Infectious Agents and Cancer

BRIEF REPORT

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Conventional therapy for genital herpesvirus and remission of HPV-related lesions: a case series

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Abstract

This report covers the case of 7 women affected by pathologies related to genital Herpesvirus and Papillomavirus. They were referred to the gynaecology outpatient clinic for colposcopic examination, and received pharmacological antiviral treatment. The patients presented clinical signs of genital Herpesvirus infections in the cervix and vulva. Cervical lesions and condylomatosis, which are characteristic of Papillomavirus infections were also detected, and patients underwent cervical cancer screening. Patients received oral and topical treatment with Acyclovir or oral treatment with Valacyclovir. During weekly or biweekly gynaecological follow-up visits, patients showed different times of remission of genital Herpesvirus. During the antiviral treatments, the vulvar and cervical Papillomavirus lesions also showed complete resolution with *restitutio ad integrum* of the tissues, and no recurrence at follow-up visits. Herpesvirus and Papillomavirus infections are often associated in genital infections and, as sexual transmitted infections, share the same risk factors. In the cases presented, the observed remission of HPV-related pathologies during Acyclovir and Valaciclovir treatments may suggest that antivirals are also effective in the treatment of HPV lesions. The cases described could pave the way for further investigations and clinical studies.

Keywords Acyclovir, Valacyclovir, HHV-2, HPV, Condylomatosis, STI, Cervical lesions

Main text

Patient characteristics

The pathologies described in this report regard women who had been to the outpatient clinic of a specialist in obstetrics and gynaecology. Following colposcopic examination, patients showed clinical signs of genital herpesvirus type 2 (HHV-2) and Papillomavirus (HPV)-related lesions. The patients' clinical data are summarised in Table 1, and the colposcopic images of the pathologies treated are shown in Fig. 1. Patient ID and age are reported in Table 1, in columns A and B. All patients had vulvar or cervical lesions caused by genital HHV-2 (column C), and underwent cervical cancer screening, including cytology by ThinPrep specimens, HPV testing and typing, and cervical biopsy in one case (ID 32). HPV-DNA test was performed only in case of cytology abnormalities. The HPV-related pathologies detected are listed in column D. Atypical squamous cells of undetermined significance (ASC-US) were observed in ID6 Pap-test, while low-grade squamous intraepithelial lesions (L-SIL) were observed in ID 17, 29 and 37 Pap-tests. Patient

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Table 1 Clinical data of patients

ID	Age	Genital HHV-2	PAP TEST HPV-DNA	Condylomatosis	Other STI	Oral antiviral dosage	ACV/VCV topical dosage	Times of remission (d, m, y)
A	B	C	D	E	F	G	H	I
6	27	Cervical lesions	ASCUS HPV16-HPV66	Vulvar micro-condylomatosis	Severe candidiasis	VCV 3000 mg/d/90d	No	2 m
12	39	Vulvar lesions	NILM	Vulvar micro-condylomatosis	(Past laser treatment of CIN2)	ACV 1600 mg/d/15d	No, due to vulvodynia	20d
17	27	Vulvar lesions	L-SIL HPV16-HPV42	Vulvar condylomatosis	Candidiasis	VCV 2000 mg/d/30d	5% (2x/d/20d)	2 m
25	40	Vulvar and cervical lesions	NILM	Vulvar micro-condylomatosis	Vulvo-perineal candidiasis	ACV 1600 mg/d/15d	5% (3x/d/10d) 2 times with 7d interval	15d
29	42	Cervical lesions	L-SIL HPV negative	Vulvar micro-condylomatosis	Candidiasis	VCV 1000 mg/d/42d	No	5 m
32	40	Vulvar HHV-2 recurrent	H-SIL CIN2 HPV16	Perineal and anal condylomatosis	Candidiasis	VCV 2000 mg/d/90d	5% (1x/d/45d)	6 m
37	48	Vulvar lesions	LSIL HPV16	nd	nd		5% ACV (intravaginal appl 4x/d/15d) 4 times with 7d interval	7 m

