



# Transtubal Spread of Endocervical Adenocarcinomas: An Unnoticed Mechanism of Metastasis

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## Abstract

We report the case of a 49-year-old woman with isolated, unilateral, ovarian metastasis of endocervical adenocarcinoma *in situ* four years after undergoing total hysterectomy. Extensive workup (including colonoscopy and upper endoscopy) excluded other sites of active disease. Histopathology review confirmed the absence of an invasive component of endocervical adenocarcinoma and both tumor samples had the same histological characteristics and were P16-positive tumors by immunohistochemistry analysis, supporting the interpretation of the ovarian neoplasms as a late recurrent of endocervical adenocarcinomas, simulating primary ovarian surface epithelial neoplasms. The patient underwent bilateral oophorectomy with complete tumor resection, followed by six cycles of chemotherapy. The patient remains alive with no evidence of disease after seven years of follow-up. The lack of recognizable stromal invasion, absence of lymph node involvement, and distal organ metastasis make transtubal spread the most likely route of dissemination in this presented case, and it might not result in an adverse outcome.

**Keywords:** Endocervical adenocarcinoma; Ovarian metastasis; p16-positive

## Introduction

Uterine cervical cancer is one of the most common malignancies of the female genital tract. Histologically, 90% to 95% of invasive cervical cancers are squamous cell cancers and adenocarcinoma constitutes less than 5% of cervical cancers in most developing countries [1]. Human Papillomavirus (HPV) is a common sexually transmitted infection, and it is the primary underlying cause of cervical cancer [2].

As the stromal invasion progresses, it may directly involve the vagina, parametrium, pelvic sidewall, bladder, ureter and rectum. Regional lymph node metastasis occurs along with the local invasion of uterus lymphatics, and it evolves into a lateral pelvic route along the lateral parametrium and along the vesicouterine ligament. Distant metastases usually occur late in the disease, involving para-aortic lymph nodes, lungs, liver, bone, and other structures [3].

Ovarian involvement by cervical carcinomas is rare. It was reported in less than 0.5% of women with squamous cell carcinoma and in slightly more than 1.4% with adenocarcinoma, respectively [4]. There are at least four possible pathways for the spread of cervical carcinoma to the ovary: Direct invasion, lymphatic metastasis, hematogenous dissemination, and transtubal spread. The extension into the lower uterine segment and corpus endometrium may be a risk factor, and the retrograde uterine/transtubal spread is the possible spread mechanism [4].

## Case Presentation

A 49-year-old female patient was referred to the Oncology Unit due to a left ovarian cystic detected by transvaginal ultrasound. The patient had submitted to hysterectomy 4 years earlier due to uterine myomatosis and adenocarcinoma *in situ* of the cervix. This imaging procedure was performed during routine gynecological follow-up.

A pathological review was performed and the entire cervix was embedded sequentially and demonstrated endocervical adenocarcinoma *in situ* with no evidence of invasion of its stroma also it confirmed the diagnosis of uterine myomatosis.

Extensive workup (including colonoscopy and upper endoscopy) was performed and it excluded other sites of active disease (absence of pelvic or retroperitoneal lymph node enlarged;

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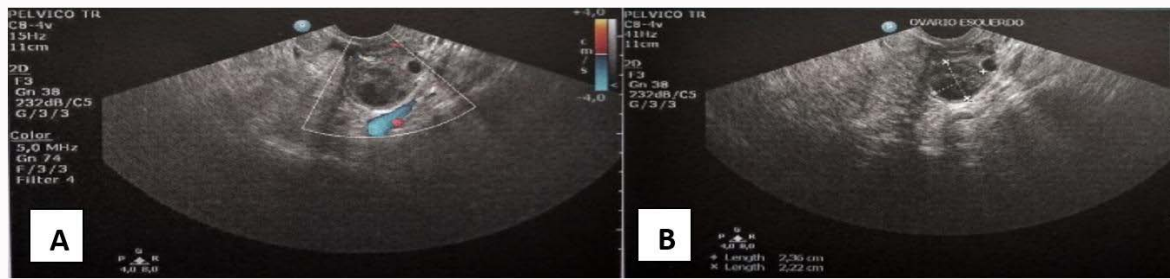
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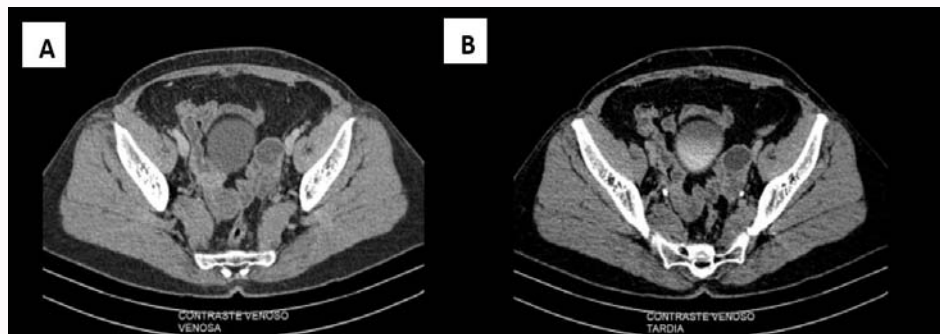
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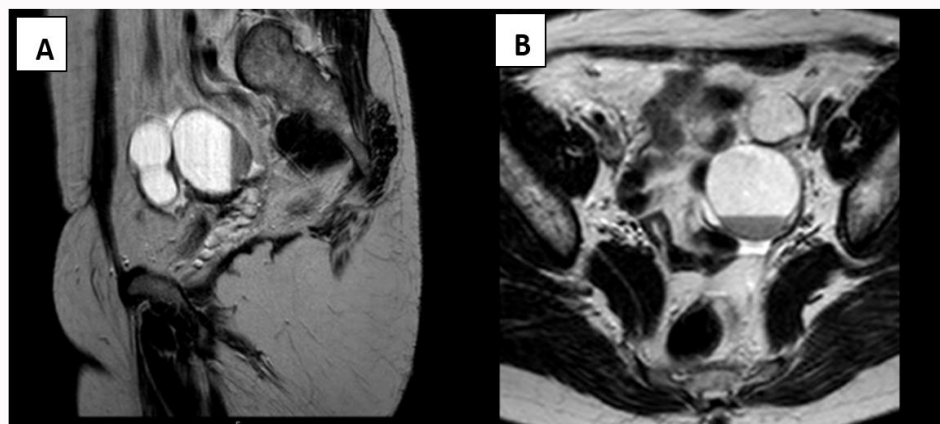
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**Figures 1A, 1B:** Pelvic ultrasound showed a rounded, hypoechoic formation with no flow on color Doppler (left) and fine septations (right), located in the left ovary.



