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Association of endometrioid ovarian carcinoma arising from endometriosis, endometrioid endometrial carcinoma, and high-grade undifferentiated endometrial sarcoma: a case report

L. Di Benedetto, A. Guarino, M. Mallozzi, D. Caserta

Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea Hospital, Faculty of Medicine and Psychology, University of Rome "Sapienza", Rome (Italy)

Summary

Endometriosis is a chronic disease that affects women of reproductive age. Malignant transformation in endometriosis is considered to be an unusual event, only occurring in 0.7–0.1% of cases. However the association between endometriosis and endometrial cancer is not well defined. Also in literature, rare cases of uterine sarcoma, about 3% of all uterine malignancies, associated with endometriosis have been reported. The authors report a case of a 47-years-old Italian woman with histologic diagnosis of endometrioid ovarian carcinoma arising from endometriosis, endometrioid endometrial carcinoma, and undifferentiated endometrial sarcoma. Therefore there have been few studies addressing the relationship between endometrial stromal sarcomas (ESS), and endometriosis. Novel scientific findings are necessary to investigate a possible common pathway and an effective treatment, although complete tumor resection can reduce the recurrence rate.

Key words: Endometriosis; Endometrial stromal sarcomas; Endometrial cancer.

Introduction

Endometriosis is a chronic disease that affects women of reproductive age. Malignant transformation in endometriosis is considered to be an unusual event, only occurring in 0.7–0.1% of cases. However, according to several epidemiological studies, endometriosis is related to increased risk of various tumors with the best evidence for ovarian cancer. Endometriosis has been found to be associated with clear cell and endometrioid histological sub-type of ovarian carcinoma [1]. Some studies indicate that patients with endometriotic lesions harbor a higher risk for developing endometrial cancer. However the association between endometriosis and endometrial cancer is not well defined [2]. The etiopathogenesis of endometriosis and endometrial cancer is multifactorial, but a yet unidentified common link may exist. Although new scientific findings are still necessary to fully explain the exact mechanisms between these two disorders, it seems that endometriosis and endometrial cancer share common etiological mechanisms, including estrogen stimulation and chronic inflammation [1]. Also in literature rare cases of uterine sarcoma, about 3% of all uterine malignancies, associated with endometriosis have been reported [3]. There are a few literature studies regarding the relationship between enometrial stromal tumours (ESTs) and endometriosis.

Case Report

The authors report a case of a 47-years-old Italian woman, G2P2, referred to the present Gynecology Emergency Department with severe pelvic pain since three days. On her medical history, she had two vaginal deliveries, no previous surgery, and no familiarity for gynecologic malignancies. Transvaginal ultrasonography revealed: uterus increased in side, nonhomogeneous endometrial echo pattern, hyperechoic and vascularized tissue in the uterine cavity, measuring 25×12 mm in diameter, a 15 ×12-mm mass in left ovary, and free fluid in Douglas cavity. Total body computed tomography revealed a 15-cm partially solid and partially cystic lesion of left ovarian origin, enlarged lomboaortic lymph nodes, and ascites. Serum levels of BhCG, CEA, CA 15.3, and alpha-fetoprotein were negative, while CA 125 was 132,20 UI/ml (normal laboratory values 0.00-35.00) and CA 19.9 was 352.24 UI/ml (normal laboratory values 0.00-37.00). The patient underwent laparotomic surgery in which uterus, ovaries, fallopian tubes, mass originating from the left ovary, omentum, appendix, and pelvic and lomboaortic lymph nodes were removed. Cytological analysis of fluid washed from the abdominal cavity and peritoneum was performed. The removed material was sent to cytological and histological laboratory. Histologically, in the endometrium there was a localized endometrioid endometrial carcinoma with evidence of tumor infiltration in the myometrium; the complex ovarian mass was heterogeneous, characterized by both solid and cystic areas. The cystic component presented solid foci and histologically was confirmed as an endometriotic lesion with endometrioid ovarian carcinoma. The solid component was composed of pleomorphic round and oval to spindled cells. Their nuclei were polymorphous vesicular with coarse chromatin and large nucleoli. The cytoplasm was scant. More than 12 mitotic

