increases with the severity of the underlying lesion: 27.6% in CIN I, 39.8% in CIN II lesions, 58.2% in CIN III, and 60% in CCs[1].

Although genotypes 16 and 18 have been classically labeled as the most oncogenic types, studies of the prevalence and virulence of other viral genotypes have been studied in recent decades.

Figure 1 shows the cancer load attributable to HPV on different locations of the anogenital area and the head and neck. It shows that almost all cervical cancers are attributable to HPV (99%), which is also the case for the anal region (85%). The association is 70% and 40% for the vagina and vulva respectively, while on the penis, half of the cancers are HPV-dependent. Causality is 38% for head and neck cancers.

Figure 2 also shows the cancer fraction attributable to HPV viral genotypes 16-18, which are the viral types most commonly found in all locations. It is worth noting that the vast majority of anal cancers and HPV-dependent head and neck cancers develop due to these genotypes, 87% and 84.9% respectively. In the cervix, penis, and vulva, the association to genotypes 16-18 is found in >70% of HPV-positive cancers (70.8%, 70.2% and 72.6% respectively). In the vagina, the fraction of genotypes 16-18 attributable to HPV-dependent cancer would be somewhat lower (63.7%)[2-5].

Viral load. The usefulness of viral load as a prognostic factor is currently up for discussion and there are very different comments regarding its clinical value. There aren't enough studies showing an association between viral load and increased risk of CC, and the presence of a lower viral load should not be considered when ruling out a severe lesion at present. Furthermore, a high viral load is also detected in recently acquired mild precancerous lesions, as is also the case for genital warts.

Viral integration. Integration of viral DNA into the host's DNA seems to be crucial for malignant transformation. However, there is a percentage of tumor lesions in which either there is no

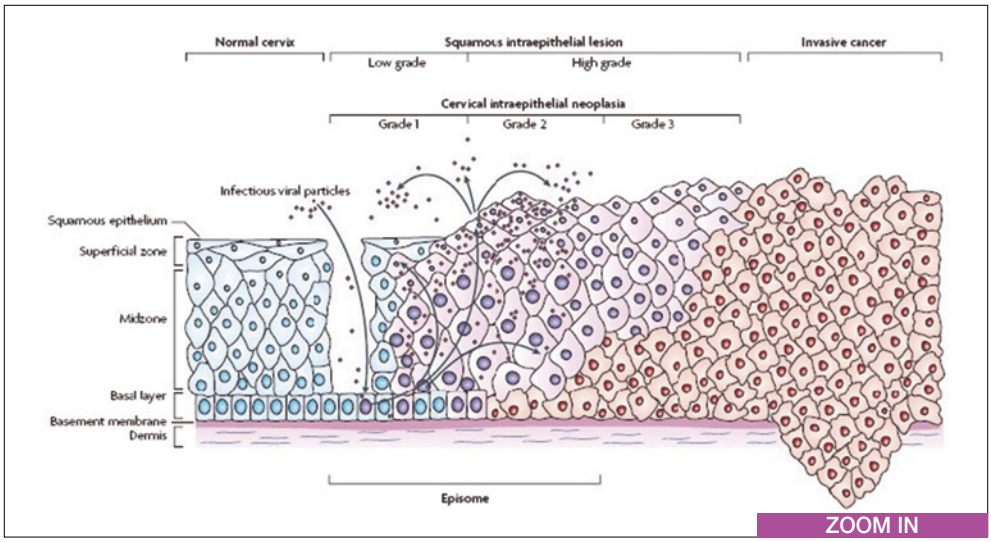

FIGURE 1. Schematic representation of HPV infection in the cervical mucosa and the potential squamous intraepithelial lesions (Source: S. de Sanjosé et al. The natural history of papillomavirus infection. Best Practice & Research Clinical Obstetrics and Gynaecology, 2018).

evidence for integration or rather that episomal and integrated forms co-exist.

Multiple HPV infections. Multiple HPV infections appear to increase the risk of virus persistence and can contribute to cervical dysplasia progression[6]. Low grade lesions tend to be caused by a single virus, while inflections by various genotypes is more commonly observed in high grade lesions.

Host/behavioral cofactors

Along with viral characteristics, there are other factors that can modify the natural history of HPV infection, fostering viral persistence or reinforcing its oncogenicity, as such favoring progression to a cervical intraepithelial lesion or CC[7]. Notable progression-regression factors include:

Smoking. Long-term smoking produces a state of local immunosuppression that makes viral clearance difficult. Furthermore, nicotine and cotinine, and the carcinogens contained in tobacco smoke, such as benzopyrenes, have a direct and harmful actions on cell DNA.

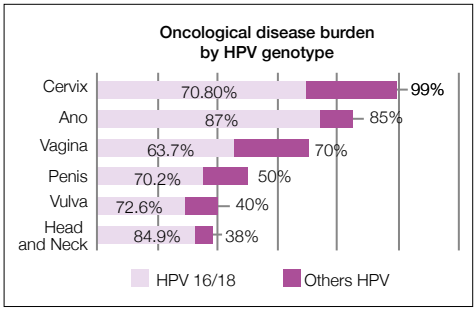

FIGURE 2. Risk of HPV-dependent cancer in different locations, fraction attributable to HPV 16-18 (S. de Sanjosé et al. Lancet Oncology, 2010; L. Alemany et al. International Journal of Cancer, 2015; L. Alemany et al. European Urology, 2016; X. Castellsagué et al. Journal of the National Cancer Institute, 2016).

Human immunodeficiency virus infection (HIV). This infection is considered a cofactor associated with the risk of developing CC. The immunosuppression produced by HIV, and not

the virus itself, is responsible for increasing the risk of progression. A recent meta-analysis shows that patients adhering correctly to antiretroviral treatments reduce the risk of acquiring HPV, and the incidence of intraepithelial lesions and their progression[8].

Multiparity. It has been suggested the high levels of estrogens and progesterone in particular during pregnancy are responsible for changing the squamocolumnar junction, leaving the exocervix exposed to HPV for many years and contributing to the persistence and progression of intraepithelial lesions and cancer. Another potential mechanism is pregnancy-associated immunosuppression, which could increase the role of HPV in carcinogenesis[9].

Hormone-based contraceptives. Taking this hormone-based therapy for longer than 5 years appears to increase the risk of precancerous lesions in the cervix and CC by up to 3-5 times. The mechanism by which this effect occurs is unknown, but the influence of hormones is believed to potentially enhance the expression of certain HPV genes[10]. However, the risk reduces 5-10 years after stopping using the method.

According to the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) guideline, women with an HPV infection, who are long-term hormone-based contraceptive users, should be informed that the benefits of using hormone-based treatment generally exceed the risks. As such, health professionals should consider their prescription on an individual basis, evaluating every aspect of the female patient and the HPV infection.

Co-infection. The presence of a cervical infection, particularly those caused by *Chlamydia trachomatis, Neisseria gonorrhoeae, Virus Herpes Simplex* or *Trichomonas vaginalis,* can increase the risk of infection by HPV and potentially cause cervical cancer[11].

Sexual behavior. The early onset of sexual relationships and sexual promiscuity are factors associated with a higher risk of exposure to HPV, and as such, a higher risk of infection[12].

Condoms. A range of *in vitro* studies show that condoms are impermeable barriers for the transfer of pathogens. As such, they are the method that offers protection against STIs, such as HIV and HPV. However, the protection observed during in vitro studies is much higher than observed clinically, given that the grade of protection depends on adherence and suitable use, making it difficult to estimate their effects during real-world conditions. All the same, the reduction in risk of infection is generally estimated to be approximately 60-70%[13].

Among people with an HPV infection, correctly and consistently using a condom reduces the risk of lesion progression and favors virus clearance, as well as the regression of the lesions.

Copper intrauterine device (IUD). according to the AEPCC guideline, when compared to hormone-based IUD users, the copper IUD can reduce the risk of an HPV-caused lesion progressing to CC, favoring viral clearance. However, according to the recommendations of the Faculty of Sexual and Reproductive Healthcare of The Royal College of Obstetricians and Gynaecologist in the United Kingdom from 2018, current scientific evidence is of insufficient quality to lead to a change in recommendations. As such, they state that CC prevention cannot be included as a non-contraceptive effect of the IUD for the time being.

Genetic predisposition. There seem to be several HLA system genetic profiles and p53 gene polymorphisms that predispose CC development. In addition, genetic predisposition could favor integration of viral DNA into cell DNA, which would favor oncogenesis.

Vaginal microbiota. Studying the relationship between the vaginal microbiota and the risk of viral persistence and lesion progression has aroused greater interest in recent years. A range of works analyze the potential role of different species of *Lactobacillus* in HPV clearance[14]. However, evidence to enable establishing a clear relationship.

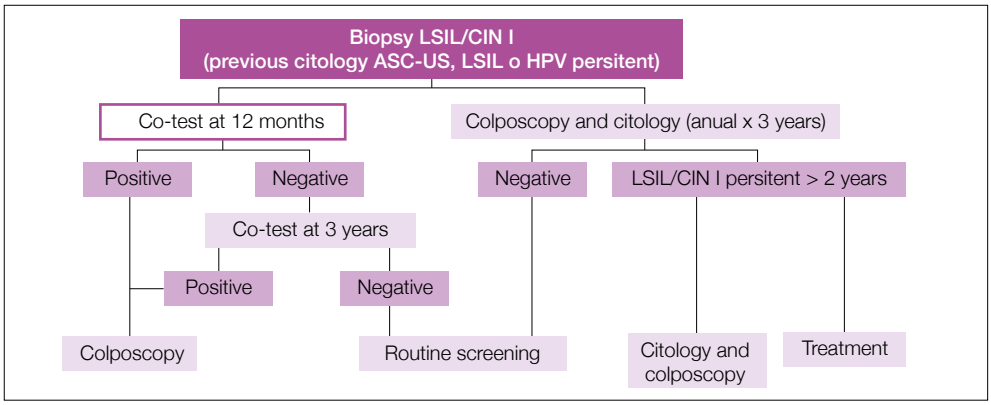

FIGURE 3. Treatment of CIN I preceded by mild cytology changes (Source: AEPCC guía. Prevención del Cáncer de Cuello de Útero, 2014).

ZOOM IN

MEDICAL HISTORY AND ANAMNESIS

A 30-year-old female referred to the Basurto Teaching Hospital (HUB) Cervical Disease Unit for an LSIL type cytology change.

The patient does not present any family history or medical-surgical history of interest when visiting our unit. She inform us that she does not take any regular treatment and that she is a social smoker.

When it comes to gynecological and obstetric history, she is a nulligravid woman with a regular menstrual pattern. She doesn't have a history of other STIs and has a stable partner. For a contraceptive method she uses oral hormone-based treatment.

It is confirmed that the patient presents prior suitable screening for CC and has not been vaccinated against HPV.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

The patient's gynecological examination is normal and other STIs are ruled out by taking genital cultures and performing serologies.

