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Rapid progression of HPV16 infection to high-grade cervical intraepithelial neoplasia (CIN3) in a young woman: a case report

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ABSTRACT

The main etiological factor of cervical intraepithelial neoplasia (CIN) and cervical cancer is persistent infection with oncogenic types of human papillomavirus (HPV). Most HPV infections regress spontaneously, while progression to high-grade lesions usually takes several years. We describe the case of a 24-year-old woman, unvaccinated against HPV, who had a very rapid progression of HPV16 infection — from a normal cervical cytology result to histologically confirmed CIN3 within nine months. The patient presented no clinical symptoms and regularly attended cervical cancer screening, i.e., cytology. A Pap smear performed in December 2022 revealed no signs of dysplasia, but nine months later, an LBC cytology test revealed ASC-H with suspected HSIL, and HPV DNA testing confirmed HPV16 infection. A Colposcopy identified suspicious areas and biopsies confirmed CIN3. Histopathology after the first Loop Electrosurgical Excision Procedure (LEEP) showed CIN3 with positive margins. After the first LEEP procedure, the patient started a course of Gardasil-9 vaccinations. Because positive margins persisted, the gynecologist repeated the LEEP twice. The second procedure revealed CIN2 with a positive surgical margin, while the third showed the absence of intraepithelial neoplasia. In April 2025, a control LBC cytology test showed no neoplastic changes, and an HPV test result was negative. This case is remarkable due to the patient's age and rapid the HPV16 progression. The case emphasizes the role of molecular biomarkers in risk assessment and the importance of HPV vaccination in primary prevention.

Keywords: cervical intraepithelial neoplasia; human papillomavirus type 16; cervical screening; loop electrosurgical excision procedure; surgical margins

1. INTRODUCTION

Cervical cancer is still one of the most serious public health issues, even though there are effective primary and secondary prevention methods (Walboomers et al., 1999; Bosch et al., 2002; Muñoz et al., 2003). Most cases of this cancer are directly

related to persistent human papillomavirus infection, as confirmed by epidemiological and molecular studies (Walboomers et al., 1999; Muñoz et al., 2003). HPV 16 and 18 are exceptionally oncogenic, responsible for approximately 70% of cervical cancer cases worldwide (Clifford et al., 2003; Khan et al., 2005).

HPV infection is most common among women of reproductive age, but most infections are transient and resolve spontaneously within 1–2 years. Sustained infection with oncogenic HPV types plays a central role in the development of precancerous lesions and cervical cancer (Hildesheim et al., 1994; Koshiol et al., 2008). HPV16 and HPV18 infections pose a substantially higher risk of progression to high-grade intraepithelial neoplasia (CIN2/3) and invasive cancer (Hildesheim et al., 1994; Khan et al., 2005).

Current screening strategies in many countries include cytology and molecular testing. The HPV DNA test was shown to have higher sensitivity in detecting precancerous lesions compared to cytology only, as confirmed in large population studies, including the ATHENA and POBASCAM studies (Rijkaart et al., 2012; Wright et al., 2015). The standard treatment for high-grade intraepithelial lesions remains surgical excision, such as the loop electrosurgical excision procedure (LEEP) or conization; however, some patients remain at risk of recurrence and disease progression despite successful treatment (Soutter et al., 2006; Strander et al., 2007; McCredie et al., 2008).

In recent years, the importance of molecular biomarkers, such as the analysis of gene methylation has been increasingly emphasized. They can aid in the diagnosis, segregation, and risk stratification of patients with positive HPV test results (Wentzensen et al., 2009; Clarke et al., 2012; De Strooper et al., 2014; Verhoef et al., 2014; Lorincz, 2016; Luttmer et al., 2016). HPV vaccination constitutes a significant element of primary prevention.

The present case is remarkable for the patient's very young age (24 years) and the exceptionally rapid progression of HPV16 infection—from a typical cytology result to CIN3 within a few months. An additional therapeutic challenge was that the patient required three LEEP procedures because of persistently positive surgical margins.

