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Incidentally Diagnosed Ovarian Metastasis of a Previously Unrecognized Cervical Squamous Cell Carcinoma in a Patient With Ovarian Cyst: A Case Report

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Abstract

Introduction: Primary cervical cancer with synchronous ovarian metastasis is a rare clinical entity; it is more common in cervical adenocarcinoma than squamous cell carcinoma.

Case Presentation: We discuss the case of a 38-year-old female who presented in 2012 with a 15-cm-large cyst of the right ovary, with negative cervical smear cytology. Right adnexectomy was performed laparoscopically, and metastatic cystic squamous cell carcinoma probably originating from the endocervix was reported. One month later, radical hysterectomy (Piver type I) and left adnexectomy were performed; a 15-mm-large high endocervical papillary squamous cell carcinoma was diagnosed. There is no evidence of local recurrence or distant metastasis to date.

Conclusion: This case shows that these kind of (primary) cervical and (secondary) ovarian tumors are almost always discontinuous, without any evidence of direct invasion from cervix to ovary, and it also supports the notion that in cases of cervical cancer originating from the endocervix or cervical canal and protruding into or involving the isthmus, the prevalence of ovarian metastasis is higher. This unique case is a good example of unintentionally—and fortunately—diagnosed squamous cell carcinoma of endocervical origin with unilateral ovarian metastasis.

Keywords: Cervical cancer, Ovarian metastasis, Oncology

Introduction

Cervical cancer is the fourth most common cause of cancer-related death among women both in developed and developing countries worldwide (1). Most cases are squamous cell carcinomas (2), and early detection with combined surgical and oncologic treatment is essential in management. Although cervical cancer screening is widely available, a significant proportion of cases are diagnosed in advanced stages, and recurrence is also a challenge to face in clinical management (3). Amongst younger patients, the proportion of missed diagnosis of cervical cancer is relatively common, despite the widely available screening.

Primary cervical cancer with synchronous ovarian metastasis is a rare clinical entity; it is more common in cervical adenocarcinoma than squamous cell carcinoma (4). Ovarian metastasis of cervical cancer is usually a postoperative histopathological finding following radical hysterectomy and adnexectomy (and pelvic lymphadenectomy) performed after the definitive diagnosis of cervical cancer (confirmed by previous cervical conisation or biopsy and histopathological assessment), and it is generally a microscopic, unilateral, synchronous metastasis of the primary cervical neoplasm (5). In cases of cervical cancer with ovarian dissemination, the disease is considered locally advanced, with relevant oncologic consequences in its therapeutic approach. The prevalence of cervical cancer with ovarian metastasis is generally low, and it is more common in patients over 45-50 years (6).

The prognosis of cervical squamous cell carcinoma (CSCC) and adenocarcinoma with ovarian metastasis are equally poor (7). In this report, we discuss the case of a 38-year-old female. Laparoscopic right adnexectomy was performed because of the diagnosis of a right ovarian cyst, with negative preoperative cervical smear cytology. The histopathological assessment of the right ovary revealed an ovarian metastasis of CSCC adventitiously. A few weeks later, radical hysterectomy was performed, and the histopathological examination confirmed the primary CSCC.

Besides the stochastic diagnosis of the metastatic neoplasm in the ovary, the very low prevalence of CSCC with ovarian metastasis, and the relatively young age of

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the patient with this subtype of cervical cancer, with a preoperatively negative cervical smear cytology, the case is clinically intriguing as the patient has a >10-year-long disease-free survival, with no evidence of recurrence to date.

Case Presentation

Patient Information, Clinical Findings and Timeline

The patient had a routine gynecological check-up in December 2012; vaginal examination and cervical smear cytology were performed. Vaginal ultrasound described the previously inserted intrauterine device (IUD) in the uterus, and a 15-cm-large cyst in the right ovarium, without any ultrasound signs suspicious of malignancy. It should also be noted from the antecedents, that the patient had two Cesarean sections in her obstetric history, and she did not take any medications. Preoperative Cancer Antigen 125 (CA125) level in the serum was 182.2 U/mL (reference range: <30 U/mL). Although the CA125 level was elevated, the ovarian cyst was not considered to be suspicious for malignancy, as ultrasound did not reveal any characteristic sign (e.g. papillary structures within the cyst, increased vascularization of its wall) associated with primary or secondary adnexal neoplasms; the elevation of CA125 was considered to be a possible sign of endometriosis, as the patient had dysmenorrhea in her medical history.