Subsequently and given the cytology LSIL diagnosis, a colposcopy is performed. This test was suitable and the patient presents a type 1 TZ, with a lesion compatible with grade 1 changes. After sampling an exocervical biopsy using the Schumacher forceps, a type CIN I (Cervical Intraepithelial Neoplasia grade 1) histological lesion is identified.

TREATMENT AND EVOLUTION

Given a CIN I histological result preceded by a mild cytology change (LSIL), and in accordance with the latest recommendations from AEPCC in the 2014 Cervical cancer prevention guideline, she is indicated a check-up at 12 months with a cytology and HPV testing, given the high likelihood of unaided regression of the lesion. Treatment would be reserved for persistent cases over 2 or more years, although performing follow-up using the annual co-test can continue (Fig. 3).

Additionally, the patient is indicated to stop smoking and consistently use a condom. The link between taking hormone-based contraception and HPV infection is explained. She was also recommended to be vaccinated against HPV, and lead a healthy lifestyle.

After one year, the patient returns to our unit, informs us that she has stopped smoking, stopped taking hormone-based contraceptive treatment, and consistently uses a condom

with her stable partner. She has also completed vaccination against HPV with Gardasil 9.

The co-test results show us the persistence of the LSIL cytology change and HPV. Given these results, the colposcopy is repeated again, again finding grade 1 changes. A new sample is taken for exocervical histological study, confirming CIN I persistence.

Given these findings, the patient is explained that viral clearance sometimes takes longer and that we recommend another cytology check-up in one year. We also explain the possibility of treatment with Papilocare® vaginal gel.

The next check-up confirms HPV clearance and the regression of the previous cytology change. Given the resolution of the viral infection and no cytology changes, the patient is discharged from our unit, recommending to continue outpatient check-ups with her gynecologist.

FINAL DIAGNOSIS

CIN I resolution.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Although most HPV infections are temporary and clear in one year, this infection persists in a percentage of patients, representing the main risk factor for presenting a precancerous lesion and subsequent CC. Avoiding this viral persistence reduces the possibility of patients having progressive lesions, leading to the importance of establishing strategies for modifying cofactors involved in cervical carcinogenesis in the host. The vaginal microbiota is one of the main variables. Preparations like Papilocare® vaginal gel are potential strategies for preventing HPV persistence.

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REGRESSION OF A PERSISTENT LOW GRADE INTRAEPITHELIAL LESION IN A YOUNG PATIENT

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ABSTRACT

A 27-year-old patient with repeated low grade intraepithelial lesion cytology tests requiring active treatment to resolve it.

KEY WORDS: Persistent LG-SIL. Cytology. Colposcopy. *Coriolus versicolor.*

MEDICAL HISTORY

This is a 27-year-old patient without any history of interest. She is nulligravid, does not use contraceptive methods and already presented a cytology "negative for intraepithelial lesion" two years ago. She has had two sexual partners in her lifetime. She currently is in a relationship with a stable partner and she is asymptomatic. The patient visits her midwife in 2015 for routine cytology for cervical cancer screening. Said cytology presents a "low-grade intraepithelial lesion" result.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS AND DIFFERENTIAL DIAGNOSIS

The patient presents normal external genitals during the gynecological examination. In the speculoscopy, the cervix is well-epithelialized, macroscopically normal, pink. On observing normality during the physical examination, with the patient asymptomatic, the decision is taken to perform a non-clinical colposcopy check-up on the patient, observing findings within the normal range.

TREATMENT AND EVOLUTION

At one year (in 2016), she also presents a cytology result of similar characteristics to the previous one (low grade intraepithelial lesion), so colposcopy performed with findings described within the normal range (no colposcopy photographs available as undertaken in a private center), annual check-up decided again.

In 2017, she again presents what is described as a "low grade intraepithelial lesion" in the cytology, so another colposcopy performed, with a "type 1 transformation zone, colposcopy grade I", observing the images in Figure 1, leading to another cytology suggested within one year (Fig. 1).

In 2018 similar results are repeated, presenting a "low grade intraepithelial lesion" in the cytology and another colposcopy performed, with a "type 1 transformation zone with normal findings" observed (Fig. 2).

In 2019, the patient had another cytology and colposcopy check-up. The cytology again shows a "low grade intraepithelial lesion" result and this time a Co-test is performed (evaluation of cytology and determination of high-risk HPV), determining that the patient presented HPV serotype 53

FIGURE 1. 2017, type 1 transformation zone, colposcopy grade I.

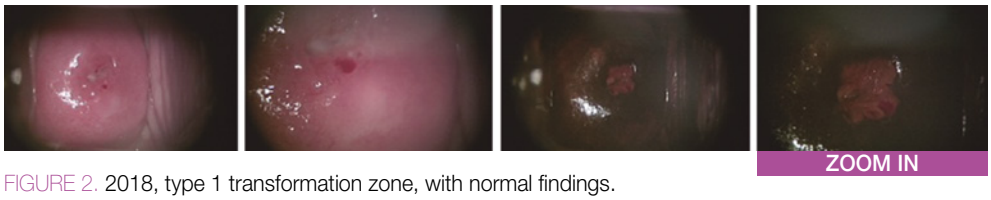

FIGURE 2. 2018, type 1 transformation zone, with normal findings.

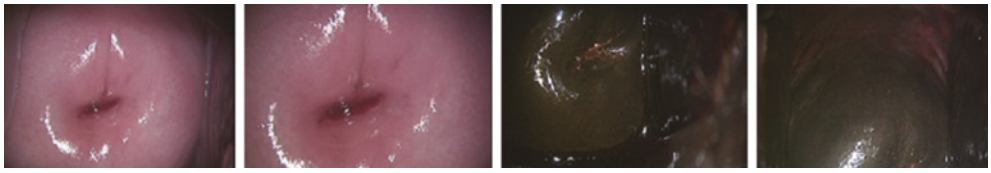

FIGURE 3. 2021, type II TZ, with normal spectroscopy. Schiller Lugol's solution test positive and normal vaginoscopy (Normal findings).

persistence. The patient underwent cryotherapy during this visit.

In September 2020, the patient has another cytology check-up after the cryotherapy, again presenting a "low grade intraepithelial lesion " with high risk HPV +. At this point, the patient is proposed having a check-up at 6 months with cytology and colposcopy, having taken treatment with *Coriolus versicolor*-based vaginal gel on a regimen of 21 consecutive days and every other day for the remaining 5 months.

In March 2021, another cytology check-up was performed, presenting a "negative for intraepithelial lesion" result. Colposcopy check-up also performed, observing "type II TZ, with normal spectroscopy, Schiller's Lugol's solution test positive and normal vaginoscopy (normal findings) (Fig. 3).

FINAL DIAGNOSIS

A patient with persistent HPV-caused low grade intraepithelial lesion, currently resolved.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

In our setting, HPV is a virus that affects over 80% of the sexually active population. It is the causal agent of cervix lesions, starting from low grade intraepithelial lesions and progressing in stepwise form towards invasive cervical cancers.

Among the different HPV serotypes, there are high and low oncogenic risk serotypes. The higher oncogenic risk serotypes are 16 and 18, causing 70% of invasive cervical lesions, and other 10 types account for the remaining 25-35% of cases[1,2].

Most patients with HPV involvement do not develop any type of cervical lesions and the virus clears with the first two years of contagion. Among patients that do develop a type of lesion, if this lesion is low grade, most (approximately 80%) will also clear the virus and the lesion will regress unaided. There are patients for whom the lesion becomes persistent due to a lack of virus clearance, and therefore, are potentially at risk of progression towards a malignant cervical lesion[1].

A clinical case was chosen whereby the patient did not present initial virus clearance, remaining present for over 7 years, perpetuating a low-grade lesion. On the seventh year of cytology and colposcopy check-ups, the patient was observed to present regression of the lesion and negativization for detecting high risk HPV,

This case study involves a 27-year-old patient who, since 2015 (and repeatedly during check-ups), presents a low-grade cervical lesion (LSIL) caused by Human papillomavirus (HPV) during cytology. The patient presented regular colposcopy and cytology check-ups without HPV clearance, until September 2020 when she started to use *Coriolus versicolor*-based vaginal gel with a regimen of 21 consecutive days and every other day during the subsequent 5 months. In March 2021, during the cytology and colposcopy check-up, the patient presented a cytology result that was "negative for intraepithelial lesion" and colposcopy with normal findings.

The lesion presented repeatedly in this patient and did not improve over several years. Despite being persistent, the lesion presented by the patient did not evolve to another type of more serious lesion or cervical cancer.

The patient is referred for colposcopy control, repeatedly presenting different findings during the check-ups, which are generally either normal or low grade, as such only requiring follow up with regular check-ups, until the patient finally presented regression of the lesions after using *Coriolus versicolor*-based vaginal gel, meaning that the patient is only to continue with cytology or co-test check-ups to evaluate virus persistence.

This clinical case is important because it begins a debate on whether this patient was treated suitably from the outset using only cytology and colposcopy check-ups, or whether the intraepithelial lesion could have been actively treated earlier[3]. On reviewing the case, we find actions that don't fit the current guidelines for treating this type of lesion, such as not referring the patient for colposcopy check-up after her first cytology.

The case is also important as it shows that although most patients clear HPV unaided, there is a percentage of patients that don't, and furthermore, the virus starts to cause a cervical lesion. When the lesions start, it is very important to monitor the patient to observe whether or not the lesions progress[4]. At first, this patient was treated conservatively with check-ups. However, on presenting several positive check-ups for intraepithelial lesion, a more active treatment was decided, from proposing cryotherapy through to using *Coriolus versicolor*-based vaginal gel, observing negativization of her lesion in 2021. The latter corroborates the positive results of certain active treatments against this type of lesions[5].

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COMPLETE REMISSION OF A HSIL-CIN II LESION AFTER TREATING THE CERVICAL TRANSFORMATION ZONE WITH A REEPITHELIALIZING VAGINAL GEL

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ABSTRACT

Patient on a waiting list for cervical conization for HSIL CIN II. Decided to treat with Papilocare® vaginal gel in the meantime, presenting a conization piece with complete lesion remission.

KEY WORDS: HPV. HSIL. Highgradedysplasia.

MEDICAL HISTORY

A 30-year-old patient

Operations received: laparoscopic salpingectomy due to ectopic pregnancy, 2 breast fibroadenomas.

Allergic to penicillin.

A disease history of a benign ovarian cyst, followed up using ultrasound. Personal history: primary care doctor, non-smoker, no stable partner, uses condoms, not HPV vaccinated.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

June 2018. Patient visits for gynecological check-up providing evidence for negative CC with HPV 16/18 positive. Interpreted as a recent infection given the patient's personal history.

Indicated vaccination with Gardasil 9.

June 2019. Check-up repeated at one year, providing evidence of HSIL CIN II CC with HPV 16/18 positive. Colposcopy performed observing: colposcopy suitable, type III TZ, mild acidophilia in the entire margin of the external orifice of the cervix, no Lugol's solution negative zones, biopsy performed at 12 o'clock, obtaining a HSIL CIN II result.

