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Case Report

Ovarian clear cell carcinoma associated with endometriosis: a case report and literature review

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Summary

Purpose: The purpose of this report was to confirm that endometriosis, although a benign gynecological disease, in some patients, can give rise to ovarian cancers. *Case Report:* The authors report a case of clear cell carcinoma in a patient suffering of endometriosis. The patient, a 38-year old nullipara, had a history of bilateral ovarian cysts diagnosed on routine check-up by ultrasound scan four years ago. After admission to hospital, due to cramping lower abdominal pain, MRI showed tumorous mass, with solid and cystic components, located between abdominal wall, lateral pelvic walls, and lumbosacral part of spine belonging to ovaries. The patient underwent appropriate extensive surgery. Histopathological investigation revealed ovarian clear cell adenocarcinoma Stage IIIa, along with endometriotic cyst found on the contralateral side. *Conclusion:* This report confirms the strong link between endometriosis and ovarian cancer and sends an appeal for urgent and precise definition of parameters relevant for determination of patients' groups with the risk for malignancy.

Key words: Clear cell carcinoma; Endometriosis; Ovarian tumor.

Introduction

Endometriosis is a benign gynecological disease that can occasionally give rise to ovarian cancers with specific histology such as endometrioid and clear cell carcinoma [1-3]. Although endometriosis is a benign disease, it has many features of neoplasia. Moreover, it is well recognized that there is an increased risk for malignant transformation in ovarian endometriosis [2-4]. The aim of this report was to confirm the contiguity between endometriosis and ovarian cancer in order to strengthen the hypothesis that endometriosis can undergo malignant transformation.

Case Report

A 38-year-old nulliparous patient was referred to this Clinic in January 2012. due to moderate cramping lower abdominal pain existing for few weeks at that time. Written informed consent was obtained from the patient for all diagnostic and therapeutic procedures upon admission to the Clinic. On a routine regular gynecological examination, with ultrasound scan, four years earlier she was found to have bilateral ovarian cysts up to 30 mm in diameter. As the menstrual cycle was regular, patient was not advised to take contraceptives. Unfortunately, the patient did not go for further regular check-ups.

Upon admission, gynecological and ultrasound examination revealed a large multilocular tumor in pelvic cavity and lower parts of abdomen. It consisted of solid and cystic components, with the largest cyst (100×90 mm) in the upper part. Only a small amount of free fluid was found in pelvis and perihepatic space. The uterus was normally shaped, measuring 76×35×54 mm, with an endometrial thickness of 7 mm. Color Doppler sonography demonstrated regular blood flow of the both ovarian vessels as well as within the tumor. Magnetic resonance imaging showed that both ovaries were transformed into tumor masses, with numerous solid and cystic components, localized between abdominal wall, lateral pelvic walls, and lumbosacral part of spine (Figure 1a). There were also bilocular hemorrhagic cysts, up to 94×57×61 mm in diameter, continuous to the main tumor tissue, suggesting preexisting endometriosis.

Preoperative laboratory analyses confirmed mild anemia, and an elevated erythrocyte sedimentation rate up to 95, while all other data were within normal range. Tumor marker HE4 and CA 125 levels were elevated (403.4 IU/ml, and 249.8 pM/ml, respectively), while the levels of all other tumor markers (AFP, CEA, CA 19-9, and beta-hCG) were within normal range.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy, total omentectomy, appendectomy, and adhesiolysis were performed (Figure 1b). Histopathological investigation revealed ovarian clear cell adenocarcinoma Stage IIIa, along with endometriotic cyst found on the contralateral side (Figure 2). Clear