**Figures 2A, 2B:** Pelvic Computed Tomography (CT) scan showed a late venous contrast, and a coarsely septated lesion on the left side, between the bladder and rectal region.



**Figures 3A, 3B:** Pelvic Magnetic Resonance Imaging (MRI) scan showed a left adnexal multiseptated cystic with liquid-liquid level, suggesting hematic content. There is no evidence of papillary projections or associated solid mural nodules.

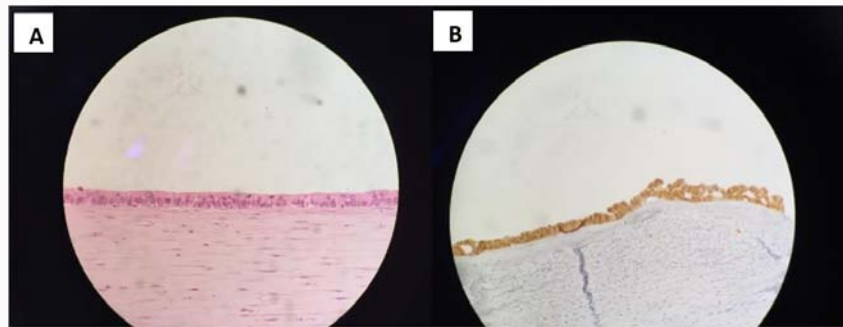
no evidence of metastatic disease). Serum tumor markers showed no abnormalities (CA125, lactate dehydrogenase, Beta-HCG, and alpha-fetoprotein).

A transvaginal ultrasound showed a round formation measuring 2.4 cm × 2.2 cm (Figures 1A, 1B). A Computed Tomography (CT) scan of the thorax, abdomen, and pelvis was performed as a staging procedure which demonstrated a left adnexal multiseptated cystic (5 cm) (Figure 2A, 2B). An MRI, to further characterize the left adnexal cyst, demonstrated a 5.4 cm × 3.7 cm multiseptated cyst (Figure 3A, 3B). On the T1 fat-saturated image, some bright signals raised the possibility of some hemorrhage within the cyst. The patient had no complaints at the time of admission to the oncology unit.

The multidisciplinary team decision was upfront debulking

surgery. The patient underwent an inventory of the abdominopelvic cavity that revealed several solid-cystic lesions in the left ovary with a total size of 10 cm adhered to the vaginal dome. The pathologist's report described the left ovary tumor as an unusual ovarian cystic tumor, covered by very atypical mucinous-type epithelium. Immunohistochemical studies of this mucinous cystic neoplasm in the left ovary showed diffuse positive staining with p16 (Figure 4); positive cytokeratin 7, 8, and 18; negative cytokeratin 20; negative CDX2, compatible with ovarian metastasis of endocervical adenocarcinoma.

Workup ruled out another tumor site and the patient received six cycles of chemotherapy based on paclitaxel associated with carboplatin, every 3 weeks. No additional oncological therapy was performed and the patient evolved without evidence of active disease



**Figure 4:** 4A) Image of the cyst wall with neoplastic cells in the lining tissue with epithelium displaying abnormal nuclear features. H&E morphology was compatible with mucinous cystic neoplasia (100x magnification). 4B) Immunohistochemistry image showed diffuse positivity for the p16 marker (100x magnification; staining >75% of tumor cells). The p16 immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections cut at 4 mm thick using the CINtec p16INK4A assay, according to the manufacturer's instructions (CINtec Histology Kit; Ventana Medical Systems, Tucson, AZ).

after seven years of follow-up.