Therapeutic Intervention

Uterine curette (in order to remove the IUD) and a laparoscopy were performed under general anesthesia in January 2013. During laparoscopy, the ovarian cyst ruptured - it contained serosanguinous fluid, which was aspirated during surgery. The right uterine tube was adherent to the large ovarian cyst, and the gynecologist performing the operation could not identify intact ovarian tissue on the right side, therefore a right adnexectomy was performed laparoscopically. The uterus, the left adnexa, the pelvic wall and peritoneum were without any signs of inflammatory or neoplastic disease, and the postoperative period was uneventful. The patient was discharged from hospital the next day.

Diagnostic Assessment

Postoperative gross pathological examination of the right adnexa described an intact Fallopian tube, and the internal wall of the ovarian cyst was found to be hoarse, with an average thickness of 2-3 mm. Focally, a protruding, velvet-like area was described in the wall of the cyst, with a diameter of 15 mm. Microscopically, the cyst wall showed a multilayer epithelium; in the protruding area, squamous cell carcinoma was found with pronounced nuclear polymorphism, high mitotic activity, and a papillary structure. Focally, hemosiderin pigment was identified and the lack of collagen IV around the cell nests (suggesting the lack of a basement membrane) was also found. With immunohistochemistry, p16, high molecular weight cytokeratin (HMWCK) and p63 were diffusely positive, while cytokeratin (CK) 7, CK20, CA125, and Wilms' tumor 1 (WT1) protein were negative. The histopathological diagnosis of metastatic cystic squamous cell carcinoma was established (Figure 1).

Staging examinations were done in February; abdominal and pelvic contrast-enhanced computed tomography (CT) did not describe any pathological findings (follicles were found in the left ovary, and a slightly increased endometrial thickness was described, which was probably due to luteal phase; to note, histology of endometrial tissue was not performed after the curette, because only the IUD was extracted by the intervention).

In virtue of the available findings, laparotomy was performed in March, and radical hysterectomy (Piver type I), left adnexectomy, infragastric omentectomy, bilateral parailiacal and paraaortic lymphadenectomy, and diagnostic excision of parietal peritoneum were performed. There were no signs of malignancy macroscopically neither in the pelvis nor in the abdomen. Peritoneal wash fluid cytology did not demonstrate malignant cells. The postoperative interval after the laparotomy was also uneventful.

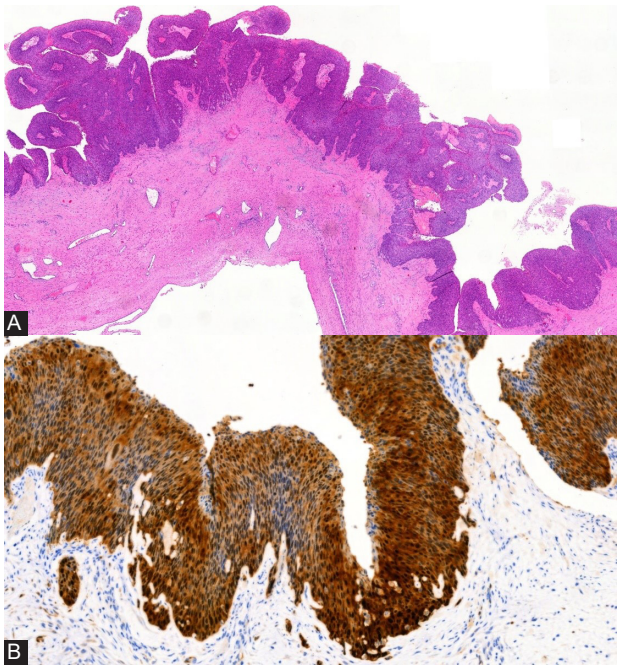

Figure 1. Photomicrographs of the Ovarian Metastasis. (A) (hematoxilin-eosin stain, x3.5): Photomicrograph of the inner epithelial surface of the ovarian cyst: multilayer epithelium characterized by various thickness and significantly disorganized growth pattern. The nuclei of the epithelial cells focally demonstrate marked polymorphism. Mitotic activity is high, and focally dyskeratinocytes are also present. The tumor both macroscopically and microscopically has papillary areas, but the majority of the cyst lining surface epithelium was flat, multilayer squamous epithelium. The border of the epithelium and connective tissue is mostly sharp. Hypocellular subepithelial connective tissue is also discernible. **(B)** (p16 immunhistochemical stain, magnification: x20): Photomicrograph of the inner epithelial surface of the ovarian cyst: diffuse p16 block positivity is observable in the epithelium of the neoplasm.