The columns report from left to right in order: A) ID patient identification number, B) age, C) presence of clinical herpesvirus (HHV) lesions, D) PAP and HPV-DNA test results, E) presence of condylomatosis, F) Candida co-infections, G) ACV or VCV oral antiviral dosage, H) topical dosage administered and I) time of remission, indicating the time elapsed from the first visit to the visit in which *the restitutio ad integrum* of the tissue was ascertained. HPV DNA test was not performed in ID12 and ID25 patients, because their Pap-test result did not show cytology abnormalities

HPV Human Papillomavirus; *ASC-US* atypical squamous cells of undetermined significance; *NILM* Negative for intra-epithelial lesions and malignancy; *LSIL* Low-grade Squamous intraepithelial lesion; *HSIL* high-grade Squamous intraepithelial lesion; *HHV* Human Herpesvirus; *ACV* Acyclovir; *VCV* Valacyclovir; *d* day/s; *m*: month/s; *y* year/s. *1x; 2x; 3x*:1, 2, 3 times repeated; *Nd* not detected; *Appl* application

ID29's HPV-DNA test was negative, while the other mentioned patients had HPV-DNA test positive for the high-risk (HR) HPV16. HR-HPV66 and low-risk (LR)-HPV42 genotypes were also detected in cervical specimens from patients ID6 and ID17, respectively. Patient ID32 showed a high-grade intraepithelial lesion which was found to be CIN2 on histological examination after biopsy (column D). Patients ID12 and ID25 showed no cell abnormalities or HPV infection in Pap smear of cervical cells. HPV-related genital condylomatosis was observed in all patients except ID37 (column E), and candidiasis was observed in patients ID6, ID17, ID25, ID29 and ID32 (column F). The colposcopy images of clinical signs (blisters) of HHV-2 in vulva (ID12, 17, 25, 32 and 37) or cervix (ID6, 25 and 29), the perineal and anal condylomatosis (ID32), the vulvar microcondylomatosis (ID6, 12, 17, 25 and 29), and the HPV-related cervical lesions (ID6, 17, 29, 32 and 37) are shown in Fig. 1.

Treatments

Patients were treated with oral and topical standard doses of Acyclovir (ACV), or its derivate Valacyclovir (VCV), which has a higher oral bioavailability [1]. ACV and VCV are the gold standard drugs for the treatment of HHV-1 and HHV-2 infections [2].

For each patient, systemic treatment with ACV or VCV, alone or in combination with topical treatment, was recommended for different periods in relation to the severity of the case and the patient's health conditions, as deduced from the Summary of Product Characteristics (SPC) in force in Italy. A biweekly gynaecological visit, including a colposcopy examination when necessary, was scheduled as a follow-up of HPV-derived pathologies. Instead, patient ID32 with CIN2 diagnosis received a weekly visit in the first period of therapy. In Table 1, column G, the oral antiviral dosage is indicated for each patient. The topical administration of 5% ACV cream was suggested to the patients with HHV-2 vulvar lesions with the exception of the ID 12 patient who was affected by vulvodynia. In cases of candidiasis, the patients were treated topically with 1-week cycles of 1% Econazole nitrate (Pevaryl). The patients received instructions regarding daily personal hygiene (Additional file 1).