DIFFERENTIAL DIAGNOSIS

High grade cervical dysplasia due to recent infection vs progressive infection.

TREATMENT AND EVOLUTION

September 2019. Offered strict evolution control at 6 months as the patient is young and the option of control vs cervical conization. The patient prefers cervical conization, signs the IC and is added to the waiting list. Meanwhile treatment indicated with Papilocare® vaginal gel until the surgical intervention.

January 2020. LLETZ type cervical conization with a semicircular loop and endocervical tub performed for type III TZ, obtaining both pieces negative for dysplasia and free margins.

June 2020. Visits for post-surgical intervention check-up: CC negative and HPV negative.

June 2021. Visits for check-up: CC negative and HPV negative.

FINAL DIAGNOSIS

Infection from high grade HPV 16/18 resolved.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

The case's importance derives from the observation that applying the reepithelializing gel on the transformation zone resolves the lesions and the surgical piece infection.

USING PAPILOCARE® VAGINAL GEL TO TREAT HPV-INDUCED VAGINAL WARTS: A CASE STUDY

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ABSTRACT

Cervical cancer is the second most common cancer among women worldwide, requiring persistent infection by high-risk human papillomavirus (HPV) to develop. The incidence of HPV infection among women aged 18 to 65 years old in Spain is 14.3%, with prevalence higher among the 18-25 year old subgroup. Infection persisting more than 6 months is related to increasing age, multiple co-infection, and certain oncogenic types.

Condylomas, also known as genital warts or condylomas acuminatas, are benign lesions caused by HPV infection. It is currently considered one of the most common sexually transmitted infections, meaning its diagnosis and treatment is important.

KEY WORDS: Condylomas. Warts. HPV.

MEDICAL HISTORY

A 30-year-old patient without any history of interest and nulligravid. Referred from primary care to the office for cervical disease due to ASCUS cytology with HPV 18 and 31 positive infection. No toxic habits.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS AND DIFFERENTIAL DIAGNOSIS

The examination shows vulvar and perianal condyloma, a vagina with protruding lesions on the rectovaginal pouch and nonspecific leukorrhea. Colposcopy with suitable vision. TZ 2. Acetic acid and Lugol's solution with no changes in the exocervix, but numerous acetowhite protrusions in the rectovaginal pouch suggestive of condylomas. Representative biopsy taken with an anatomopathological result of condyloma.

TREATMENT AND EVOLUTION

Prior to visiting the unit, the patient refers to having been treated with green tea, Aldara, and podophyllotoxin with a partial response. She does not want to receive cryotherapy.

On analysis of the prior treatment, imiquimod at 5% initiated and no variation observed in the lesions after 4 weeks of treatment. This led to the decision to propose treatment with external cryotherapy in combination with external Papilocare® gel on the genitals (EGG) to improve the evolution of the consequences, and patient requested to visit in one month to evaluate the evolution and complete treatment.

As regards the rectovaginal pouch lesions, treatment initiated with a vaginal tampon soaked in green tea, combining treatment with Papilocare® vaginal gel.

During the clinical evaluation at a month, the condyloma lesions have disappeared.

The patient completes treatment with Papilocare® up to 6 months after the condyloma lesions disappeared.

The patient visits for her annual check-up with a co-test for viral infection, with the cytology result normal and negativized for HPV.

FINAL DIAGNOSIS

On completing the treatment, the lesions that were observable macroscopically have completely disappeared. Treatment with co-adjuvant vaginal Papilocare® to eliminate the viral infection maintained. Requested to visit for a check-up at 3 years in accordance with protocol in view of the elimination.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Cervical cancer is the second most frequent cancer among women worldwide, given its high incidence among developing countries, and it can appear at younger ages than other cancer types do[1].

A high-risk human papillomavirus (HPV) infection is necessary to cause cervical cancer to develop, with sexual interaction the transmission route. Cervical cancer is an uncommon viral infection complication, despite the high prevalence of HPV among young women[2].

The incidence of HPV infection among women aged 18 to 65 years old in Spain is 14.3%, with prevalence higher among the 18-25 year old subgroup. Infection persisting more than 6 months is related to increasing age, multiple co-infection, and certain oncogenic types. Over 80 type of HPV have been sequenced, with 40 identified in the genital tract. These viruses are classified as low-risk when it comes to condyloma acuminatas and high-risk (HR-HPV) when it comes to cervical cancer. The Agency for Research of Cancer (ARC) classification is used for the different types of HPV[3].

HPV 16 and 18 are responsible for approximately 70% of cervical cancer cases. HPV 16 is involved in over half of the cases (54.6%) around the world, whereas HPV 18 is involved in 15.8%.

Condylomas, also known as genital warts or condyloma acuminatas[4], are benign lesions caused by human papillomavirus (HPV) infection. It is currently considered one of the most common sexually transmitted infections. The HPV types that cause these lesions are designated "low oncogenic risk"[5], i.e. they are not related with cancer. However, up to a third of patients with condylomas have a co-infection with other types of "high oncogenic risk" HPV.

In this presented case, the limited response to the local treatment in the current protocol for treating condylomas is worth noting. It is also worth noting the good co-adjuvant vulvar response from cryotherapy, as well as in the vagina, a difficult-to-treat location, and its format favors the elimination of warts and the virus, the main source of cervical disease, hence its importance.

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USING EXTERNAL *CORIOLUS VERSICOLOR*-BASED GENITAL GEL TO CLEAR A CYTOLOGY-DIAGNOSED HUMAN PAPILLOMAVIRUS LESION

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ABSTRACT
Cervical cancer is the third most common cancer among women worldwide. Suitable and sustained screening of healthy women using cervical cytology has managed to reduce the incidence and mortality from cervical cancer by 80- 90%.
Atypical squamous cells of undetermined significance (ASCUS) are diagnosed in 2-5% of cytologies. Human papillomavirus (HPV) infection prevalence among these women ranges from 33-51%. The presence of high grade lesions among patients with an ASCUS cytology ranges from 5-12%, and 0.1- 0.2 % for cervical cancer.

A 32-year-old, nulligravid patient with no personal history of interest and asymptomatic.

Screening cytology performed with an ASCUS finding, and HPV genotyping identifying her as HPV59, HPV58, HPV52, and HPV51 positive.

Colposcopy performed in accordance with clinical guidelines. The colposcopy evaluation was suitable, with a type 1 transformation zone, with evidence of fine spotting on the anterior lip, leading to an exocervical biopsy being performed at the 12 o'clock reference. The outcome of the biopsy was a low-grade squamous intraepithelial lesion (LSIL), meaning initiating treatment with *Coriolus versicolor* vaginal gel was proposed to the patient, with a check-up at 6 months.

The check-up after 6 months included carrying out another cytology and HPV genotyping, with a normal cytology result, but with persistent

HPV virus of high oncogenic risk, neither 16 nor 18. The colposcopy showed the resolution of the visible lesion on which the biopsy was performed.

Continuing treatment was recommended, using it every other day, and resting during the period. During the next six-monthly check-up, another cytology was performed with HPV genotyping, with both tests negative, confirming that the cytology change had resolved and the virus had cleared.

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A CASE STUDY: VIRAL-INDUCED SEQUENTIAL LESIONS IN THE LOWER GENITAL TRACT

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ABSTRACT
A 42-year-old female who shows evidence of cervical dysplasia with HPV+ determination while being studied and treated for vulvar condylomas.

KEY WORDS: Human papillomavirus. Cervical intraepithelial neoplasia. Condyloma acuminata. Papilocare®.

INTRODUCTION

Human Papillomavirus infection is considered the most common sexually transmitted disease among humans worldwide[1,2]. Over 200 HPV subtypes have been identified. Around 30 are associated with invasive intraepithelial anogenital lesions in both men and women[3,4]. The subtypes with very high oncogenic risk (16 and 18) are particularly important, especially regarding gynecological and non-gynecological cancers.

Very effective screening programs for cervical cancer have been adopted, reducing incidence and mortality around the world, but the disease hasn't been eradicated[5]. The human papillomavirus (HPV) vaccine is administered to prevent this type of cancer and other precancerous lesions in the female genital tract.

Types 16, 18, 31, 33, 35, 45, 51, 52, 58, and 59 pose the highest oncogenic risk, with prevalence higher in Africa and Latin America[4]. The most common subtype in the world is 16, apart from in Indonesia and Algeria, where HPV 18 is the most common[7,8], and HPV 45, which is very common in Western Africa[6]. Types 33, 39 and 59 are found most in Central and South America[3,6,7].

The highest prevalence of cervical HPV when tested using a PCR (Polymerase Chain Reaction) occurs between the ages of 20 to 25 years old[6,7], 10-20% of women who are HPV positive in the cervix present abnormal cytologies[6]; 20% of young women without sexual activity present HPV in the cervix, with that figure rising to 60% for sexually active women[3, 6, 8]. The prevalence of women with a negative PAP (Papanicolaou test) for HPV ranges from 3.7 to 47.9% depending on the method and studied population[6]; 40-60% of men whose partners have cervical HPV have clinical or subclinical lesions.

There is evidence that human papillomavirus (HPV) infection is required but not enough for precancerous and cancerous lesions to develop in the cervix. Only some of the more than 200 currently known subtypes of HPV are a potential oncogenic risk. Of the 15 risk-type HPV that affect the cervix, five (16,18, 33, 31 and 45) are associated with higher risk, with subtypes 16 and 18 causing 60% of CIN III and 70% of cancers.

HPV infects the skin and some mucosae, presenting selectivity based on HPV type. It enters the epithelium via several mechanisms: microtrauma during sexual interaction, direct

contact with the skin and infected objects, during pregnancy and the perinatal period it can ascend vertically, and the latency period to clinical expression varies (months to years).

Most HPV infections are temporary and almost 90% of cases resolve unaided within 18-36 months, particularly when it comes to lower risk viruses. 10% of infections are persistent and generally involve the higher risk viruses. This viral "clearance" is attributable to innate immunity, the mechanisms for which are not fully understood. However, this local immunity falls short when it comes to ensuring permanent protection, so new infections by the same virus or a different virus are possible.

The strategy for preventing the cancerous lesions caused by human papillomavirus is vaccination. The tetravalent and nonavalent vaccines indicated for both genders protect against genital warts, other lesions, and anal cancer. Using condoms, on the other hand, reduces HPV contagion by 60-70% due to contact in the genital areas that remain exposed. Cytological screening using the Papanicolaou technique has been and remains the key strategy for the early detection of precancerous cervical lesions. It has contributed significantly towards reducing morbidity and mortality from cervical cancer by more than 75% among populations on which it is performed systematically and continuously.

Viral persistence is the most relevant marker for the lesion. Different factors have been described as viral persistence markers, but particularly age, immunosuppression, smoking, chlamydia infection, and oral contraceptives. These are also risk markers for cervical cancer. Viral persistence induces morphological changes in cells. Some of these changes, particularly so-called low-grade lesions (L-SIL), can improve or disappear as natural adaptive immunity gradually commences. High-grade lesions (H-SIL) are considered a risk as they can develop into cancer.