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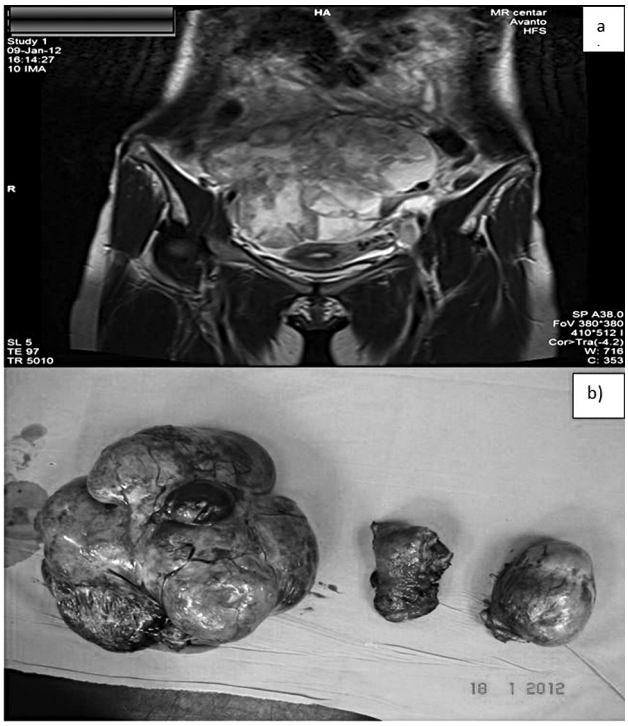

Figure 1. — a) Preoperative MRI showing bulky pelvic mass. b) Removed uterus with both ovaries.

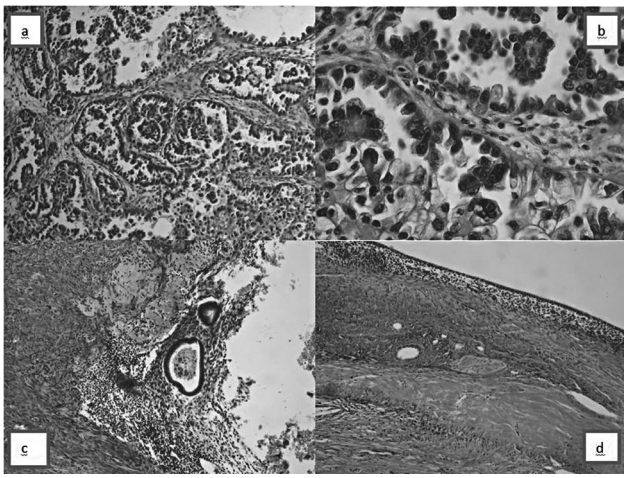

Figure 2. — Histopathological findings. (a) Clear cell carcinoma magnification ×5. b) Clear cell adenocarcinoma magnification ×20. c) Endometriosis on the contralateral side. d) Capsule of the hemorragic cyst).

cell carcinoma was of tubular structure with prominent multinuclear cells and large necrotic and hemorrhagic areas. There were no malignant cells in the parametrial tissue or on the other ovary. However, microscopic secondary deposits were registered on the serosa of the appendix. Moreover, focal mezotel proliferations were detected on the omentum. Peritoneal washing cytology examination did not confirm the presence of malignant cells. Postoperative hospital course was uneventful. Patient was discharged with an advice to receive adjuvant chemotherapy with taxel and carboplatin.

Discussion

Endometriosis, defined as the implantation of endometrium-like glandular and stromal cells outside their normal location in the uterus, is a common disease of women in their reproductive age [2, 3]. One of the usual localizations for endometriosis is the ovary. There are numerous explanations for its etiopathogenesis, such as retrograde menstrual bleeding, implantation, and the metaplasia theories, but the exact mechanism of endometriotic lesions initiation still remains unclear [1].

Endometriosis might be viewed as a neoplastic precursor mostly of endometrioid and clear cell carcinomas. The incidence of malignancy in ovarian endometriosis according to literature data ranges from 0.7% up to even 45% [5, 6]. Furthermore, ovarian endometriosis is identified in about 30% of synchronous endometrial and ovarian cancers, especially of endometrioid type [7]. In the case presented, endometriosis was synchronous with clear cell carcinoma on the contralateral ovary. It also seemed like the carcinoma derived from previous ovarian endometrial lesions.

