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Ovarian tumors: Should the cervix be examined first?

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Summary

There is a controversy regarding ovarian metastasis in early-stage adenocarcinoma of the uterine cervix. The authors present the case of a 51-year-old woman that at the time of diagnosis was thought to suffer from a Stage II cervical carcinoma and a synchronous ovarian carcinoma, that turned out to be an ovarian metastasis from the endocervical adenocarcinoma, as attested morphologically, histochemically, and immunohistochemically. Radical hysterectomy with oophorectomy, excision of the omentum, lymph node excision, and cytological sampling of the peritoneal cavity were carried out. It is important to always bear in mind that even low-grade adenocarcinomas of the cervix can be metastatic to the ovaries. Clinicians have to be careful when managing those cases, while further investigation is needed in order to determine the exact mechanism of those metastases and the criteria needed in order to preserve the ovaries in young patients.

Key words: Ovarian metastasis; Endocervical adenocarcinoma; Fertility-sparing surgery.

Introduction

Cervical cancer is the third most common cancer in women, with estimated 529,828 new cases and 275,128 deaths reported worldwide in 2008 [1]. The human papillomavirus (HPV) is detected in 99% of cervical tumors, in particular the oncogenic subtypes such as HPV 16 and 18 [2]. The WHO recognizes three categories of epithelial tumors of the cervix: squamous, glandular (adenocarcinoma), and other epithelial tumors including neuroendocrine tumors and undifferentiated carcinoma. Squamous cell carcinomas account for about 70%-80% of cervical cancers and adenocarcinomas for 10%-15% [3]. It is important to mention that cervical adenocarcinoma is actually a disease occurring mostly in young and premenopausal women [4]. Younger patients could be interested in preservation of the ovarian function, turning medical interest into fertility-sparing options, including ovarian preservation.

Although ovarian preservation in premenopausal women with early-stage squamous cell carcinoma of the cervix has been widely accepted since the publication by McCall *et al.* in 1958 [5], there is a great controversy regarding ovarian preservation in cervical adenocarcinoma, since there have been a few series and case reports published in the literature suggesting higher rate of ovarian metastasis in early-stage adenocarcinoma of the uterine cervix [6-9]. The authors present the case of a woman that at the time of diagnosis was thought to suffer from a Stage II cervical carcinoma and a synchronous ovarian carcinoma, that turned out to be an ovarian metastasis from the cervical carcinoma.

Case Report

A 51-year-old gravida 7 para 2 patient visited the 3rd Department of Obstetrics and Gynecology, General University Hospital "Attikon", National University of Athens, Greece, with complaints of lower abdominal pain for a month and incidents of abnormal vaginal bleeding. From her medical history, she suffered from diabetes mellitus type II under treatment with metformin and sitagliptin, as well as from hypertension, for which she has been taking telmisartan and bisoprolol. She has been also receiving daily alprazolam due to generalized anxiety disorder.

Ultrasonography revealed normal endometrium and right ovary with normal echotexture, whereas the left ovary was enlarged (62×70×68 mm) due to a cystic lesion with projections showing increased vascularity. Those findings were indicative of high risk lesions. Upper and lower abdomen CT showed micronodular lesions in peritoneal and omental fat diameter to eight mm, a cystic lesion of diameter 8.4 cm dashing out from the left parametrium, as well as a mass (4.8 cm maximum diameter) in the cervix extending to the endometrial cavity. No pathologic lymph nodes were detected. Lower abdomen MRI showed the same lesions, the endocervical lesion (dimensions 5.2×2.7 cm) with no expansion beyond the cervical limits and the cystic lesion (6.6×8.2 cm) in the left minor pelvis. Colposcopy findings set the differential diagnosis between heavy dysplasia and infiltrative growth. So, a cervical biopsy was taken, that revealed endothelial carcinoma without infiltrative growth in the existing material. Chest CT, mammography, and breast US findings were normal. Endometrial cytology showed hyperplasia without atypia (ACE-L). As far as tumor markers are concerned, CEA and CA125 levels were increased, while AFP, CA15.3, CA19.9, and SCC were normal.