2. CASE PRESENTATION

A 24-year-old woman with unremarkable medical and family history had been undergoing routine cytology since 2019. She had smoked for two years and had not received HPV vaccination. The patient was asymptomatic and her previous screening tests were part of routine preventive care. The first HPV test, conducted in 2019, was negative. Table 1 presents a detailed schedule of diagnostic and therapeutic procedures.

Table 1. Timeline of diagnostic and therapeutic events

Date / Period	Clinical event
2019	First HPV test – negative
December 2022	Conventional cytology: normal result (Candida infection, no dysplasia)
August 2023	Liquid-based cytology: ASC-H (suspected HSIL); high-risk HPV test positive for type 16
September 2023	Colposcopy and biopsy: CIN3 confirmed
November 2023	First LEEP – CIN3 with positive surgical margins
December 2023	Start of HPV vaccination (nonavalent, Gardasil-9)
April 2024	Second LEEP – CIN2 with positive margins (p16+, Ki-67+)
September 2024	Third LEEP – no intraepithelial neoplasia detected
April 2025	Follow-up cytology and HPV DNA test: negative results

Abbreviations: CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus; LEEP – loop electrosurgical excision procedure; HSIL – high-grade squamous intraepithelial lesion; ASC-H – atypical squamous cells, cannot exclude HSIL.

In December 2022, a conventional cytology smear showed results consistent with group II by the Papanicolaou classification. The sample revealed Candida spp. Infection with inflammatory changes but without signs of intraepithelial lesions or dysplasia. Nine months later, in August 2023, a follow-up liquid-based cytology (LBC) test showed abnormalities corresponding to group III according to the Papanicolaou classification — atypical squamous cells of undetermined significance (ASC-US), with suspicion of HSIL. Concurrent HPV DNA testing detected HPV type 16. In consideration of the positive HPV16 result and cytological abnormalities, testing for other sexually transmitted infections (HIV, HBV, HCV, syphilis) was performed, with negative results. In September 2023, a

colposcopy revealed a TZ2 transformation zone with minor mosaicism and a positive reaction to acetic acid in the transformation zone and the external os (Figure 1).