MEDICAL HISTORY AND ANAMNESIS

A 42-year-old female visiting for routine cytology and gynecology check-ups referring to lesions and discomfort in the genital region over the past few months.

Anamnesis

The patient visits her private gynecologist for a cytology due to the appearance of lesions and discomfort on the external genitals.

Personal history

No allergies to medicinal products. First menstruation aged 12 years old. Has not had the papillomavirus vaccine. History of two normal vaginal births. Does not use contraceptive or barrier methods because her husband had a vasectomy and is her regular partner. Does not refer to any other medical-surgical history of interest.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Physical examination

On examining the external genitals, there are pimple-like lesions on the inner face of both lower lips and the raphe region of the genitals, along with three protruding keratosis growths 5 mm to 15 mm in size, pink without any bleeding, appearing as large cauliflower-type formations (Fig. 1).

Cytology performed in the gynecology office, along with an HPV test and a biopsy on the warty lesions to confirm the histology.

No other complementary tests were required, given the normal clinical and histopathological diagnosis for these lesions.

Differential diagnosis

- Flat condylomas: presenting on the secondary syphilis. These lesions have a flat surface, and are sometimes erosive and exudative, rather than papillomatous. In the event of doubt, the dark-field exam will reveal multiple treponema on syphilis-derived lesions.
- Pearly penile papules: a non-pathological anatomical variant observed in 30-40% of

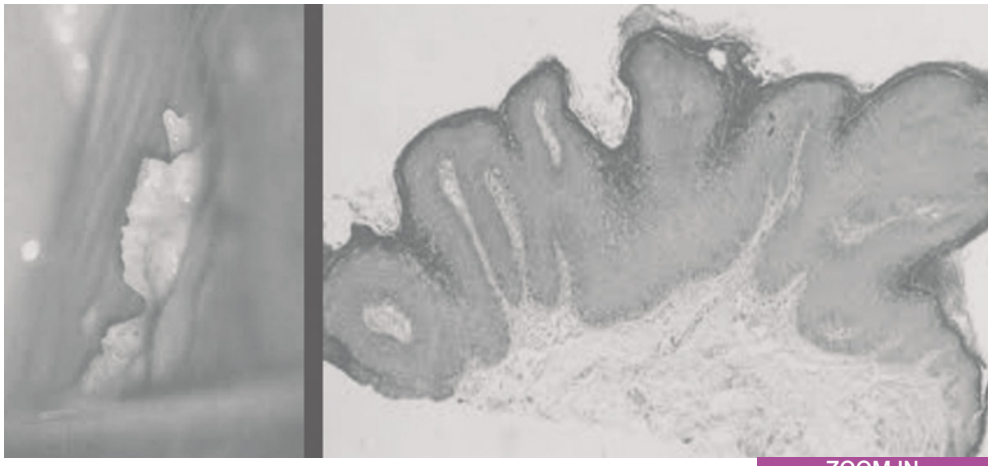

FIGURE 1. Vulvar condyloma acuminata.

young males generally on the crown of the gland or vestibular papillomatosis in the introitus and on the lower lips of women. This is the condition that causes the most differential diagnosis problems with condylomas.

- Bowenoid papulosis: intraepithelial neoplasia of the anogenital region (penis, vulva, perianal), associated with HPV-16, which manifests as small pimple-like structures, generally numerous and often with pigmentation, more common in young or middle-aged adults. Clinically they can be confused with vulgar warts, seborrheic keratosis, or melanocytic nevus[3].

TREATMENT AND EVOLUTION

Treating the condyloma acuminata did not require any additional treatment other than excision + biopsy in the office, given that the benefit of wart surgery is the initial elimination of lesions, with cures representing up to 90 % of treated cases.

Once the wart biopsy results had confirmed the condyloma diagnosis, the cervical cytology result of ASCUS and positivity for HPV 16 and 58 was also obtained. This led to the recommendation for administering the nonavalent vaccine for human papillomavirus, along with co-adjuvant treatment with Papilocare® vaginal gel.

The patient showed evolution initially at the first check-up (3 months) after having initiated both treatments, with the histopathology of the Papanicolaou test and cervical biopsy changing to CIN I. Subsequent check-ups at 6 months remained the same, but at the 12 month check-up and once the vaccination regimen had completed, while remaining on local treatment with Papilocare®, they are complication-free and have an ASCUS cytology.

FINAL DIAGNOSIS

Vulvar condylomas and cervical dysplasia

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

As with all sexually transmitted diseases, total abstinence remains the only 100% guaranteed way of avoiding HPV transmission. Condoms effectively prevent HPV infection, but lesions still appear, and their treatment in combination with co-adjuvant treatments like Papilocare®, appear to offer a barrier effect to HPV infection persistence, aiding its elimination. Despite this, we should

continue to investigate into HPV, and into these novel preventive strategies in particular.

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USING *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL TO TREAT SYMPTOMATIC CERVICAL ECTROPION IN A WOMAN CARRYING HPV

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ABSTRACT

Human papillomavirus (HPV) is the causal agent of almost all cervical cancers and precursor lesions. The incidence of infection by this virus is high during the first few years of sex life, although most infections are temporary and resolve unaided.

KEY WORDS: Human papillomavirus. Screening. Colposcopy. Cervical ectropion.

MEDICAL HISTORY

A 30-year-old female, G1P1, with no history of interest. Used a levonorgestrel IUD for a year.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Patient visits the cervical disease office for coital bleeding of 4 months' evolution. Cytology screening correct (last cytology 3 years ago, not suspicious). Marked cervical ectropion observed on examination (Fig. 1). Sample taken for HPV detection at this time.

DIFFERENTIAL DIAGNOSIS

Cervical ectropion vs HPV infection-caused intraepithelial neoplasia.

TREATMENT AND EVOLUTION

HPV detection positive for serotype 41. Cytology performed on the same sample but not suspicious. Colposcopy normal, so no need to obtain a biopsy.

Treatment with Papilocare® vaginal gel initiated daily for 21 days, and subsequently every other day after 7 days' rest. The patient referred to improvement to symptoms over a 3-month period. As indicated in the Spanish Association of Cervical Pathology and Colposcopy protocol[1], another sample was taken for HPV determination one year later, which was negative.

FINAL DIAGNOSIS

Cervical ectropion in a patient carrying HPV serotype 41.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Cervical ectropion is a benign condition in which endocervical glandular cells are present on the ectocervix. It is normally a casual finding in up to 50% of women[2] and related to high

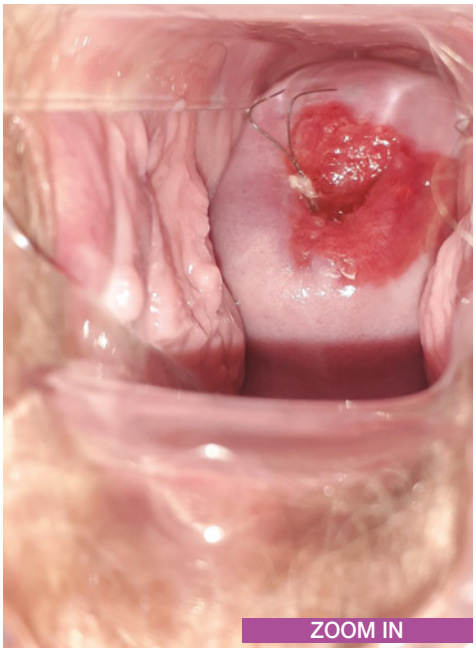

FIGURE 1. The patient had florid ectropion that could justify their clinical picture in itself.

estrogen levels. Its most common symptoms are vaginal discharge without an unpleasant odor and post-coital bleeding[2], only requiring treatment if the symptoms affect the patient's everyday life.

Despite its normally benign nature, post-coital bleeding can be a sign of cervical intraepithelial neoplasia (CIN). Up to 11% of patients consulting for this motive have cervical cancer, and the risk increases with increasing age of the patient presenting post-coital bleeding[3]. In a study by Cohen et al.[4] in 2019, 48.9% of patients consulting for coital bleeding required a cervical biopsy due to colposcopy changes, of which 30.3% reported CIN I. 0.7% of women consulting for coital bleeding had a high grade dysplasia (CIN II or above). As such, coital bleeding should be considered as risk factor for cervical dysplasia. In our case, the patient screening was correct, with the last cytology three years ago. However, if the last cytology was taken less than three years ago, a new sample should equally be taken to determine HPV, with a colposcopy performed in the event of a positive result.

Although almost every case of cervical ectropion resolves without treatment, intervention is sometimes required should the symptoms persist and cause the patient discomfort. Cryocoagulation is the most used treatment[5], which, as well as being an effective treatment for symptomatic ectropion, is also recommended for patients with a history of sterility, given that it improves cervical mucosa quality[6]. Other treatments are CO_2 laser, microwaves, boric acid suppositories, and local treatment with interferon alfa. Alongside Corolius versicolor-based vaginal gel, the latter two have the advantages of being not very aggressive treatments for patients and convenient to use, since the patient can administer them at home and does not need to visit the office. This is why they could be a first step towards treating symptomatic cervical ectropion before switching to other, more aggressive treatments.

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USING *CORIOLUS VERSICOLOR*-BASED GENITAL GEL TO TREAT VULVAR WARTS AND CERVICAL INTRAEPITHELIAL LESIONS

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ABSTRACT

Genital infection by human papillomavirus (HPV) is the most common sexually transmitted infection. It is the causal agent behind cervical cancers and its precursor lesions due to its persistence. Condyloma acuminatas or genital warts are another form of its clinical expression. There are multiple forms of lesion presentation and extension, and there isn't a unique effective therapy for every patient, necessitating personalization when choosing from the range of available procedures.

MEDICAL HISTORY AND ANAMNESIS

A 33-year-old female.

Nulligravid with no diseases of interest.

Non-smoker and received complete bivalent HPV vaccination.

Surgical history of cervical conization due to high-grade intraepithelial lesion with complete extirpation of the lesion.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Visits for the six-monthly check-up, with the following findings:

- Examination: External genitals with several protruding lesions with hyperpigmentation, around 5 mm long, located along both upper lips. An isolated 1cm lesion at the entry of the introitus. Vagina and cervix normal.
- Colposcopy: Suitable. Type 2 TZ with normal findings. Vaginoscopy: normal.
- Cytology satisfactory for evaluation. Changes suggestive of Low-grade Squamous Intraepithelial Lesion (L-SIL)
- HPV Genotype 42, HPV Genotype 58 (High oncogenic risk) and HPV Genotype 84.

TREATMENT AND EVOLUTION

Treatment initiated with *Coriolus versicolor* vaginal gel with a posology of 1 cannula a day for 1 month, followed by 1 cannula every other day for 6 months and external Imiquimod at 5% three times a week.

