



Italian Journal of Gynæcology & Obstetrics

September 2025 - Vol. 37 - N. 3 - Quarterly - ISSN 2385 – 0868

Adenocarcinoma *in situ* of the cervix in a young patient: a diagnostic problem

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ARTICLE INFO

History

Received: 26 September 2024

Received in revised form: 16 November 2024

Accepted: 17 December 2024

Available online: 30 September 2025

DOI: 10.36129/jog.2025.198

Key words

Adenocarcinoma; cancer; cervix; HPV; uterus.

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ABSTRACT

Background. Glandular lesions of the cervix are an entity that has been on the rise in the last two decades, due to their relative rarity and the difficulties of diagnosis and management.

The screening methods (PAP test and HPV test) have significantly reduced sensitivity and specificity in the diagnosis of glandular lesions.

The treatment is surgical and fertility-sparing in young patients: a fundamental role is attributed to the integrity of the margins. The risk of recurrence is such that long-term follow-up is required.

Case presentation. This case report is about an interesting case concerning a young patient, whose diagnosis of Adenocarcinoma *in situ* (AIS) is almost fortuitous and certainly unexpected.

Conclusions. Diagnosis of AIS is still a great problem: clinical outcome can be unpredictable; it is mandatory improves our diagnostic skills.

INTRODUCTION

Cervical cancer is the second most common cancer among women worldwide and the most common in low- and middle-income countries [1]. Squamous cell carcinoma and adenocarcinoma are the two main histological types of cervical cancer. Most cervical neoplasia cases are attributable to persi-

stent sexually transmitted infections caused by oncogenic strains of human papillomavirus (HPV), most of all HPV 16 and 18 [2]. Adenocarcinoma, which represents 10-20% of all cervical cancers, has been increasing in the last two decades, unlike squamous cell carcinoma which is proportionally decreasing [3]. Adenocarcinoma *in situ* of the cervix (AIS) is a precursor of invasive adenocarcinoma.

Invasive and pre-invasive lesions are often concomitant on histological findings [4].

AIS lesions of the cervix are generally asymptomatic and silent on macroscopic examination. The average age of patients with AIS is young. The ability to detect AIS reduces the incidence of invasive forms. The PAP test has a sensitivity of only 45% in detecting glandular lesions [5].

Although there are risk factors that can intervene on the oncogenic process in a negative and unavoidable way, such as reactive oxygen species [6], there are conditions on which we can intervene effectively.

The most recent acquisitions highlight how the HPV vaccine, recommended for both sexes during adolescence, abstinence from smoking and the use of barrier contraception methods may contribute to prevent HPV infection.

Colposcopy allow the detection of early-stage cervical carcinoma. In the early-stage cervical carcinoma fertility sparing treatment is available. The risk of recurrence is strictly linked to persistence of HPV infection and positive endocervical margins [7].

The HPV vaccine reduce the HPV infection persistence rate and should be performed even in the absence of the uterine cervix: HPV vaccination would protect against develop lower genital tract dysplasia [8].

CASE PRESENTATION

A 32-year-old Italian patient living in London regularly performed her cervical cancer screening checks: in February 2019, at the age of 27, she carried out a PAP test with a negative result; as per the Guidelines for her age group, she was invited again to Screening check in May 2022 and, as she had turned 30, she underwent to an HPV test with negative results. As reported in the response letter, the next appointment was set for May 2025. The patient returned to Italy in January 2024 and, upon her return, she decided to be reinserted into the National Screening belonged to the USL Umbria 1 Screening System. She performed an HPV test with a positive result (HPV 18), on the same sample was performed the PAP triage test which showed atypical glandular cells of endocervical origin (AGC). She performed Colposcopy at the Colposcopy Service of the USL Umbria 1: Squamocolumnar junction (SCJ) visible, clear area on the cervix at iodine staining. Preliminary to col-

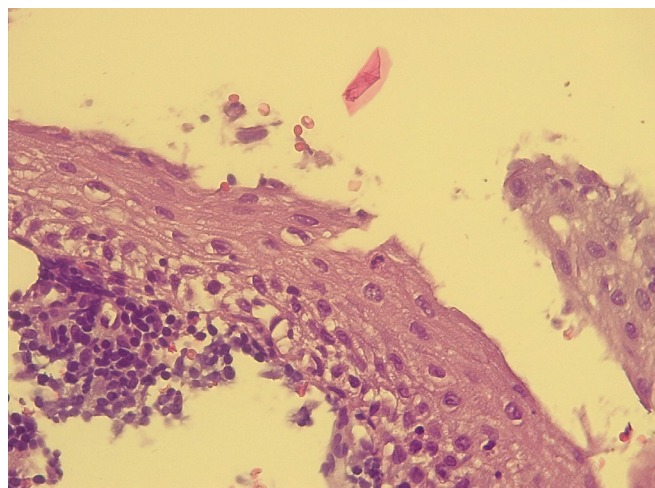


Figure 1. Exocervical biopsy 40x: koilocytosis (pathognomonic lesion due to HPV infection).

The cells (especially of the stratum spinosum) present pyknotic, shrunken nuclei, surrounded by light halos, with extensive vacuolization.