Observations at follow-up

The specialist offered to patients with multiple infections a gynaecological visit including a colposcopic examination, if necessary, every 1–2 weeks. Through these follow-ups, the specialist was able to balance the drug treatment period and observe disease improvements, including the remission of HPV-related cervical

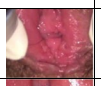
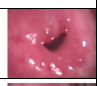
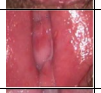
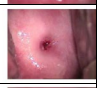
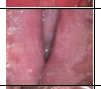
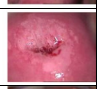
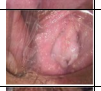
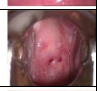
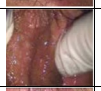
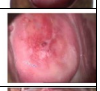
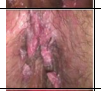
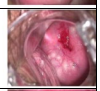
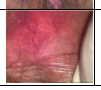
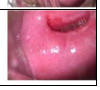
ID	External genitalia pathologies		Cervix pathologies	
A	B		C	
6	Microcondylomatosis 5x		ASCUS HPV16-HPV66 10x	
12	Microcondylomatosis 10x		NILM 10x	
17	Microcondylomatosis 10x		L-SIL HPV16-HPV42 10x	
25	Microcondylomatosis 10x		NILM 5x	
29	Microcondylomatosis 10x		L-SIL 10x	
32	Perineal and anal condylomatosis, 5x		H-SIL CIN2 HPV16 5x	
37	Vulvar herpetic lesions 10x		L-SIL HPV16 10x	

Fig. 1 Colposcopy images of genital pathologies of women treated with antivirals. The columns report: **A** ID patient identification number; **B** images of clinical lesions in the external genitalia; **C** images of the cervix and Pap-test results, according to the Bethesda system are also reported for each patient; the magnification (5x, 10x and 20x) of images is indicated. Herpetic lesions are evident in ID6, 25 and 29 cervix and in ID12, 17, 25, 32 and 37 vulva. Colposcopic inspection was performed with the Binocular colposcope OP-C2, OPTOMIC with 5X, 10X and 20X magnifications. Digital images were archived using the Sinet healthnet suite 6.0 program by CSI NET srl

lesions and vulvar condylomatosis. During the antiviral treatment, the follow up gynaecological visits revealed not only the healing of the herpetic lesions, but also the remission of the cervical and vulvar HPV-related lesions.

In HHV-infected cells, for antivirals to function, they must be phosphorylated by viral thymidine kinase (HHV-TK) to inhibit DNA synthesis and viral replication by HHV-DNA polymerase, for which ACV has a high affinity [3]. However, it has been shown that cellular thymidine kinase can replace viral kinases [4], and ACV also showed inhibitory activity against cellular DNA Polymerases [5, 6]. Importantly, an in vitro study showed that the ACV treatment of HPV18-transformed HeLa cell line induced growth arrest, cell proliferation inhibition, and reduced cell survival with the formation of micronuclei [7]. Furthermore, the efficacy of ACV has also been demonstrated by intralesional administration in cutaneous warts [8, 9], as well as by postoperative therapy in Recurrent Respiratory Papillomatosis [10], both HPV-related pathologies. Two clinical trials on the efficacy of ACV against plantar warts are currently ongoing (NCT05429151; NCT05324904).

Conclusions

To our knowledge, these are the first clinical observations on the possible efficacy of ACV on HPV-related anogenital lesions. Genital HHV infections have increased enormously in recent years [11], and the possible efficacy of ACV also on HPV-related clinical manifestations could have an impact on the high epidemiological burden of anogenital HPVs in countries where HPV vaccination is not widespread [12, 13].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13027-023-00511-0.

Additional file 1. Instructions to the patient for intimate hygiene.

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Disclaimer

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Author contributions

MB collected the clinical evidence, designed the therapy, and revised the manuscript; CCS performed the cytology and histology tests; ARG, MVC, LA analysed and discussed the data and revised the manuscript; PDB analysed and discussed the data, and wrote the manuscript. All the authors have read and approved the manuscript.

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Availability of data and materials

Anonymous patient records are available for consultation upon specific request and in compliance with the laws in force in Italy.

Declarations

Ethics approval and consent to participate

The reported observations in this paper derived from MB's clinical practice. Patients voluntarily visited MB's outpatient clinic for conventional gynaecological treatment and gave their consent to use their medical records for scientific purpose.

Consent for publication

After acceptance.

Competing interests

The authors have no competing interests.

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