Visits the office at 6 weeks due to poor tolerance to the treatment with erythema and vulvar pain, with partial disappearance of the condyloma lesions.

Proposed performing treatment combined with cryotherapy on the wart located in the introitus and external Coriolus gel applied twice a day, with good tolerability and disappearance of the lesions at two months of treatment.

The 6-month check-up shows normalization in the cytology with HPV clearance.

DISCUSSION

Coriolus versicolor boosts cell immunity.

Among patients with an HPV infection, a regression effect has been observed in low-grade squamous intraepithelial lesions in the cervix, as well as significant negativization for the virus.

The treatment of patients with condyloma acuminata represents a significant health care

commitment given the high frequency and recurrence. Using *Coriolus versicolor*-based gel may be a treatment option with good tolerability.

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TREATMENT WITH *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL FOR ERYTHROPLAKIA AND PERSISTENT CERVICAL HPV IN A YOUNG PATIENT. A CASE STUDY

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ABSTRACT

The human female genital tract, which includes the vaginal fluids present in the cervix-vaginal mucosa, contains all the essential elements for a series of functions, such as the response to genital pathogens, lesion reepithelialization, and maintaining general vaginal health. The vaginal ecosystem plays an important role in preventing urogenital infections, such as Human papillomavirus (HPV). HPV is one of the most common sexually transmitted infections and the most important etiological agent for cervical cancer. Most HPV infections are asymptomatic and clear within 2 years without treatment. The hypothesis has been put forward that HPV integration could be minimized by reducing the potential mitotic surface for reepithelialization.

KEY WORDS: Cervical erythroplakia. Coital bleeding. PersistentHPV. *Coriolus versicolor.* Cervical epithelialization.

MEDICAL HISTORY AND ANAMNESIS

A 29-year-old patient without any history of interest and nulligravid. Combined hormone-based contraception user.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The patient has been followed up in our office for four years after consulting for intermittent coital bleeding. During the screening cytology when 25 years old, coinciding with the original consultation, a cytology diagnosis of ASCUS was concluded, with a positive HPV test and a normal colposcopy, apart from erythroplakia on the anterior and posterior lips. Cytology check-ups and subsequent colposcopies were normal, but the patient presented with persistent high risk HPV genotyping and erythroplakia in the colposcopy.

TREATMENT AND EVOLUTION

Local treatment indicated with other active agents (hyaluronic acid, *Centella asiatica)* for two months and coagulation of the friable zone, with the erythroplakia, coital bleeding, and HPV ultimately persisting. Lastly, it was decided to initiate treatment with *Coriolus versicolor*-based vaginal gel (Papilocare®) for six months, initiating a daily dose for 21 days and subsequently every other day.

After that period, the subsequent check-up showed that the erythroplakia plaque observed in colposcopy had practically disappeared. The patient refers to gradual remission of the coital

bleeding until none occurred during the previous 4 months. Furthermore, the annual check-up with cytology and HPV were negative.

FINAL DIAGNOSIS

Maintenance treatment with Papilocare® gel was maintained for a further year, for 10 days a month for the first six months and then every other month afterwards. The subsequent check-up provided evidence of very limited extension erythroplakia and the patient refers to not experiencing symptoms to date.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Cervical metaplasia is a regular process in sexually active women, even more so if they use hormone-based contraception, wear an IUD or have already had children. In this specific case, we encounter persistent erythroplakia and coital bleeding in a nulligravid patient, hormone-based contraceptive user, persisting over time and with associated HPV.

Furthermore, in the CLEOPATRE trial, the mean detection percentage for HPV among Spanish women aged 18 to 65 years old was 14%, with a flat curve around 30% for the 18-30 year old age group to which our patient belongs.

We have consistent signs that *Coriolus versicolor*-based vaginal gel (Papilocare®) provides very significant improvement in the reepithelialization of the cervix (95% of cases), so we consider the hypothesis that by adopting this approach, this gel could make it difficult for HPV to integrate, rather than prevent. This is because it reduces the reepithelialization in the epithelial transformation zone with intense cellular activity, representing the perfect target for HPV integration. A well-epithelialized cervix considerably reduces the anchoring potential for the potentially oncogenic HPV virus. As such, it could be said that we have a new preventive strategy, which is easier to apply and with no appreciable side effects, for use as primary or secondary prevention of HPV-caused lesions.

We had a dual objective in this case involving improving cervix epithelialization to reduce the zone of erythroplakia, as such, reducing coital bleeding and improving the quality of life of our patient, and favoring HPV clearance by improving this epithelialization.

Aware that more investigation is required, the «barrier effect» produced by Papilocare® enables contemplation of the potential for using it on patients with cervical changes to make HPV integration difficult and prevent the infection.

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TREATING LOW GRADE CERVICAL LESIONS WITH CORIOLUS VERSICOLOR VAGINAL GEL: A CASE STUDY

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ABSTRACT
The existence of *Corolius Versicolor*-based vaginal gel (Papilocare®) enables the treatment of women with HR-HPV through the repithelialization and modification of the vaginal microbiota.

KEY WORDS: CIN I. HPV. Vaginal gel. Colposcopy lesion.

MEDICAL HISTORY AND ANAMNESIS

A 30-year-old patient without any history of interest.

Visits the general gynecology office referring to a persistent stinging feeling after sexual intercourse, which both members of the couple present.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Vaginal cultures grown, along with cervical cultures for *Chlamydias,* which are negative. Cytology and HPV taken, with cytology normal and HPV 16-18 positive.

Patient visits the cervical disease office for annual persistence of HPV 16-18 and normal cytology. Colposcopy performed without findings, referred again for an annual check-up.

During the annual check-up, the patient continues to be an HPV 39, 81 carrier, with a negative cytology. In the colposcopy, tenuous acetowhite epithelium, iodine negative, compatible with type 1 changes. Biopsy performed with a CIN I result (Fig. 1).

TREATMENT AND EVOLUTION

Decided to start treatment with Papilocare® vaginal gel and a check-up at 6 months to control evolution of the cervical lesions. On performing the colposcopy, normal transformation zone observed, without acetowhite or iodine negative lesions. Given the findings, decided to perform a viral study and a cytology, with HPV genome detection negative and a normal cytology.

During subsequent cytologies and HPV tests at 3 years, the patient continues to present normal cytology and HPV negative (Fig. 2).

DISCUSSION

HPV infection appears to be responsible for 99% of cervical cancers, 97% of anal cancers,

FIGURE 1. Colposcopy low grade. Changes minors. At a closer approximation we appreciate an epithelium dim acetowhite between 6 and 8 o'clock.

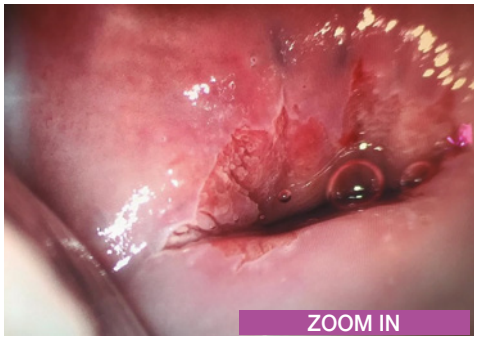

FIGURE 2. Colposcopy normal. Mature pink squamous epithelium surrounding the normal external columnar epithelium and separating both normal transformation zone epitheliums, in this case, type 1.

70% of malignant vaginal cancers, 47% of malignant penis cancers, 40% of vulvar cancer, 47% of malignant oropharyngeal tumors[1].

Persistent infection with high risk HPV is considered necessary for developing cervical cancer. The severity of the diagnosis along with the colposcopy findings, determine the treatment standard.

Recently, a non-hormone based vaginal gel has been approved as a medical device in Europe. This treatment would enable avoidance of more aggressive treatments, both destructive and excisional surgeries, for a significant number of patients[2].

Treatment with Papilocare® has shown a higher clinical benefit than the conventional watch-and wait approach in clinical practice for HPV positive patients, particularly for those with HR HPV[3]. The protection against viral aggression is based on the already described premises. Firstly, the normalization of vaginal microbiota[4]. Secondly, there is evidence that the polysaccharides and β-glucans in *Coriolus versicolor* have antioxidant, immunomodulating, and anti-tumor properties[5]. Lastly, improvement in the epithelialization of the squamocolumnar junction with subsequent reduction of mitotic activity can reduce cell susceptibility to HPV infection[6].

In this clinical case, using Papilocare® improved the results of HPV-DNA, cytology, and colposcopy test in line with the data presented in most published studies.

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RAPID POSTPARTUM HUMAN PAPILLOMAVIRUS PROGRESSION: A CASE STUDY

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ABSTRACT
Human papillomavirus causes over 95% of cervical cancer. The virus' natural history and population screening has led to a 70-80% reduction in cervical cancer incidence and mortality in some countries. This is due to the detection of asymptomatic premalignant lesions whose diagnosis and treatment prevents progression to invasive cancer.
HPV infection during pregnancy is estimated to range from 5.4 to 68.8%[1].

KEY WORDS: HPV. Persistence. Pregnancy. Cervical neoplasia.

MEDICAL HISTORY

A 33-year-old patient with a family history of cervical cancer (mother), and no personal history of interest for the case. Stable partner for over 10 years.

Annual gynecological check-ups with cytologies normal to date, latest during postpartum quarantine after her first birth (normal).

PHYSICAL EXAMINATION, COMPLEMENTARY TESTS AND DIFFERENTIAL DIAGNOSIS

Visits for annual gynecological check-up. Cervical cytology performed, cervix macroscopically normal, although the results report severe dysplasia (HSIL).

Colposcopy performed satisfactorily with a type 1 transformation zone, showing negative for Lugol's solution in the region from 1 to 3 o'clock, biopsy performed (Fig. 1).

Biopsy result of severe epithelial dysplasia (CIN III), carcinoma *in situ.*

TREATMENT AND EVOLUTION

Normal conization performed with amplification of margins from the same 1 to 3 o'clock zone for the biopsy without incidents.

Anatomopathological study reports CIN III, high grade SIL, carcinoma *in situ* located at 3 o'clock. Amplified margins show CIN III and carcinoma *in situ* with no lesions in the intraepithelial dysplastic lesion margins.

Patient post-operative period normal and prophylaxis with a monovalent vaccine initiated, along with treatment with Papilonare® vaginal gel.

FINAL DIAGNOSIS

Another examination performed at three months with correct postconization epithelialization and check-up cytology negative for dysplasia and/or cervical cancer.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

Human papillomavirus is a sexually transmitted virus that causes cervical cancer,

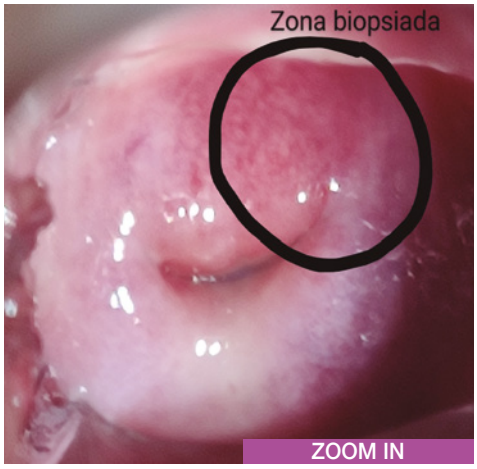

FIGURE 1. Image of the cervix, macroscopically healthy. The circle marks the 1 to 3 o'clock region, where a biopsy was performed with a CIN III result, carcinoma *in situ.*

the third most common cancer among women worldwide.