Mean age of patients with endometriotic malignant transformation is usually during the fourth decade, and the majority of the women are premenopausal, just like our patient. These data support the notion that ovarian endometrioma should be viewed as a neoplastic process, especially in perimenopausal women [2, 3, 8]. In patients with endometriosis-associated ovarian cancer, benign-appearing ovarian masses are typically present several years before the diagnosis of the cancer [7]. This was proven to be true in the case reported. The clear cell carcinomas tend to be unilateral and large in size (mean diameter 15 cm), which was the case in the present patient as well [4, 6, 7]. The major symptoms of both endometriosis and ovarian carcinoma (dysmenorrhea, dyspareunia, chronic pelvic pain, subfertility, and hormonal abnormalities) depend of both localization and disease stage, and may be misleading during diagnostic procedure [1, 9].

The most commonly used technique in screening for ovarian cancer is bimanual pelvic examination followed by ultrasound (US) imaging of the ovaries plus testing for serum carbohydrate antigen (CA) 125 and human epididymis protein 4 (HE4) as tumor markers, or sequential use of the two modalities [2-7]. Sonographic features of clear cell carcinomas are non-specific usually presenting as complex, predominantly cystic masses, which is similar with endometriotic cysts [2, 10]. Therefore, in the presented case the authors also used MRI for obtaining more detailed image. Studies have confirmed that CA125 level is usually slightly elevated for substantial time before the diagnosis of ovarian cancer due to the CA 125 elevations caused by endometriosis [11-14]. Patients with the non-serous carci-

noma types usually have long intervals of only benignant endometriosis before developing ovarian cancer (mean: 4.5 years; range: 1–16 years). In contrast, serous-type ovarian cancer may exhibit a rapid progression, with sudden elevations of CA 125 levels, possibly due to de-novo carcinogenesis. On the other hand, serum and urinary HE4 levels appear to be more affected by carcinogenesis than by other pathologic processes [2, 13]. Moreover, HE4 serum levels are related to progression of carcinoma stage. Elevations of HE4 or CA 125 are significant in serous subtypes of ovarian carcinoma. However, other histological types of ovarian cancer or non-gynecologic malignancies (breast, endometrial, pancreaticobiliary, and renal cell carcinomas) usually exhibit weak expressions of HE4 proteins. Furthermore, HE 4 is not elevated in benignant ovarian diseases such as endometriosis [13, 14]. Therefore, CA 125 used together with HE 4, are currently the best markers for differentiation between endometriosis and ovarian carcinomas [8, 15, 16].

The process of malignant transformation of endometriosis is believed to undergo a few phases: 1) an endometrial cyst development, 2) its epithelium undergoes initiation, thus giving rise to atypical endometriosis consisting of dysplastic or intraepithelial neoplastic epithelium, and 3) the atypical endometriosis undergoes further initiation and gives rise to the atypical clear cells, that ultimately leads to clear cell carcinoma [1-3]. There are six essential alterations in cell physiology: oxidative stress and detoxification, proteases, signal transduction, adhesion, transcription, and metabolism, but the exact mechanisms that turn endo-metriosis into a cancer precursor are still under research [17, 18].

The risk factors, such as advanced age, earlier menarche, and lower parity, are similar for both of these diseases [8]. Age above 40 years and the size of the endometriomas above 9 cm are found to be independent predictors of the development of ovarian cancer among the women with ovarian endometrioma [7]. Several studies suggest that iron-mediated oxidative stress is the key element of the inflammatory reaction associated with endometriosis. Retrograde menstruation or repeated hemorrhage in endometriotic cysts present pro-oxidant factors heme and iron to the ovarian tissue [1]. Excess iron accumulation can result in toxicity and may be one of the factors contributing to the development of endometriosis and subsequently ovarian carcinoma [7].

It has been observed that clear cell carcinoma specifically displays lower expression of estrogen receptors [2, 19]. Researchers have found that the loss of estrogen receptor expression can be a result of different mechanisms such as the hyper methylation of the ER-α promoter, histone modification (deacetylation and methylation of histones), chromatin remodeling, and ubiquitin ligase activity. Moreover, mediators of oxidative stress like heme and iron may modify genomic DNA and, subsequently, cause ER depletion. This loss of estrogen function may be a main reason for progression and aggressiveness of the clear cell carcinoma [19, 20]. However, currently as the main basis of connection between endometriosis and ovarian carcinomas are considered to be the same alterations of the genome or molecular biochemical parameters that are the origin of both endometriosis and ovarian carcinomas. These changes are associated with the loss of expression or upregulation of a number of key regulatory genes [3, 6]. Alterations of the genome that can cause both endometriosis and ovarian carcinomas can also involve the loss of heterozygosity, allelic loss, comparative genomic hybridization, mutation, methylation status, microarray gene expression, and proteomics [7, 18].