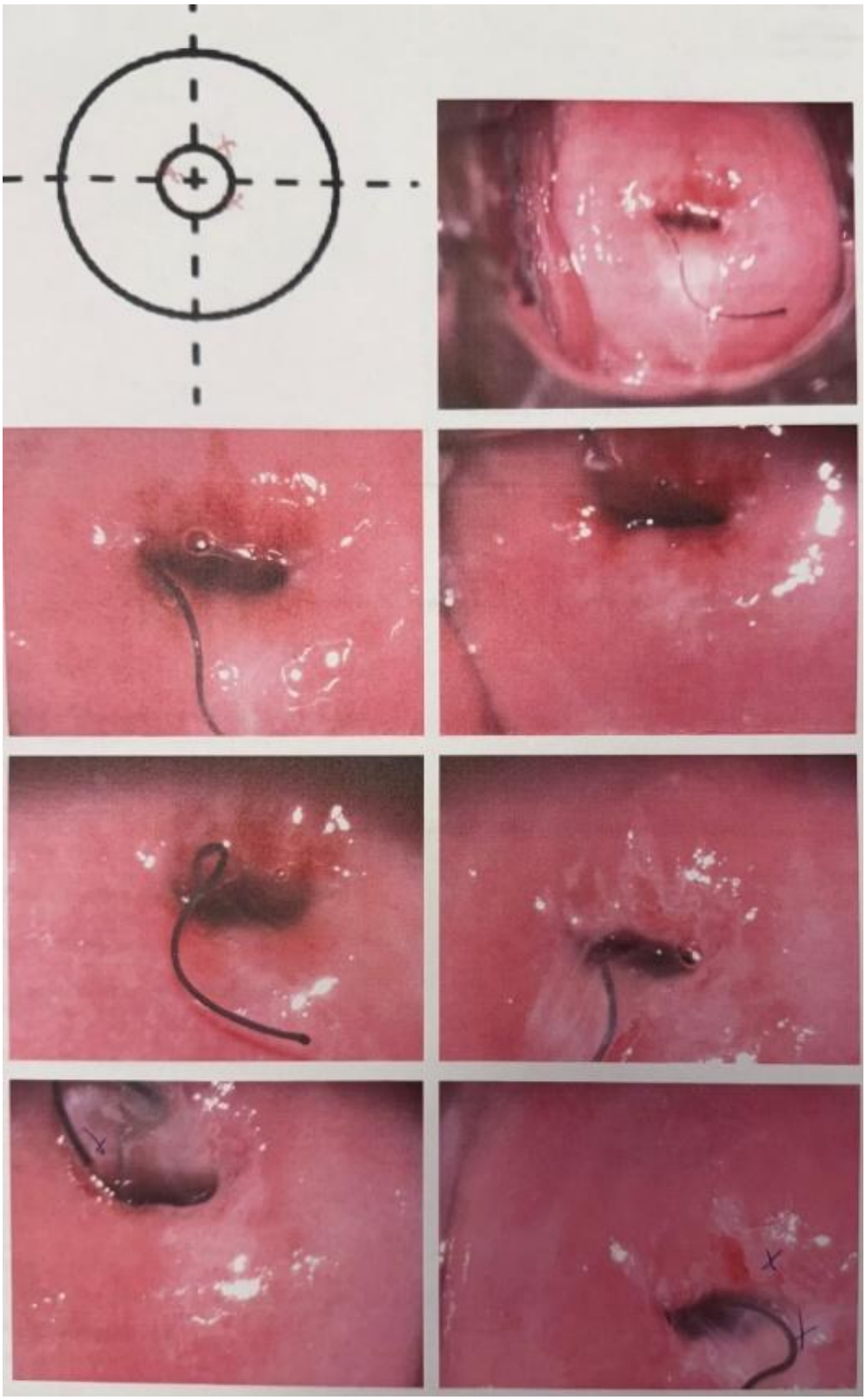

Figure 1. Colposcopic view of the cervix showing a type 2 transformation zone with distinct mosaicism and acetic epithelium after applying 5% acetic acid.

The gynecologist performed three targeted cervical biopsies, which revealed cervical intraepithelial neoplasia grade 3 (CIN3). Based on these histopathological findings, a loop electrosurgical excision procedure (LEEP) in November 2023 confirmed CIN3 with positive surgical margins.

In December 2023, the patient began a series of HPV vaccinations (Gardasil-9). In April 2024, the persistence of positive surgical margins required a second LEEP procedure. Histopathological assessment revealed CIN2 with positive resection margins. Immunohistochemical staining (p16 positive, Ki-67 positive) confirmed the diagnosis. In September 2024, the gynecologist performed the third LEEP procedure. Histopathological analysis showed no signs of intraepithelial neoplasia, and all examined fragments showed normal squamous stratified epithelium.

At the follow-up visit in April 2025, liquid-based cytology showed no intraepithelial lesions or evidence of malignancy. The smear demonstrated Candida spp. Infection with inflammatory and regenerative changes. The HPV test at the same visit showed no high-risk types. The patient continues routine outpatient follow-up. Table 2 presents significant findings from clinical, cytological, and histopathological examinations.

Table 2. Key clinical and laboratory data

Parameter	Findings
Age	24 years
Medical history	No chronic diseases, no family history of cancer
Smoking history	~2 pack-years
HPV vaccination status	Not vaccinated before diagnosis; started Gardasil-9 after first LEEP
HPV genotype	HPV16 positive
Cytology at diagnosis	ASC-H (suspicious for HSIL)
Final histopathology	CIN3 (first LEEP)
Number of surgical procedures	3 (LEEP ×3)
Final outcome (April 2025)	Cytology and HPV test negative; under surveillance

Abbreviations: HPV – human papillomavirus; LEEP – loop electrosurgical excision procedure; ASC-H – atypical squamous cells, cannot exclude HSIL; HSIL – high-grade squamous intraepithelial lesion.

3. DISCUSSION

Cervical cancer typically develops through a prolonged precancerous stage before becoming invasive. In most cases, the transition from HPV infection to high-grade lesions takes many years, often even decades (Hildesheim et al., 1994; McCredie et al., 2008; Tainio et al., 2018). In this case, the extremely rapid progression of the disease in a young woman is noteworthy — from cytology without dysplastic features to histologically confirmed CIN3 within a few months. This accelerated progression distinguishes this case from typical descriptions of the natural course of HPV infection and emphasizes the importance of individual risk assessment.

