When HPV 16 attacks on all fronts – Diagnostic and therapeutic strategies

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BACKGROUND

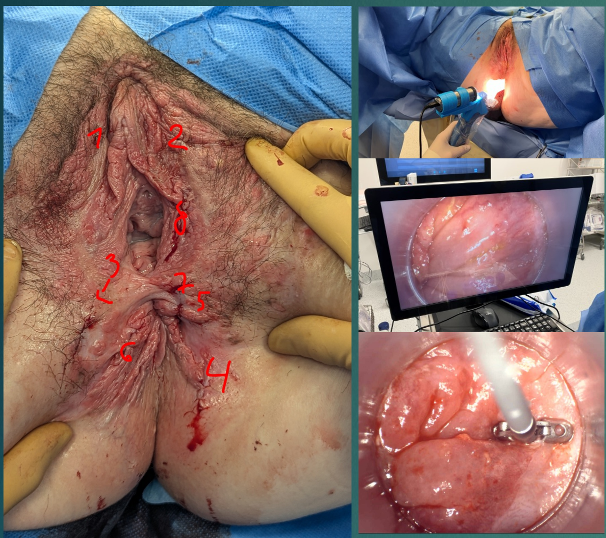
Cancers and precancerous lesions related to high risk HPV (hrHPV) are steadily increasing in Europe (1). Secondary prevention (screening) currently targets only cervical disease. Extracervical lesions occur on average 10 years after cervical lesions, are frequently multifocal, are associated with persistent infection—most commonly HPV 16—and are often linked to smoking and frequently arise in the context of immunosuppression (2). Finally, these lesions are often under-recognised by both patients and clinicians. Such lesions follow the international LAST classification (Low- and High-grade Squamous Intraepithelial Lesions) (3) and should be treated before progression to invasive disease.

CASE PRESENTATION

A 39-year-old woman was referred in 2023 for cervical HPV 16 infection with HSIL on cytology. Colposcopy-guided biopsies confirmed cervical HSIL and clinical examination (vulvar and vaginal) was unremarkable. Anal HPV testing was performed and revealed HPV 16 infection with anal LSIL. Management was postponed because of early pregnancy.

Medical history : 3 vaginal deliveries, active smoking (22 pack-years), surgery for plasma cell mastitis, social deprivation.

Following delivery, extensive vulvar lesions developed. Surgical biopsies revealed a 15 mm invasive vulvar squamous cell carcinoma with a depth of stromal invasion of 0.4 mm, without perineural invasion or lymphovascular space invasion.



Clinical examination revealed profuse HPV-induced lesions (Figure 1). No vaginal lesions were observed. Colposcopy demonstrated grade 2 abnormal transformation, and biopsies confirmed cervical HSIL.

Reflex HPV testing :

- Cervical or ENT sites : no HPV
- Anal site : Persistent HPV 16 infection, reflex cytology showing anal HSIL.

Comprehensive evaluation :

- Assessment for immunosuppression (HIV 1&2 serology, serum protein electrophoresis, full blood count, quantitative IgA/IgM/IgG, immunophenotyping with CD4 and CD8 counts).
- Screening for associated infections (hepatitis B and C, syphilis serology, PCR for *N. gonorrhoeae* and *C. trachomatis*).
- Systematic mapping of HPV-induced lesions with multiple vulvar and anal biopsies under high resolution anoscopy (Figure 1).

Results confirmed the absence of additional invasive vulvar or anal disease, with no evidence of immunosuppression or associated infection.

TREATMENT & FOLLOW-UP STRATEGY

Cervical conisation (LEEP): HSIL completely excised with clear margins; negative endocervical curettage.

Bilateral inguinal sentinel lymph node biopsy following multidisciplinary discussion,

Topical imiquimod, twice weekly, with prolonged adjunctive topical care over 20 weeks to optimise tolerance and adherence.

Electrosurgical resection of anal lesions under high resolution anoscopy.

Mandatory smoking cessation

Follow-up six months after treatment completion : Cervical HPV testing and reflex cytology, systematic high resolution anoscopy, vulvoperineal clinical review with biopsies of any residual lesions to determine the need for surgical excision or laser ablation.

DISCUSSION : DIAGNOSTIC & THERAPEUTIC CHALLENGES

Extracervical HPV-related lesions remain under-recognised. Clinicians infrequently examine the vulva (4), and patients often lack awareness of normal vulvar anatomy (5). Vulvar lesions are pleomorphic. Current French recommendations restrict systematic screening for extracervical lesions to selected contexts (6), with limited guidance regarding vulvar disease (7). However, a history of high grade cervical lesions significantly increases the risk of extracervical premalignant or malignant disease (8). Pregnancy may facilitate lesion progression due to physiological immunomodulation (9).

Management of HPV-induced disease must balance oncological safety and quality of life. Surgery has a limited but essential role : diagnostic excision when invasion is suspected and therapeutic excision for lesions resistant to medical treatment or to non-invasive modalities(6). Initial post-treatment evaluation at six months should include clinical assessment, cervical HPV testing with reflex cytology (10), vulvoperineal examination, and high resolution anoscopy. In extensive multisite disease, systematic lesion mapping with multiple biopsies and accurate anatomical documentation (drawing or, preferably, photography) is crucial (Figure 1). The role of post-treatment HPV vaccination remains debated. Early randomised trial data do not demonstrate a significant reduction in recurrence of high grade cervical lesions (11), and a dedicated randomised trial is ongoing for vaccination after vulvar HSIL (12). Smoking cessation is essential, as tobacco toxins and nicotine facilitate lesion development (13).

Briefly, similar published cases describe multifocal HPV16-related anogenital disease, frequently associated with smoking and occasionally with pregnancy or immunosuppression, underscoring the need for systematic multisite assessment and coordinated multidisciplinary management.

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