Recent biochemical studies based on genome wide expression analysis technology have noted specific expression of a transcription factor, hepatocyte nuclear factor-1ß (HNF-1ß) in clear cell carcinoma [14]. Among 54 genes highly upregulated in clear cell carcinomas, 47 genes (87.0%) were associated with the redox-related genes. Several important clear cell carcinoma–related genes overlap with those known to be regulated by HNF-1ß. The HNF-1ß-dependent pathway might provide new insights into regulation of glycogen synthesis, detoxification, and resistance to anticancer agents [14].

Literature data show that loss of heterozygosity (LOH) of many chromosomal regions (including 1q, 5q, 9p, 10q, 11q, 17q, and 22q) containing tumor suppressor genes, can be one of the mutations involved in the initiation, promotion, and progression endometriosis and ovarian carcinoma. LOH in the on 1p and 13q and p53 gene is considered to be a late event in the development of endometriosis – clear cell carcinoma sequence [2, 3, 7].

Latest studies have suggested the role of PTEN and L1 cell adhesion molecule. Mutations of PTEN, leading to its inactivation or loss of expression, seem to be an early event in the malignant process of endometriosis developing clear cell carcinoma of the ovary [7, 17]. Evidence that the PTEN–PIK3CA–mTOR pathway is also strongly implicated was demonstrated by finding *PIK3CA* mutations in 33–46% of clear cell carcinoma cases [21]. Researchers suggested L1 cell adhesion molecule (L1CAM) could promote endometriosis development by increasing enervation and aggravation. L1CAM expression is higher in endometriosis with atypical cells and therefore might represent a factor used in future screening for the development of endometriosis based ovarian carcinomas [5].

Mutations in *ARID1A*, a component of the chromatin-remodeling SWI–SNF complex, a significant tumor suppressor in clear cell carcinomas, were described in in almost half of ovarian clear cell carcinomas. Additionally, in cases with adjacent areas of atypical endometriosis, identical *ARID1A* mutations were demonstrated in both the carcinomatous and the endometriotic tissue. These findings may explain the connection between these two illnesses [6, 19-23].

Analyses have revealed that Met gene amplification oc-

curred in about 30% of primary tumors and 25% of the clear cell ovarian carcinoma cell lines. Amplification of the AKT2 gene, a downstream component of the Met/PI3K signaling pathway, was also observed in somewhat less than a quarter of samples. In some patients, both the Met and AKT2 genes were amplified. Furthermore, patients with Met gene amplification have worse prognosis. Met knockdown by shRNA resulted in reduced viability of clear carcinoma cells due to increased apoptosis and cellular senescence. This proved that the Met signaling pathway plays an important role in endometriosis – clear cell carcinoma sequence. Therefore, Met gene amplification can be used as a screening marker [24].

Further molecular studies on the mechanism of the malignant transformation of ovarian endometriosis are required. Regardless, many more studies on the direct contiguity between the endometriosis and clear cell carcinoma should be undertaken. Understanding the mechanisms of the development of endometriosis and elucidating its pathogenesis and pathophysiology are intrinsic to the prevention of endometriosis-associated ovarian cancer and the search for effective therapies.

Conclusions

The authors suggest that women, who have clinical diagnosis of endometriosis, should undergo annual ultrasound examination with Doppler velocimetry and serum CA 125 and HE4 (ROMA index) evaluation. In case of increased diameter of endometrioma and significantly elevated tumor markers, magnetic resonance should be performed and genetic analyses undertaken. If malignant transformation of endometrioma is suspected, surgery needs to be considered. This report confirms the strong link between endometriosis and ovarian cancer and sends an appeal for urgent and precise definition of parameters relevant for determination of patients' groups with the risk for malignancy.

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