## Discussion

We reported a rare case of endocervical adenocarcinoma *in situ* that presented with late recurrence, four years after total hysterectomy, as ovarian metastases in which the ovarian tumors simulated primary ovarian surface epithelial neoplasms.

Distinguishing ovarian metastasis of endocervical adenocarcinoma from primary ovarian tumors is often challenging because of several overlapping features [5]. Although it is a rare event, the possibility of minimally invasive cervical tumors to metastases to the ovary and then simulating a primary ovarian neoplasm has been diagnosed before, concurrently with, or after the ovarian metastases [6,7].

Leen et al. [8] published a clinicopathological parameters useful in the distinction of primary from metastatic mucinous ovarian carcinomas. The authors classified the presence of bilaterality, size <10 cm, surface involvement, extensive intra-abdominal spread and an extensive infiltrative pattern with desmoplasia as a major features favoring metastases, as the presence of two morphological patterns (colloid and signet ring carcinomas) as criteria to exclude ovarian origin. They considered unilaterality, large size >12 cm, smooth external surface and association with other ovarian pathology as features that favoring primary ovarian origin.

According to Ronnett et al. [6] current cases of AIS with ovarian metastasis support the concept of direct dissemination (non-lymph node and non-hematogenic) of the HPV-associated neoplastic epithelium from the endocervix to the ovarian, transported through the fallopian tubes, called the transtubal mechanism of dissemination or uterine retrograde mechanism.

Elishaev et al. [9] described a total of 8 cases in which AIS, with minimal or no stromal invasion, was associated with a concomitant neoplasm identical to that caused by HPV in an ovary. This pattern of spread is uncommon and seems to be associated with a favorable prognosis. The authors established that the detection of HPV DNA in ovarian tumors is indicative of metastasis rather than primary neoplasms. The diffuse p16 staining pattern observed in metastatic endocervical ovarian adenocarcinomas is specific and can be used as an independent marker for diagnosing such a tumor when other direct HPV DNA detection methods are not available [9].

Van et al. [10] demonstrated that p16 expression is useful as

part of a panel of immunohistochemical markers for distinguishing primary ovarian tumors from metastases and, when strong and diffuse positive (>75% positive tumor cells), is a sensitive (100%) and specific (97%) marker for identifying HPV-related endocervical adenocarcinomas metastatic to the ovary among the primary ovarian tumors and metastatic adenocarcinomas from other sites [10,11].

In the context of a mucinous ovarian lesion, the p16 immunohistochemistry test may be helpful in identifying metastatic mucinous tumors of cervical origin. Although there are potential pitfalls, diffuse expression of p16 can serve as a sensitive and specific marker for the identification of HPV related endocervical adenocarcinomas and could serve as a useful adjunct, in addition to other immunohistochemical markers [10,11].

Glennon et al. [12] also reported that immunohistochemistry may help identify metastatic mucinous tumors of cervical origin. Despite the authors pointing out that failures may occur, diffuse expression of p16 can serve as a sensitive and specific marker for the identification of HPV-related endocervical adenocarcinomas and could be included as a useful adjunct, in addition to the CK7, CK20, CDX2, and other immunohistochemical markers, during assessing the possibility of metastatic spread to the ovary.

Chang et al. [7] have highlighted the importance of recognizing this clinical situation as it is a unique variant with potential for long-term survival. The authors report 2 cases of extensive AIS associated with ovarian metastases. In both cases, primary and metastatic tumors were positive for human papillomavirus 16. Both patients were alive at the time of the last status assessment and one has had no recurrence after a follow-up period of 145 months.

Although metastatic cervical disease has been considered incurable and treated primarily with palliative intention, recent work suggests that patients with oligometastasis can benefit from local treatments, such as radiation or surgery, and in some times, these treatments can even be considering with potentially curative intent [13]. There is no randomized phase III trial to support evidence-based medicine practice in this scenario.

The lack of stromal invasion, absence of lymph node involvement, and distal organ metastasis make transtubal spread the most likely route of dissemination in this case. A multidisciplinary treatment was performed and the patient has evolved with long-term survival with no active disease.

## Conclusion

This study showed a rare case of late recurrence of endocervical adenocarcinoma *in situ* with metastatic carcinoma to the ovary from the cervical. It highlights some of the challenges in the diagnosis and the importance of follow-up for women treated for high-grade, non-invasive glandular abnormalities of the cervix.

The interaction of imaging and anatomopathological analysis methods was essential in the management of the case. The p16 immunohistochemistry stain may be used to identify the spread to the ovary from a cervical primary, especially where a diagnosis of a mucinous tumor is being considered. If the test is positive, in the absence of other markers, it is possible to prove ovarian metastasis from endocervical adenocarcinoma. Total resection surgery has been described as associated with excellent long-term survival rates, and adjuvant chemotherapy may be considered if there is no clinical contraindication.

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