Over 80% of the sexually active population will come into contact with the virus at some point in their lifetime, although only a minority will develop lesions, which regress unaided in the majority of cases.

Smoking, hormone exposure, and HIV infection are some of the risk factors for progression to cancer[2].

Given the natural history of HPV, the time between the infection and the development of a cancer is around 10 years.

However, this clinical case presented an atypical evolution of the virus-caused lesions, given that a normal cytology evolved into a severe dysplasia and carcinoma in situ within one year. This presentation makes us consider different scenarios.

The first would be a potentially false negative in previous cytology results. There are systematic reviews that conclude a higher false negative percentage in cytologies when detecting HPV[3], a reason for different scientific societies, such as the AEPCC, recommending detecting HPV as the preferred option when screening for cervical cancer[4].

The second scenario is that it is a latent infection over 10 years old that has not caused lesions, reactivating aggressively during a period of immunosuppression like postpartum. There are models in the literature that show that the papillomavirus DNA can persist after a lesion appears and regresses, remaining latent in a subgroup of cervical epithelium basal cells due to different mechanisms[5].

Lastly, we consider a recent viral infection, which has evolved rapidly due to a change in the cervical microbiota and epithelium during the postpartum period. Emerging evidence concludes that increased diversity of the vaginal microbiota, along with the reduction in Lactobacillus spp., are involved in HPV infection and persistence, and in the development of precancerous and cancerous cervical lesions[6]. This derives in considering using epithelializing treatments such as Papilocare®, which help to improve the vaginal microbiota to prevent eventual infections.

Although population screening for HPV-caused lesions is very effective at preventing the large majority of cervical cancer cases and the virus' natural history is described, more studies are still needed to describe other characteristics. These include discovering new risk factors for rapid lesion progression, the mechanisms for the virus' latency without causing cytology changes for years, or using products like Papilocare® gel either alone or in combination with other treatments to treat the cervical microbiota and epithelium after changes, like during postpartum.

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INTERNAL *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL A TREATMENT FOR PERSISTENT HPV AFTER CONIZATION AND VACCINATION

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ABSTRACT

Human papillomavirus (HPV) infection is a necessary causal agent for cervical cancer. HPV prevalence in Spain is estimated to be 14.3% among women aged 18 to 65 years old and 28.8% among women aged 18 to 25 years old[1]. 84% of HPV-positive women present high-risk serotypes, and 4.1% present one of more serotypes[2].

Cervical conization is the most widely adopted technique, mainly aiming to completely extirpate the HPV-caused lesion[3]. The lesions are completely eliminated in most cases. However, the presence of margins with involvement is currently a cause for debate during the follow-up and treatment of these patients, given the association with the risk of recurrence[4,5]. Treatment has not been clearly established for this case, and varies from follow-up using cytology and colposcopy to reconization or hysterectomy. However, recent studies have proposed the possibility of *Coriolus versicolor*-based vaginal gel managing to eliminate the HPV virus and promote cervical reepithelialization[6], potentially making it a new line of treatment for human papillomavirus persistence after conization.

KEY WORDS: Cytology. Persistence. HPV. Margins.

MEDICAL HISTORY AND ANAMNESIS

A 32-year-old female referred to the cervical disease office due to ASC-H cytology.

Personal history. Polypectomy in colon. Nulligravid at the time of the first visit.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

Satisfactory colposcopy performed, with an extensive transformation zone. Mosaic region notable at 5 o'clock and from 12 to 1 o'clock.

HPV sampling detects subtypes 16 and 89.

TREATMENT AND EVOLUTION

Conization with LLETZ during the same procedure, superficial (type 1), which includes the transformation zone, and vaccine administered against 9 HPV serotypes (6, 11, 16, 18, 31, 33, 45, 52 and 58).

The anatomopathological study result was:

I) Moderate-severe cervical dysplasia (CIN II-III) (koilocytic), with involvement of: A) Anterior lip, 9-12 o'clock region.

II) Mild cervical dysplasia (CIN I) (koilocytic), with involvement of: A) Anterior lip, 12-3 o'clock region. B) Posterior lip, 3-6 and 6-9 o'clock regions.

Six months after the conization, the cytology is negative for malignancy and HPV subtype 89 (low risk) detected.

The patient fell pregnant 8 months after the conization. Cytology and HPV negative postpartum. However, annual check-up detected

TABLE I. Baseline situation (prior to treatment) of 10 cases included in the series.

Date	Cytology	HPV sample	Result
02.2018	ASC-H	Yes	Subtypes 16 and 89
10.2018	Negative	Yes	Subtype 89 (low risk)
4.2019	Negative	No	–
10.2019	Negative	Yes	Undetected
30.2019	Negative	Yes	Subtypes 16 and 89
4.2020	Negative	Yes	Undetected

INTRODUCTION OF PAPILOCARE®

HPV subtypes 16 and 89 with negative cytology and a normal colposcopy.

Given the patient was of a reproductive age at the time, treatment initiated with internal Papilocare® genital gel. Cytology negative and HPV negativized at 6 month check-up. Colposcopy rigorously normal.

FINAL DIAGNOSIS

After surgical treatment (loop conization) and HPV vaccination failed to clear the virus, treatment with internal Papilocare® genital gel initiated for six months, achieving HPV negativization.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

This case's relevance is based on the use of internal *Coriolus versicolor*-based vaginal gel in our everyday clinical practice becoming a potential new line of treatment in the event of failure with other conservative measures, such as conization or vaccination, when treating cytology changes and virus persistence in the cervix. This new option could also be the choice for young patients of a reproductive age, for whom another conization or hysterectomy compromises their reproductive future. It can also be proposed as a complementary treatment after conization and vaccination to both reduce the risk of relapse in the event of involved margins in the conization piece and to prevent the development of new cervical lesions, both in the case of reinfection due to early sexual contact or virus persistence in the healthy epithelial mucosa.

After the satisfactory result using Papilocare® in clearing HPV persistence in the cervix, more studies are needed to generate information and support for this new conservative strategy, and to enable the introduction of new less invasive therapeutic possibilities that allow fertility to be conserved among young patients.

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USING *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL TO TREAT CIN II WITH HR-HPV INFECTION (16 AND 18): A CASE STUDY

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ABSTRACT

Using *Coriolus versicolor*-based vaginal gel to treat CIN II with HR-HPV infection (16 and 18) in a 27-year-old patient with dysplasia in only one cervical quadrant, in the Lleida HUAV Cervical Disease Unit.

MEDICAL HISTORY

A 27-year-old patient referred for evaluation of high-SIL detected during a routine cytology in a private office.

Family history: Father has rheumatoid arthritis, nothing else of interest.

Personal history: No known allergies to medicinal products, no medical history or operations of interest, nulligravid, not taking regular medication, non-smoker.

Gynecological history: First menstruation 13 years old. M.D.: 3/28. Oral hormone-based contraception use: Sibilla daily.

PHYSICAL EXAMINATION AND COMPLEMENTARY TESTS

Colposcopy performed in the HUAV Cervical Disease Unit, using the Optomic OP-C2L colposcope, colposcopy-guided cytology, cobas HPV test, and exocervical biopsy.

Colposcopy: Suitable, type II transformation zone, with detection of a lesion with grade 2 changes at 6 to 9 o'clock, with involvement of 1 one quickly appearing acetowhite epithelial quadrant, with a fully visible thick mosaic that does not penetrate the cervical canal, selective biopsy performed, with hemostasis after Monsel's solution satisfactory.

Colposcopy-guided cytology: Cytology high-grade SIL confirmed.

COBAS HPV-TEST: Reports HR-HPV+, 16 and 18.

Cervical biopsy: Reports CIN II.

TREATMENT

Patient reviewed by the center's cervical disease committee as she is under 30 years old, with the lesion involving only one cervical quadrant. Option of follow-up and evolution control offered.

Option decided in committee explained to the patient, involving stopping taking oral hormone-based contraceptives, using condoms during sexual intercourse, the vaccination of both members of the couple, and using *Coriolus versicolor*-based vaginal gel with a regimen of 21/7 for 6 months.

EVOLUTION

6 month check-up

Colposcopy: Suitable, type II transformation zone, with detection of a lesion with (slightly less) grade 2 changes at 6 to 8 o'clock, with involvement of 1 one quickly appearing acetowhite epithelial quadrant, fully visible and does not penetrate the cervical canal, Lugol's

solution negative, selective biopsy performed, with hemostasis after Monsel's solution satisfactory.

Cervical biopsy: Reports CIN II.

**During this period, the patient completed vaccination using Gardasil 9 and we decided to continue the Coriolus versicolor-based vaginal gel regimen of 21/7 for a further 6 months*

12 month check-up

Colposcopy: Suitable, type II transformation zone, with detection of a lesion with grade 2 changes at 5 to 12 o'clock, with involvement of only 1 moderately quickly appearing acetowhite epithelial quadrant without the previously evidenced mosaic, fully visible and does not penetrate the cervical canal, selective biopsy performed, with hemostasis after Monsel's solution satisfactory.

Cervical biopsy: Reports CIN II.

TREATMENT

Given the involvement in more than 1 quadrant and 12 months of follow-up, the Cervical Disease Committee decided on type II excisional treatment using loop diathermy

Anatomical Pathology: Confirms the CIN II with exocervical and endocervical margins negative, endocervical curettage negative.

Post-treatment 6 month check-up

Colposcopy: Suitable, type II transformation zone, post-conization squamocolumnar junction visible, normal.

Cytology: Negative for malignant cells.

Cobas HPV-test: Undetected.

**Patient discharged from the unit for Primary Care control for 2 years via cytology and HPV test.*

FINAL DIAGNOSIS

CIN II.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

This case can be defined as a special situation, whereby we were able to closely follow-up a 27-year-old patient, to see the CIN II evolution. This case fulfilled the *AEPCC*[1,2] criteria to perform it, patient acceptance, potential for follow-up, colposcopy evaluable and TZ visible, lesion fully visible, lesion not extensive (<50% of the cervix), no endocervical involvement, up to 2 years follow-up time.

Due to the cervical involvement changing during follow-up, becoming more extensive at 1 year, excisional treatment offered in accordance with the *AEPCC*[1,2] protocol.

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INTRAVAGINAL GEL: PAPILOCARE® *(CORIOLUS VERSICOLOR)* FOR TREATING PERSISTENT LSIL DUE TO HPV: A CASE STUDY

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ABSTRACT

Among chronic patient carriers of Human papillomavirus (HPV), viral persistence is related to the appearance of different cervical lesions, depending on the high or low risk from the papillomavirus.