Given the findings above, surgical management followed. Radical abdominal hysterectomy with oophorectomy, total excision of the omentum, pelvic and para-aortical lymph node excision, and cytological sampling of the peritoneal cavity were carried out. The pathological findings showed that the endocervical lesion was a well-differentiated adenocarcinoma of the cervix with free margins. The lesion originating from the ovary, thought at first place

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as a synchronous carcinoma, turned out to be a metastasis from the endocervical adenocarcinoma expanding on the outer surface of the ovary, as attested morphologically (tubular cribriform-micropapillary pattern), histochemically (PAS-D positive in the cytoplasm and cellular margin) and immunohistochemically [CK7(+), CEA (intensely and diffusely positive, +) p16 (intensely and diffusely positive, +), ki-67(+, namely 80%), p53 (weakly positive, 20%), CK20(-), CDX2(-), vimentin(-), WT1(-), ER(-), and PR(-)]. The endometrial cavity, the fallopian tubes and the parametrium bilaterally were free of infiltration. Four out of 14 left pelvic lymph nodes excised, which were infiltrated by the adenocarcinoma. The right pelvic lymph nodes and the part of the omentum were free of disease. The patient was scheduled for chemotherapy (combination of platinum-based chemotherapy and taxane) and radiotherapy. Six months after the surgical management, the patient remains free of relapse. Written informed consent was obtained by the patient for the publication of this case report.

Discussion

Many series and case reports in the literature refer to a higher rate of ovarian metastasis from cervical adenocarcinoma than from squamous cell carcinoma. Tabata *et al.* reported an incidence of 7.7% of ovarian metastasis from Stage IB cervical adenocarcinoma [10]. Nakanishi *et al.* found an incidence of 6.3% [7]. Mann *et al.* reported two cases of patients with Stage IB cervical adenocarcinomas who were found to have occult ovarian metastases [6]. In the first case the ovaries were excised due to unexpected endometriosis and no vascular, lymphatic or parametrial involvement was found. In the second case, the ovaries seemed macroscopically normal, but were removed as it was decided preoperatively with patient consent. The pathological findings revealed bilateral ovarian micrometastases. Vasculolymphatic involvement as well as micrometastases in three lymph nodes were also found.

An interesting case is the one presented by Abdulhathi *et al.* [11]. The patient is a woman who presented with an ovarian mass and the cervix adenocarcinoma was found only postoperatively. The primary carcinoma was hidden, since it originated from deep crypts of the cervical glands sparing the surface epithelium. Frequent vascular invasion was found. Khor *et al.* reported two cases of minimally invasive cervical adenocarcinomas that spread to the ovary and were initially misinterpreted as primary ovarian adenocarcinomas [12]. The interesting part about those two cases is that the first one referred to an in situ adenocarcinoma (AIS) with no evidence of invasive malignancy, whereas in the second one, the histological examination revealed widespread cervical intraepithelial neoplasia (CIN 3) and AIS extending from the transformation zone to the uterine corpus. Focal invasive carcinoma was found within the isthmus and the uterine corpus but no invasive malignancy was identified within the cervix. No lymphovascular involvement was found. In the present case, both lesions were clinically obvious, but all the findings led to the hypothesis of two independent primary carcinomas, since all the other sites of the reproductive tract were intact.