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figures per 10 high power fields were readily identified. Immunohistochemical test showed an undifferentiated sarcoma characterized by cells: CK-, vimentin+, p53+, CD34+, WT1+, CD10+, cKit-, PgR-, ER-, PLAP-, inhibin- alpha, CD99-, CD45, CD30-, alpha-fetoprotein-, MART1-, S-100-, CD56-, and AML-. Based on these findings, the tumor was interpreted as high-grade undifferentiated endometrial sarcoma. Three of the 12 lomboaortic lymph nodes, two of the nine left-sided obturator lymph nodes, left parametrium, and ascites fluid were infiltrated by undifferentiated sarcoma cells. Omentum, appendix, uterine cervix, bilateral paracolpium, right parametrium, and right annex were free of tumor. In conclusion the results of histologic examination demonstrated endometrioid ovarian carcinoma arising from endometriosis, endometrioid endometrial carcinoma, and undifferentiated stromal sarcoma. The patient was sent to the present oncological center where she began chemotherapy with carboplatin, taxol, and bevacizumab.

Discussion

Endometriosis is a chronic gynecological benign and estrogen-dependent disease that involves approximately 10% of women of reproductive age. It is characterized by the presence of endometrial tissue outside the uterus, including the ovaries and other pelvic structures. Malignant transformation is a rare complication of endometriosis and it is considered to be an unusual event (0.7–0.1% of cases) [1]. The relationship between endometriosis and ovarian cancer, particularly endometrioid or clear cell carcinoma has been well established; in contrast, the relationship between endometriosis and endometrial cancer has yet to be determined [2]. Although endometriosis is not yet established as a risk factor for endometrial cancer, recent studies have discussed an influence of the epithelial-to-mesenchymal transition and stem cells in endometrial cancer. Adult stem cells occur in endometrial tissue and scientific evidence have shown a possible role in the pathogenesis of endometriosis and endometrial cancer [2, 4-7]. Two etiopathogenetic theories were formulated: estrogen stimulation and chronic inflammation. In the first theory, endometriosis is an estrogen-dependent disease that adapts to estrogen-induced signaling by increased local production [1]. Some studies have suggested that there is pathological overexpression of estrogen receptor A (ERA) in endometriotic stromal cells, because of reduced methylation of the ERA promoter, which also suppresses estrogen > (ER >) expression. In endometrial cancer ERA-to-ER > ration has been shown to be high, with ER > messenger RNA significantly lower in poorly differentiated endometrial cancer [8-11]. Another important role may be played by chronic inflammation, because endometriosis tissue is associated with increased level of cytokines, chemokines, and prostaglandins [7]. Cyclooxygenase 2 (COX-2), an enzyme in biosynthesis of prostaglandin E2, is elevated in both endometriosis and endometrial cancer. Prostaglandin E2, at first, promotes initial carcinogenesis and further tumor progression stimulating cell proliferation and neoangiogenesis, while reducing in situ immune status. Both theories can be regarded as complementary [8]. A study by Fowler *et al.* found that the aromatase is expressed in 65% of endometrial cancer patients, as it has not been expressed in normal endometrium [12]. Collins *et al.* showed an elevated ratio of COX-2 in women with ER-positive endometrial cancer. The relationship between, ER and COX-2 could have a synergetic effect [11]. Furthermore Zaino *et al.* found that in about 30% of patients with endometriosis had a synchronous endometrioid type endometrial and ovarian cancers [13]. Endometrial stromal sarcomas (ESS) in endometriotic lesions is very rarely reported, and it seems that it may result from submesothelial pluripotential Müllerian cells [14, 15]. Extrauterine EST can develop in pelvic cavity, retroperitoneum, fallopian tube, and ovary. The incidence of EST is approximately 0.2% of all malignant uterine tumors [14, 15]. The 2014 WHO classification divides ESTs into endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), and undifferentiated uterine sarcoma (UUS) [16]. ESS are divided in low and high grade tumours according to mitotic activity (< 10 mitoses per 10 high power fields for LGESS; 10 or more mitoses per 10 high power fields for HGESS) [17]. However, at present there are controversies surrounding the separation of ESS based on mitotic count [18]. Regarding UUS these include a group of high-grade, aggressive tumours that occur in older patients. They can present abnormal postmenopausal uterine bleeding with uterine enlargement in 70% of cases, pelvic pain, dysmenorrhea, and extrauterine spread in about 30–50% [15]. UUSs present a destructive infiltrative growth into the uterine wall, associated with necrosis and/or haemorrhage, lymphovascular invasion, and increased mitotic activity with atypical figures [16]. The treatment includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, while lymphadenectomy is controversial [15-17]. The five-year overall survival rate is about 25–55%. Adjuvant therapy with doxorubicin and/or ifosfamide is discussed [19]. ESS arising from endometriosis is considered a rare tumor with uncertain etiology. This unusual neoplasm presents a good prognosis, but 25 years after first diagnosis, metastases and late recurrence can occur [20]. The targeted treatment is total abdominal hysterectomy with bilateral salpingo-oophorectomy, because complete tumor resection may reduce the recurrence rate [7, 19] However in extrauterine ESS, as well as in disseminated disease, there is a controversial discussion for the treatment. Some authors recommended a primary surgical procedure with complete tumor resection and possible organ resection in absence of the residual disease. The best choice of adjuvant therapy remains unknown currently because the response is limited; the radiotherapy does not change overall survival. Similarly, there have been no standard recommendations for hormonal therapy [15, 16]. Thus, new therapeutic strategies for this tumor are