The patient's young age makes this case particularly notable. Most cases of CIN3 and cervical cancer are diagnosed in women over 30 years of age (Khan et al., 2005; Tainio et al., 2018). In contrast. HPV infections are most frequently detected in younger women, but they usually clear spontaneously within 1–2 years (Hildesheim et al., 1994; Koshiol et al., 2008). Persistent infections— those caused by HPV16 and HPV18—are associated with the highest risk of progression (Walboomers et al., 1999; Khan et al., 2005; Koshiol et al., 2008). Reports of such rapid progression in women under 25 years of age are rare, making this case particularly noteworthy. Environmental factors, including smoking, have also been identified as contributing factors to the persistence of infection and progression of lesions (Koshiol et al., 2008).

Another important aspect involves the presence of positive surgical margins after initial LEEP procedures. Several studies have shown that positive surgical margins considerably increase the likelihood of residual or recurrent CIN (Salani et al., 2009). Strander et al., (2007) and Soutter et al., (2006) observed that, despite apparently successful local treatment, women with positive margins remain at an elevated risk of progression to invasive cancer and therefore require careful follow-up.

McCredie et al., (2008) also reported that the risk of developing invasive cancer may persist for many years after treatment for CIN3, especially in cases of positive surgical margins.

In recent years, increasing attention has been focused on molecular testing, particularly the analysis of DNA methylation of genes such as FAM19A4 and miR124-2. These biomarkers may help identify lesions with low and high oncogenic potential and can serve as tools to distinguish women with positive HPV test results. Studies have shown that methylation markers are effective in detecting CIN3+ lesions and show higher specificity than HPV16/18 genotyping alone (Wentzensen et al., 2009; Clarke et al., 2012; De Strooper et al., 2014; Verhoef et al., 2014; Luttmer et al., 2016). Luttmer et al., (2016) suggested that incorporating methylation testing could enhance risk stratification for women who need close observation. Based on this evidence, broader implementation of molecular biomarkers could help identify patients who are prone to rapid disease progression, as shown in this case.

The HPV vaccination is a crucial element in this case. The patient was not vaccinated before diagnosis and started vaccination after the first LEEP procedure. Epidemiological and clinical studies show that HPV vaccination is most effective when performed before the initiation of sexual activity, decreasing the risk of CIN2+ and cervical cancer by more than 80% (Garland et al., 2016; Lei et al., 2020; Kjaer et al., 2021). Long-term follow-up studies confirm that vaccine-induced protection remains effective for many years (Joura et al., 2014).

Beyond preventing cervical cancer, HPV vaccination also lowers the risk of infections at other anatomical sites, including the oral cavity and reduces related malignancies (Drolet et al., 2021). In a meta-analysis of Asian populations, Ren et al., (2022), showed that prophylactic vaccination significantly decreases the likelihood of both CIN and cervical cancer. This case illustrates a missed opportunity for primary prevention – earlier vaccination might have significantly lowered the patient's risk of disease progression.

This case report also has some limitations. The absence of molecular biomarker testing before the first LEEP procedure limited the early assessment of progression risk. In this young patient, the rapid disease progression may reflect the influence of unrecognized risk factors that standard diagnostics did not reveal.

4. CONCLUSION

This case describes an exceptionally rare and rapid progression of HPV16 infection to CIN3 in a young woman. The findings point to key risk factors, including young age and smoking. They also show how positive surgical margins and molecular biomarkers can play an important role in predicting disease outcomes and refining individual risk assessment. Finally, the report stresses the value of early HPV vaccination programs for both girls and boys as a foundation of primary prevention.

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Author contributions

K.B. – conceptualization, case analysis, manuscript writing;
W.J.A. – data collection, patient documentation, histopathological data review;
A.T. – literature review, preparation of references, figure preparation;
J.C. – clinical supervision, critical revision of the manuscript;
W.J.B. – overall editing, English language review, final approval of the version to be published.
All authors read and approved the final version of the manuscript.

Informed consent

Written & Oral informed consent was obtained from the participant included in the study.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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