Macroscopic pathological examination of the uterus described normal-appearing ectocervix and cervical canal, and a 15-mm polypoid lesion was found, originating from the endocervix and expanding into the isthmus. The endometrium, myometrium, right tube and ovary were macroscopically normal, as well as the resected peritoneal specimen, omentum and lymph nodes.

Microscopic evaluation of the specimen (Figure 2) revealed normal epithelium in the ectocervix and cervical canal, but the polypoid tissue of the endocervix and isthmus was a papillary squamous cell carcinoma with an exophytic growth pattern. The surface of the neoplastic tissue was parakeratotic, and nuclear pleomorphism was moderate. Lymphovascular invasion was also present, and the tumor infiltrated only the superficial myometrium of the isthmus. The endometrium, the right ovary and Fallopian tube did not show any signs of malignancy; the omentum, the peritoneal tissue and all of the resected lymph nodes were also free of disease. In short, papillary squamous cell carcinoma of the uterine isthmus was diagnosed, and the phenotype of this primary tumor was found to be identical to the previously analyzed metastatic neoplasm of the left ovary. Accordingly, the ovarian metastasis of the primary CSCC was diagnosed first as a casualty, and the clinically occult primary neoplasm was found based on that incidental finding.

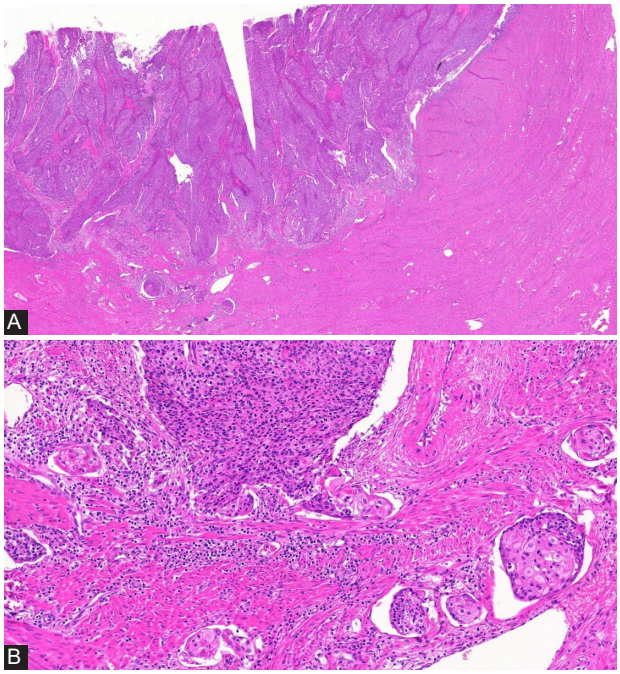

Figure 2. Photomicrographs of the Primary Neoplastic Tissue of the Cervical Isthmus (Hematoxilin-Eosin Stain). (A) (magnification: x2): Epithelial neoplasm is characterized by peaky, eminent papillae with a narrow fibrovascular shaft. The papillae are covered with neoplastic squamous cells having a characteristic eosinophilic cytoplasm. The surface demonstrates parakeratosis. **(B)** (magnification: x20): Nuclear pleomorphism is moderate. The growth pattern of the tumor is decisively exophytic. Lymphovascular invasion is obvious. Considering the phenotypic congeniality of the ovarian neoplasm, the tumor of the cervical isthmus is considered the primary neoplasm, while the ovarian lesion is regarded as a metastasis.

Primary CSCC with spread to the ovary is associated with unfavorable prognosis, and the described lymphovascular invasion was also a poor prognostic factor, however, the peritoneal wash fluid and the lymph nodes were free of malignant cells, and the resection margin of the cervical tumor was free of tumor, therefore, this case was considered to have both positive and negative prognostic features difficult to weight against each other.

Postoperative adjuvant chemotherapy (four cycles of carboplatin), high-dose rate brachytherapy (two fractions, 6 Gy/fraction) and concomitant pelvic irradiation (up to a total dose of 46.8 Gy, 1.8 Gy/day over five weeks) were the adjuvant treatment.

Follow-up and Outcomes

Follow-up of the patient includes orderly contrast-enhanced abdominal and pelvic CT and annual positron emission tomography CT, and there is no evidence of local recurrence or distant metastasis to date (November 2024). To date, the patient does not have any signs of complications of surgery, or recurrence of the malignancy; her long-term health status is excellent.

Discussion

This unique case is a good example of unintentionally—and fortunately—diagnosed squamous cell carcinoma of endocervical origin with unilateral ovarian metastasis; the patient was pronouncedly younger at the time of diagnosis compared to the average age of patients with this kind of metastatic cervical neoplasm (8).