Endocervical carcinomas rarely metastasize to the ovaries; the most common patterns of spread is local expansion in the adjacent pelvic sites or distant metastases [13]. Routes of spread to the ovary in cervical cancer have been controversial when it comes to smaller carcinomas. Wu *et al.* suggested that lymphatic spread and transtubal implantation might be possible pathways of metastases from cervix to the ovaries [14]. On the contrary, Tabata *et al.* reported thar ovarian metastasis might occur via hematogenous spread of cervical carcinoma [10]. Shimada *et al.* found that eight of nine distant recurrent patients with squamous cell carcinoma showed lymphatic spread, while seven of nine patients with adenocarcinoma had hematogenous metastasis, implying that the route may differ by histological type [15]. In the present case, transtubal implantation could serve an explanation since the ovarian neoplasm develops in the outer surface of the ovary. Furthermore lymphatic expansion could also be present, since the pathological findings revealed malignant infiltration in four left pelvic lymph nodes.

It is of great clinical importance to determine the risk factors for ovarian metastasis in adenocarcinoma of the cervix. Nakanishi *et al.* [7] associated pathological endometrial extension, lymph node metastasis, pathological parametrial invasion, tumor size of > three cm, with a higher risk of ovarian metastasis. Landoni *et al.* [16] found that age > 45 years, deep stromal invasion, and FIGO Stage are independent risk factors for ovarian metastases. Hu *et al.* [17] identified lymph node metastasis, corpus invasion, and parametrial invasion to be significantly associated with the risk of ovarian spread. They also found on multivariate analysis that neoadjuvant chemotherapy was an independent protective factor against ovarian metastasis in adenocarcinoma. Shimada *et al.* [15] found that the presence of ovarian metastasis did not correlate with lymph node involvement or parametrial invasion and stated that ovaries must be removed in all patients with cervical adenocarcinoma. Touhami and Plante in a recent review of the literature [18] proposed some criteria to identify candidates for ovarian preservation in the surgical treatment of ovarian adenocarcinoma. These criteria are divided in preoperative and intraoperative findings. The preoperative characteristics are further divided in patient's characteristics (age ≤ 45, patients who desire to retain ovarian function, no familiar predisposition to ovarian cancer), and tumor characteristics based on clinical examination and pelvic MRI (FIGO Stage ≤ IB, tumor size ≤ four cm, no parametrial invasion, no corpus invasion, no deep stromal invasion, no evidence of lymph node metastasis, and no LVSI). As far as the intraoperative findings are concerned, they include no evidence of extrauterine spread, no evidence of lymph node metastasis, and normal appearing ovaries.

It is easily concluded that ovarian preservation in cervical carcinoma is a controversial issue and gynecologists should think carefully, taking into account all recent scientific data,

and personalizing the management of every case. It might be useful, even in low grade adenocarcinomas, to carry out endometrial cavity washing and send the sample for cytological examination; this could help recognize the existence of free malignant cells. Immunohistochemistry can also prove useful in cases like the present where distinguishing a synchronous ovarian neoplasia from a metastatic ovarian tumor may be difficult. Immunohistochemistry for hormone receptors can be a helpful option, since most low-grade ovarian endometrioid neoplasms are ER/PR positive, contrary to primary endocervical malignancies [19]. Recent studies have suggested that HPV is absent or only rarely detected in primary ovarian neoplasia, whereas more than 90% of cervical adenocarcinomas of common histological type are HPV positive [20-24]. This clearly indicates that the presence of identical HPV DNA in tumors of both sites can be a strong evidence for the cervical origin of the ovarian tumor in such cases. Ovarian adenocarcinomas (mucinous or endometrioid type) have been reported to show p16 protein expression only in a minority of cases, whereas endocervical neoplasms are typically strongly immunoreactive for this marker [25]; however, focal or diffuse p16 immunoreactivity in 74% of advanced stage ovarian mucinous and endometrioid neoplasms has been noted [20].

Concluding, a case of a Stage II adenocarcinoma of the cervix with a metastatic tumor to the left ovary has been presented. It is important to always bear in mind that even low-grade adenocarcinomas of the cervix can be metastatic to the ovaries. Clinicians have to be very careful when managing these cases, while further investigation is needed in order to determine the exact mechanism of the metastases and criteria are needed in order to preserve the ovaries in these patients.

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