needed. Future investigations should be directed about PDGFR that was expressed in several cases with ESS arising from endometriosis for a future possible targeted therapy with imatinib mesylate. Also in the study by Moinfar *et al.* an elevated rate (70%) of ESS tumors demonstrated positive for EGFR. In 76% of cases of extrauterine ESSs, the ovary is the primary site and these can be site of usual type and pure stromal endometriosis (foci of gland-free endometrial stroma in the ovary) or directly from ovarian stromal cells with neometaplasia into endometrial stromal-type cells [6, 14]. Ovarian ESSs are rare cancer; in literature there are about 50 cases. Histological examination is represented by cells resembling stromal cells of normal proliferative endometrium. These tumors occurred at any age, but most of them in the fifth and sixth decades [14, 15]. Clinical finding include non-specific abdominal symptoms attributable to the presence of a pelvic mass; for this reason often most of ovarian ESSs are diagnosed at an advanced stage. The patients' ages range from 20 to 76 years. According to several authors, the traditional division of ESSs into low and high grade is no longer used. At present, the differentiation between lesions is not made on mitotic count, but on the basis of nuclear pleomorphism and necrosis [15]. The term "undifferentiated endometrial sarcoma" (UES) was introduced. UESs are highly aggressive tumours with a very poor prognosis (less than two years' survival) [21]. UES is characterized by severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and represents a high-grade sarcoma that lacks specific differentiation and that bears no histological resemblance to endometrial stroma. Therefore the term ESS is now considered best restricted to LGESS and HGESS and should be regarded as an undifferentiated sarcoma [4, 15]. Immunohistochemical features comprise reactivity to antibodies specific for vimentin, ER, and CD10, and non-reactivity to antibodies against CD117, smooth muscle actin (SMA), and cytokeratin (CK) [5, 6]. CD10 is the acute lymphoblastic lymphoma antigen (CALLA) and it is considered a marker for normal and neoplastic endometrial stromal cells. This cell surface enzyme reduces cellular response to peptide hormones. Thus, several hormone-sensitive and peptide-sensitive cells, as well as their corresponding tumors, express CD10 antigen as normal endometrial stroma and ESS [6]. Although CD10 has been defined as marker for ESS, in literature other uterine neoplasms like malignant Müllerian mixed tumors, uterine smooth muscle tumors, adenosarcomas, endocervical adenocarcinomas, uterine tumors resembling ovarian sex cord tumors, and gestational trophoblastic disease may present CD10 [6]. CD10 expression of UES of the ovary is not well defined, and these tumors should be diagnosed after excluding an undifferentiated carcinoma or a malignant mixed Müllerian tumor. Recently CD10 immunoreactivity is a very useful marker of ESS, but CD10 expression is not of diagnostic value and is not indicative of endometrioid stromal differentiation [6, 15]. Regarding progesterone receptor, while ESSs present elevated sensitivity to antibodies against this antigen, this marker is less specific for differentiating ESS from other mesenchymal neoplasms. Also, estrogen receptor and CD34 may be more useful in the diagnosis of extrauterine extraovarian EST [14, 15].

Conclusion

Larger studies are needed in order to better assess the relationship between endometriosis and endometrial cancer, to identify a possible molecular link, and to understand their etiopathogenesis. Therefore there have been few studies addressing the relationship between EST, ESSs, and endometriosis. Novel scientific findings are necessary to investigate a possible common pathway and an effective treatment, although complete tumor resection can reduce the recurrence rate.

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Corresponding Author:
L. DI BENEDETTO, M.D.
Department of Medical and Surgical Sciences
and Translational Medicine
Sant'Andrea Hospital, Faculty of Medicine
and Psychology, University of Rome "Sapienza"
Via di Grottarossa, 1035/1039
00189 Rome (Italy)
e-mail: luisadibenedetto@outlook.it