MEDICAL HISTORY AND ANAMNESIS

A 53-year-old patient. Post-menopausal.

2 normal births, normal menstruation, no stable partner, and sexual intercourse without protection on several occasions.

Patient visits the office in 2013 to obtain a second medical opinion given a LSIL diagnoses. Another cytology performed and she is prescribed the Cervarix vaccine (not vaccinated). Liquid-based cytology result: LSIL: does not visit the office. Cannot be located. Returned in 2017.

CLINICAL-THERAPEUTIC EVOLUTION

March 2017: cytology: ASCUS + *Candida.* PCR HPV: (+) for 18 . Serology negative. Colposcopy: Satisfactory. However, Biopsy at 12 o'clock: LSIL. Endocervical curettage: normal. Starts vaccination with Gardasil 9.

November 2017: Liquid-based cytology: LSIL. Initiates Papilocare® intravaginal gel for 6 months.

June 2018: Liquid-based cytology: LSIL + vaginosis.

October 2018: (+) for OTHER HRs; (–) for 16 -18.

Receives treatment with Papilocare® intravaginal gel for 21 days and treatment with Fluomizin for vaginosis.

December 2018: Liquid-based cytology: LSIL. Colposcopy: discreet PCOS. Biopsy at 6 and 12 o'clock: No HPV data. Endocervical curettage: unrepresentative material.

June 2019: Liquid-based cytology: hyperparakeratosis. Treatment with Papilocare® intravaginal gel for 6 months.

January 2020: Colposcopy: mild ectropion. Satisfactory. PCR HPV (-), Endocervical curettage (-). Requests HRT due to intense vasomotor symptoms, prescribed Activelle.

February 2020: PCR HPV (-). Endocervical curettage (-) . Bx Cx (-) for HPV.

June 2020: Stopped smoking Sept 2019. Liquid-based cytology: negative. Venereal disease serology due to unprotected sexual intercourse: negative.

September 2020: Another serology request due to unprotected sexual intercourse: negative.

November 2020: Added treatment with oral Hupavir for 6 months. Cytology: Negative/ Bacterial vaginosis: Treatment with Fluomizin.

April 2021: PCR HPV (-).

TREATMENT AND EVOLUTION

Given the persistent LSIL diagnosis, 2 cycles of treatment with Papilocare® intravaginal gel for 6 months undertaken, with a 21 day cycle in

between because the patient couldn't afford the full 6-month period.

FINAL DIAGNOSIS

Persistent LSIL in a patient carrying HR-HPV and other HRs.

DESCRIPTION OF THE CASE'S IMPORTANCE

Always bearing in mind that this is one of the most common sexually transmitted infection of the world and its causal association with cervical cancer, this case's HPV infection was not temporary before resolving as occurs in 90% of cases.

In addition to the vaccination against HPV and regular surveillance undertaken, I believe that it was the perseverance with the Papilocare® intravaginal gel treatment regimen for 6 cycles that led us to clear the virus and normalize the cervical lesion, despite the middle cycle not being completed for financial reasons. I would also highlight that the patient stopping smoking and that they became more aware of the disease as other important factors. The patient continues to receive regular check-ups.

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CLINICAL CASE

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ABSTRACT
HPV-induced condyloma lesions represent 90-95 % of infections by subtypes 6 and 11.
Some of the more than 200 described HPVs cause benign lesions, whereas others have the ability to cause cell and tissue-altering lesions. Subtypes causing condylomas are so-called low-grade, whereas the others are high-grade.
HPV 6 and 11 are classified within the low-grade lesions.

MEDICAL HISTORY

First visit on 2-26-2021.

Visits as part of the "Projecte DONA" program, carried out in conjunction with ACTUA VALLÈS, aimed at monitoring and protecting sex workers (SW).

The result of a previous blood test carried out in the reference hospital laboratory (Parc Taulí Hospital in Sabadell) was provided during the visit, with an HPV positive result, a prior infection, with the other serologies negative.

She is informed about the Gardasil 9 vaccine as a preventive measure for high risk HPVs and HPV 6 and 11. She is informed that it isn't covered under the national health system. The patient accepts the vaccination, part of Projecte DONA.

DATE OF LAST PERIOD 2-12-2021

She refers to always using a condom, but "whenever it is possible" with oral interactions.

A. Family history: a diabetic mother / iatrogenic cirrhosis
B. Personal history: does not refer to any diseases
C. TPAL 0000. Non-smoker

Breast examination: moderately dense breasts.

Ultrasound digital vaginal examination right adnexal cyst, serous in appearance.

Cervical ectropion that bleeds easily and an exophytic lesion on the upper right part, abundant leukorrhea.

Vaginitis wet mount test Gardnerella.

We perform a cytology and cervical, pharyngeal, and rectal cultures.

We arrange an appointment to perform a colposcopy after the cytology result.

3 ovules of Dalacin are prescribed.

Sibilla prescribed for 3 months as a treatment for the serous adnexal cyst.

3-9-2021

Positive result for chlamydia in a cervical and pharyngeal culture

3-12-201

Provided and explained the result of the culture and treatment established with Azithromycin 1 gram.

The disease is reported.

4-30-2021

Cytology result negative for intraepithelial or malignant lesion.

Marked acute inflammation.

Coccobacilli mixed flora.

Vaginal cytology hormonal evaluation in accordance with age.

SUMMARY

DATE OF LAST PERIOD 4-16-2021
CONDOM CONTRACEPTION

Cervical evaluation.

We perform pharyngeal and cervical cultures after infection by chlamydia and adnexal cyst check-up.

We perform cultures.

Colposcopy suitable, type1. Warty image from 9 to 12 o'clock compatible with condyloma. Sample taken for anatomopathological study.

Ultrasound digital vaginal examination within gynecology ultrasound normality.

On receiving the result, we arrange an appointment with the patient for cervical lesion excision.

5-6-2021

Negative culture result.

5-12-2021

Biopsy results condyloma acuminata.

5-14-2021

Biopsy result provided and explained .

Appointment for lesion excision arranged for 5-26-2021, which will be performed under local anesthetic and after a PCR test to rule out COVID-19.

5-26-2021

DATE OF LAST PERIOD 4-27-2021
CONDOM CONTRACEPTION

Excision performed under an outpatient regime after local asepsis and anesthetic of the right anterior cervical lesion with an electric scalpel.

Colposcopy after staining with acetic acid and complete viewing of the lesion.

Check-up in 4 weeks.

6-17-2021

Cervical biopsy result:

- Low-grade squamous intraepithelial lesion (CIN I) with intraglandular extension.
- Changes compatible with HPV infection.

Follow-up pending

CASE DISCUSSION

In the event of clinically suspicious lesions, there is a need to follow up with the diagnostic tests considered necessary to reach a correct and convincing diagnosis, despite some results being normal.

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TREATING CERVICAL CONDYLOMA AND LSIL USING PAPILOCARE® VAGINAL GEL AS A CO-ADJUVANT. A CASE STUDY

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ABSTRACT

Infection by human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. It is estimated that at least 70% of sexually active women have been exposed at least once in their lives. Infection is proportionally related to an individual's number of partners and sexual practices. A new infection can be quickly detected after coming into contact with an already infected partner and most of them are detected during the first year[1].

Infection is most common among young people with peak prevalence among 20-25 year olds, with HPV positive patients accounting for 20-25% (30). Approximately half of high-risk HPV cases will develop a carcinoma when infected before the age of 21 years old, rising to 75% before 31 years old, and over 85% before 40 years old[2].

HPV infection prevalence data in Spain vary across different studies from 2.7% to 17.5%. The CLEOPATRE trial[3] obtained 14.3% HPV infection and 12.2% for high-risk genotypes.

Viral infection clearance is a controversial issue (4) because of the design of the completed studies, but it appears to occur during the first six months after infection for more than 90% of cases. This probably occurs because of cell immunity. There is evidence that patients who clear the virus earlier have a larger number of Langerhans cells in the endocervix compared to those presenting persistent lesions or reactivated previous infections. The relationship between viral clearance and the type of cervical microbiota has also been studied, with evidence of more lactobacillus of a certain species *(L. Gasseri)* among patients with viral clearance. Conversely, there is less Lactobacillus spp. among patients that don't present clearance, along with bacterial vaginosis among those with persistent infection.

Despite the low risk of progression to cancer and the high probability of clearing the infection during the first two years, HPV infection comes with a significant emotional burden. If we add that treating infection involves follow-up, particularly in the case of low-grade lesions, patients can find the situation sometimes becomes very stressful. This is why a treatment with evidence for helping to repair this type of lesion, such as Papilocare® (Procare Health, Valencia, Spain), may be very useful in these cases[5].

Condyloma acuminatas are the most common clinical manifestation of HPV infections. However, they are not included in surveillance systems in most countries, so worldwide epidemiological data is limited. Additionally, the estimated disease burden is derived from studies based on people that consult for symptoms, so it is potentially underestimated. They are generally detected on external genitals, but we can also find them in the cervix or on the vagina during a detailed examination. Cervical condylomas are sometimes overdiagnosed as dysplasia, although they often co-exist together. Young patients present a higher incidence of cervical condylomas[6].

KEY WORDS: Cytology. Persistence. HPV. Margins.

SUMMARY

FIGURE 1.

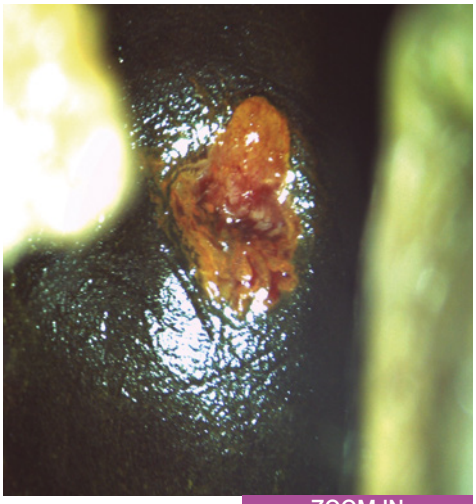

FIGURE 2.

MEDICAL HISTORY AND ANAMNESIS

A 26-year-old patient referred for consultation after a cytology with LSIL, HR-HPV, neither 16 nor 18. No history of interest, nulligravid. Not HPV vaccinated. Stable partner. Asymptomatic.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

On examination: external genitals and vagina normal, colposcopy suitable, TZ2 satisfactory. Aceto-reactive changes with fine spotting at 12 o'clock, partial Lugol's solution, compatible with G1 changes.

TREATMENT AND EVOLUTION

Annual check-up recommended, along with using a condom and initiating nonavalent HPV vaccination.

The patient visits for a check-up at one year. She remains asymptomatic, has used condoms, and completed the vaccination a month ago.