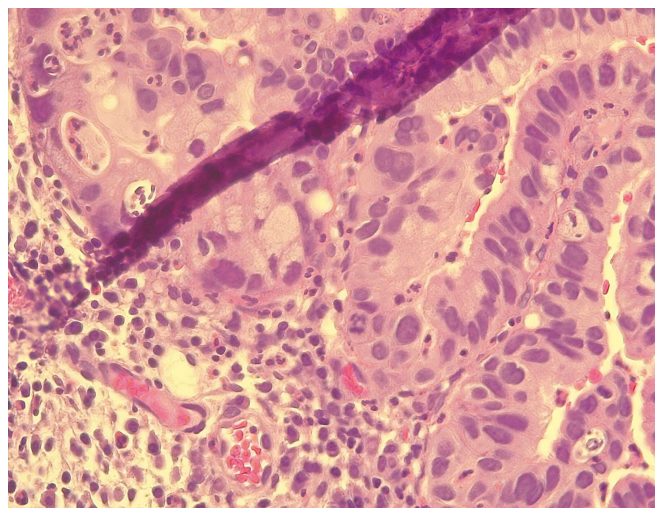


Figure 2. Adenocarcinoma in situ of the cervix: particular on mitosis.

poscopy, was performed a confirmatory PAP test, then an exocervical biopsy (CIN I) (**Figure 1**) and an endocervical biopsy (negative). The PAP test performed before the colposcopy had a result like the previous one (AGC). The patient underwent to follow up because of discordance between cervical cytology and histology and finally had cervical conization surgery (LLETZ) with histological diagnosis of foci of Adenocarcinoma in situ of the cervix (**Figure 2**), HPV related (p16+) (**Figure 3**) + LSIL, margin free from 3 mm [9].

The patient is currently under follow-up as per the oncological protocol [10, 11].

She already performed the first 6-months follow up, the results are as follows: HPV test negative, PAP test negative.

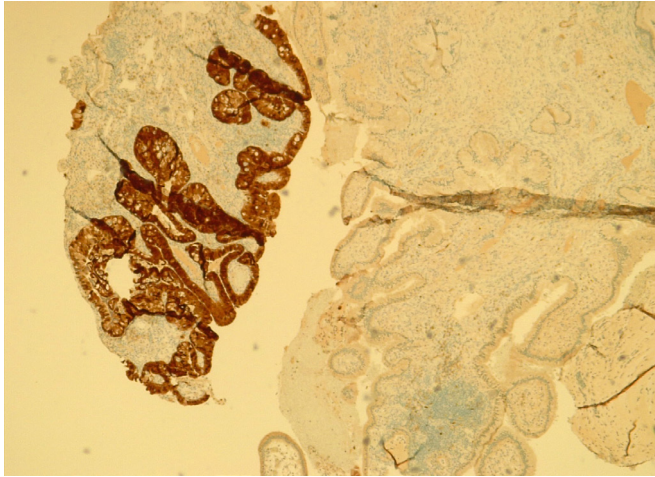


Figure 3. P16 immunohistochemistry.

P16 is a cyclin-dependent kinase inhibitor, is the product of a gene tumour suppressor which by preventing the phosphorylation of pRb prevents the cell cycle progression; the oncogenetic mechanism HPV-induced causes overexpression of p16.

DISCUSSION

Glandular lesions of the cervix are on the rise. They affect a younger side of the population when compared with squamous lesions. Their clinical course is decidedly more aggressive, and they require long-term follow-up due to a high risk of recurrence, even after many years [12, 13].

In early stages, conservative treatment is possible, especially among young women of reproductive age, with encouraging results [14]. In advanced stages a hysterectomy is required which can be carried out either in minimally invasive way or through open radical hysterectomy, without any influence on 90-day surgery-related morbidity and with excellent hope of survival in the medium/long term [15, 16].

The most recent acquisition suggests to evaluate many factors during follow up: HPV persistence, preoperative multiple high-risk human papilloma virus infection, margin involvement, re-infection with a new HR-HPV type. Post-treatment HPV persistence varies widely and is influenced by patient age, HPV-type, detection method, treatment method, and minimum HPV post-treatment testing interval. Furthermore, post-treatment HPV persistence is strongly and consistently associated with high-grade cervical intraepithelial neoplasia (CIN) grade 2/3 acquisition and is considered essential for the progression of cervical precancer to invasive cervical cancer [17].

The treatment is well planned, the main problem is related to diagnostic difficulties.

All this evidence, including that which emerges from our case report, suggests that it is essential to standardize the diagnostic and therapeutic protocol when dealing with AIS. Furthermore, it is important to standardize the follow-up methods including all cited variables. It would be essential to increase diagnostic capacity by identifying specific risk factors for glandular pathology.

CONCLUSIONS

This fortunate case reminds us of the intrinsic limits of cervical cancer screening: although in situ glandular lesions anticipate invasive lesions by up to 5 years, sometimes the clinical outcome can be unpredictable. An unconventional check-up allowed the diagnosis of a cancerous lesion at an early stage, ensuring a fertility-sparing treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

M.T., D.R.: Conceptualization, investigation, methodology, resources, software, visualization, data curation, writing – original draft, writing. D.G.C.: Supervision, writing – review & editing.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

All images and all information in this case report are reported under explicit informed consent of the patient: patient anonymity has been preserved in accordance with the Declaration of Helsinki.

Data sharing

Data are available under reasonable request to the corresponding author.

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