This report gives further support to the previous observation that in cases of synchronous endocervical and ovarian malignancies of similar type, the ovarian neoplasm is more commonly a metastasis, not a second neoplasm originating from ovarian cells (9). It is also in keeping with the notion that the prevalence of ovarian metastasis is higher in cases of cervical cancer originating from the endocervix or cervical canal and protruding into or involving the isthmus (10); in such cases, if the ovarian metastasis is diagnosed first, resection of the primary cervical neoplasm is essential as a secondary cytoreduction, since the 5-year survival of such cases is quite low (11). This case fairly illustrates the importance of tumorectomy in such instances, as complete resection of neoplastic tissue could be achieved in this case.

Usually, bulky and/or locally advanced CSCCs metastasize to the ovary (12). However, the present tumor had a diameter of only 15 mm. On the other hand, delayed recurrence of microinvasive CSCC after resection (e.g. if cervical conization is performed) is also well-known. In the presented case, a disease-free survival of more than a decade was achieved.

Accurate histopathological assessment of such tumors is essential, as rare cases of coexistent cervical and ovarian malignancies have been reported (13). The correct application of immunohistochemical stains—as in this

case—could be remarkably helpful to establish the correct diagnosis. The diffusely positive p16 in this case supports high-risk human papillomavirus (HPV) associated origin of the neoplasm (14,15), but direct HPV identification and typing were not performed. HPV DNA polymerase chain reaction (PCR) has an important role in the differential diagnosis of CSCC and primary ovarian squamous cell carcinoma (16). In the presented case, the corresponding immunohistochemical stains of the primary and metastatic neoplasm supported the phenotypic concordance.

Malignant neoplasms of the uterine isthmus have either endocervical or endometrial origin (17), although ovarian metastases in cases of endometrial malignancies are much more common compared to cases of CSCCs (18). This fact also emphasizes the importance of proper histopathological assessment of malignancies at this location.

As far as the mechanism and pathobiology of this kind of metastasis is concerned, either hematogenous (7) or transtubal spread of the primary cancer are the most plausible explanations. These kind of (primary) cervical and (secondary) ovarian tumors are almost always discontinuous, without any evidence of direct invasion from cervix to ovary (19). As the peritoneal biopsy and the wash fluid were negative for malignancy, direct peritoneal invasion had been excluded, and the relevance of lymphogenic spread is also refutable (at least in this case), as all of the studied lymph nodes were negative for metastases. Small vessel invasion referred to as (lympho) vascular invasion, can also reflect invasion of blood capillaries; no attempt to distinguish between blood and lymphatic endothelium was made. As concerns transtubal spread, tubal involvement would be very much supportive of this mechanism, but this is generally missing in cases of clonally related endometrial and ovarian cancers, too.

Superficial spreading CSCC is a subtype of cervical cancer worth to be distinguished (20), with the characteristic predisposition to involve the endometrium and adnexa, however, the growth pattern of the neoplasm described in this report suggests that superficial spread of the primary CSCC is not presumable in this case. Superficial spreading CSCC involving the endometrium is a special entity in gynecological oncology, as limited knowledge of its prognostic factors, and the lack of clinical practice guidelines of its management characterizes it (21). The case reported here is also special, as the location, histopathological subtype and clinically occult presentation of the CSCC, the incidentally diagnosed ovarian metastasis and the disease-free survival of the patient denotes the lack of evidence of prognostic factors and perspicacious pathobiological knowledge of this kind of cervical malignancy.

Our case report primarily focuses on surgical and pathological aspects of this rare gynecological oncological entity, however the essential role of adequate preoperative and postoperative radiological and oncological evaluation and multidisciplinary approach also needs to be highlighted.

This unique and rare clinical case emphasizes the significance of accurate clinical follow-up of ovarian cysts, as primary or metastatic malignancies of the adnexa could be present even in the population of young women; elevated CA125 further enhances the suspicion of malignancy. In cases of persisting adnexal cysts, histopathological evaluation has the key role in clinicopathological evaluation of the cases, making timely diagnosis possible. The screening of younger women with adnexal cysts needs to be oncologically vigilant and consider the possibility of rare manifestations, like that of metastatic cervical neoplasms to the adnexa, even in the clinical scenario of negative cervical cytology smear and young patients without any risk factors for ovarian malignancies.

Authors' Contribution

Conceptualization: István Dankó, Attila Seregély, Gábor Cserni.
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Writing–review & editing: István Dankó, Gábor Cserni.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Written informed consent was obtained from the patient to publish this case report.

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