On examination, normal genitals and vagina are observed, the colposcopy is suitable and satisfactory, TZ2, epithelium faint acetowhite protruding at 12 o'clock (Fig. 1), partial Lugol's solution (Fig. 2), suggestive of cervical condyloma. Cytology, HPV test, and biopsy performed on the lesion, extirpating it completely.

The results are LSIL cytology, LSIL and HR-HPV biopsy + neither 16 nor 18.

Patient recommended to continue using a condom and Papilocare® vaginal gel for 6 months following the standard regimen.

FINAL DIAGNOSIS

The patient visits for the annual check-up, having completed treatment with Papilocare® 5 months ago with good tolerability, and she continued using a condom. Examination and colposcopy suitable and normal. Cytology and HPV test performed, which were negative, with the patient discharged for regular follow-up in accordance with the screening program.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

The approach regarding HPV infections among young people with low-grade lesions as a general rule involves following up and informing the patient about the recommendations for lifestyle habits that can aid earlier virus clearance.

This clinical case describes a standard situation among patients starting cytology screening for cervical cancer. Given that some patients request an active approach in the event of anomalous results, having a well-tolerated and effective vaginal treatment enables the patient to palliate the negative emotional component involved with waiting and accelerate the healing process. After a year with the same findings, adding vaginal gel appears to have acted as a co-adjuvant in resolving the lesion and viral infections.

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THE BENEFIT OF USING *CORIOLUS VERSICOLOR*-BASED VAGINAL GEL ON A PATIENT WITH AN HPV INFECTION. A CASE STUDY

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ABSTRACT

Human papillomavirus (HPV) is a DNA virus belonging to the *Papillomaviridae* family. They are specific viruses, only affecting human beings in this case. HPV is the most common sexually transmitted infection worldwide, typically occurring during the first decade after starting sexual relationships (15 to 25 years old). 80% of sexually active people are exposed to HPV throughout their lifetime, with most infections being temporary in nature.

There are over 200 types of HPV, with different tissue tropisms, which include cervical cancer, with scientific evidence associating HPV with cervical cancer. Subtype 16 is responsible for 50% of cervical cancer cases, with subtype 18 accounting for 20%. Furthermore, other HPV subtypes are responsible for another 20%, which include HPV 33. For this reason, HPV detection has a clinical use during cervical cancer screening[1].

KEY WORDS: HPV. Cervicalcancer. Cytology. Intraepitheliallesion. *Coriolus versicolor.*

MEDICAL HISTORY AND ANAMNESIS

A 51-year-old patient, with notable personal history of conization in 2016 for CIN III with subsequent cytology check-ups normal, smokes 5 cigarettes a day, and first sexual interaction aged 16 years old.

Patient referred to the Cervical Disease office for cytology in February 2020 with ASC-H, asymptomatic at the time.

PHYSICAL EXAMINATION AND DIFFERENTIAL DIAGNOSIS

The initial examination shows the cervix with normal epithelialization macroscopically. Colposcopy performed, which was satisfactory and no pathological changes, meaning another cytology sample is taken, human papillomavirus requested, and patient was asked to visit again for a check-up to see the evolution. The cytology result is ASCUS, and the HPV sample is positive for subtype 33 (high risk)[2].

TREATMENT AND EVOLUTION

Given the positivity for HPV and the cytology change, but not high grade, decision taken to initiate treatment with Papilocare® vaginal gel, using a vaginal cannula for 21 consecutive days, and on every other day for the subsequent 5 months[3]. Patient requested to visit 6 months after initiating treatment for another colposcopy, with evidence of spotting at 9-12 o'clock in the transformation zone. Another cytology check-up also performed, after treatment with Papilocare®, which was negative for intraepithelial lesion or malignancy.

SUMMARY

FINAL DIAGNOSIS

Patient requested to visit the Cervical Disease office for another cytology and HPV sample check-up 6 months from the last cytology, so her evolution is still being monitored.

DISCUSSION AND DESCRIPTION OF THE CASE'S IMPORTANCE

The notable aspect of this case is that after using *Coriolus versicolor*-based vaginal gel, like Papilocare®, on a patient carrying high risk HPV, not only was there an absence of cervical lesion progression observed, but the cytology became negative[3-5].

However, the case is still being followed up, requiring another cytology check-up to confirm the absence of cervical lesion progression, along with a new HPV sample to confirm it is also negative.

Given the positive result from using Papilocare® vaginal gel on this patient, more experience is needed in order to be able to draw conclusions.

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A CO-ADJUVANT TREATMENT FOR USUAL VIN USING *CORIOLUS VERSICOLOR*-BASED EXTERNAL GEL. A CASE STUDY

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KEY POINTS

Vulvar dysplasia or VIN is a condition for which we have few therapeutic tools without causing significant side effects. It is also an underdiagnosed condition (no screening available, practically half are asymptomatic).

There aren't any consistent population records, but one study on the Spanish population included 5665 women, finding that 2% of lower genital tract disease was HPV-related.

There are 2 types of VIN:

1. Usual or HPV-related: typically during middle age from 45-55 years old.
2. Differentiated: typically from the age of 60 years old.

The risk of progression of VIN to squamous carcinoma is accepted to be approximately 7-10%.

We know that immunosuppression favors the maintenance, recurrence and progression of these lesions, particularly when it comes to usual type VIN.

MEDICAL HISTORY

This case involves a 46-year-old patient consulting for vulvar itching over the last month.

Personal history: Fibromyalgia. IDDM (Insulin) Smoker 5 cigarettes/day. No known allergies to medicinal products.

Gynecological and obstetric history: TPAL 2002 MT 4/ 31-32 FP barrier

No HPV vaccination.

PHYSICAL EXAMINATION

The examination shows a protruding plaque that partially covers both lower lips, upper and lower left, approximately 2.5 cm.

Lesion enhancement observed when performing a vaginoscopy using acetic acid. It looks more like leukoplakia and protrudes with regular margins.

Biopsy and HPV performed on the lesion, reporting usual type VIN, HPV 16 positive.

Occult invasion ruled out.

TREATMENT

Decision taken to initiate treatment with Imiquimod 5% as a precaution regarding using excisional treatment straight away and not having a CO_2 laser available.

Patient evaluated at 3 weeks referring to terrible tolerability to Imiquimod, pain and stinging.

As there was only one small-sized lesion, a less aggressive therapy was chosen, with *Coriolus versicolor* applied (external Papilocare® genital gel), while referred for CO_2 laser at the tertiary level reference center.

Patient requested for appointment in 3 weeks, still to receive the destructive treatment, observing a notable reduction in the lesion, almost a third.

FINAL EVOLUTION

CO_2 laser vaporization performed on the residual lesion with topical treatment, Papilocare®, ulterior.

SUMMARY

Practically the entire vulvar lesion had regressed at one month of treatment.

DISCUSSION AND THE CASE'S IMPORTANCE

HPV-dependent, usual VIN is a relatively common condition for which there are available treatments that cannot always preserve vulvar anatomy and functionality. As such, it would be good to have therapies, co-adjuvants or those that enable us to reduce side effects, as long as the high percentage of recurrences is considered, as well as the potential risk of progression to an invasive lesion.

Several patient sets would be required to provide clarity in this respect.

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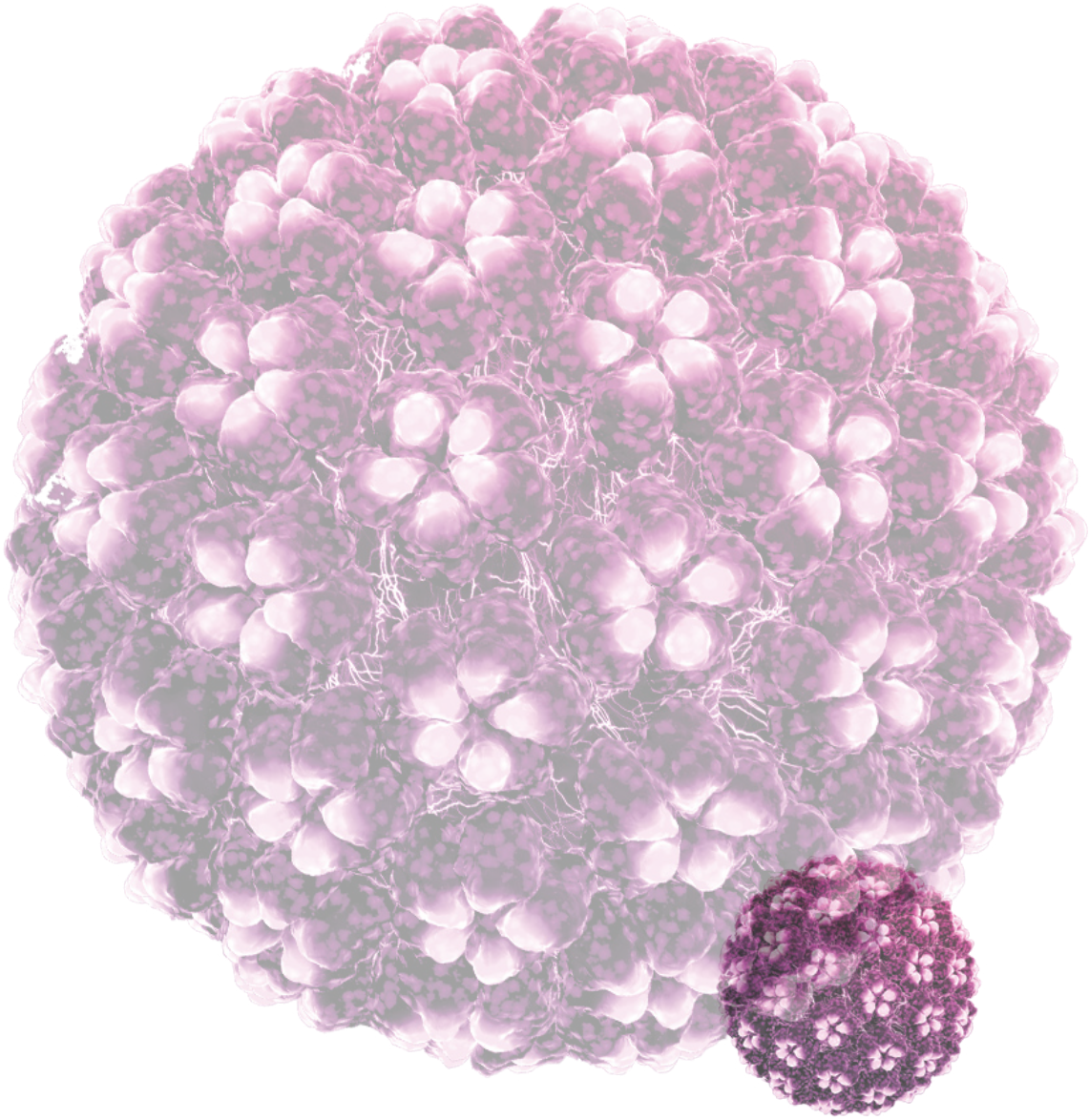

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