A Rare Case of Multiple Malignancies arising in Endometriosis: Diffuse Extra-Uterine High-grade Endometrial Stromal Sarcoma and Ovarian Carcinoma

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Abstract

Introduction: Malignant transformation of endometriotic foci is a rare event occurring in 0.7-1% of patients with endometriosis. Of neoplasms that develop, endometrial stromal sarcoma (ESS) has been described and represent an extremely rare histological subtype [1]. Since its first description in the 1920s, only a handful of case reports have been published. The gastrointestinal tract is the most common site for endometriosis associated ESS, although cases of ESS involving the mesentery, omentum, ovary, vagina, cervix, rectovaginal septum, parametrium, fallopian tube, pelvis, retroperitoneum, liver, and sciatic nerve have been reported [2-15].

Case Presentation: We present a case of diffuse metastatic high grade ESS as well as clear cell carcinoma of the ovary associated with endometriosis in a 45-year-old woman treated with complete cytoreductive surgery.

Conclusion: The development of multiple malignancies arising from disseminated endometriotic foci in the abdominal cavity represents an extremely rare event. A high index of clinical suspicion is required to reach a diagnosis. Furthermore, no gold standard management option exists and treatment should be individualized.

Keywords: Endometrial stromal sarcoma; Endometriosis; Ovarian clear cell carcinoma

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Introduction

Endometriosis represents extrauterine endometrial deposits of endometrial glands and stroma. When neoplasms arise from these endometriotic foci, carcinomas, sarcomas and mixed mullerian tumors have been reported histologies [16]. The criteria for diagnosis of a malignancy arising in endometriosis are (1) demonstration of a clear endometriotic area in the proximity of the tumor, (2) no other primary site for the tumor, and (3) histologic appearance consistent with an origin from endometriosis [17]. Since its first description by Sampson in the 1920s, only a handful of case reports have been published. The pathogenesis of extrauterine ESS is controversial. Some authors hypothesized that extrauterine ESS arise from a malignant transformation of endometriosis while others raised the possibility that they developed de-novo from mesothelial pluripotent mullerian cells [1,18].

Case report

Madam XY was a 45-year-old, Gravida 5, Para 5, pre-menopausal Malay lady, who presented with a one week history of progressive abdominal distention and bilateral lower limb swelling. She had no history of endometriosis, nor any menstrual related complaints. On examination, Madam XY appeared well, with no constitutional symptoms. Abdominal examination revealed a large abdominal mass arising from the pelvis and extending to the umbilical region. The mass was non tender. Moderate ascites was present and there was bilateral lower limb pitting edema. Biochemical investigations performed revealed an elevated Cancer Antigen (CA)-125 of 329IU/ml (normal < 35IU/ml), as well as severe anemia with a haemoglobin level of 5.7g/dl (normal range 12-16g/dl). PV and PR examination did not reveal any abnormalities. Subsequently, a contrasted computer tomography (CT) scan showed a 25 x 25 x 19 cm heterogenous solid cystic mass extending from the left adnexa to the mid abdomen. The mass was adherent to the sigmoid and descending colon and appeared inseparable from multiple small bowel loops with significant mural involvement. There were no suspicious lesions in the liver (Figure 1 and 2). An oesophagastroduodenoscopy (OGD) showed antral gastritis, as well as, a benign antral ulcer. Colonoscopy revealed no luminal or submucosal masses. However, there was extrinsic compression from an extraluminal mass that prevented complete evaluation of the large colon proximal to the hepatic flexure. The initial differential diagnoses were either that of a left ovarian carcinoma, or a Gastrointestinal stromal tumour (GIST) arising from the small bowel. A staging CT Thorax scan revealed no pulmonary metastasis.

The case was discussed at a multi-disciplinary tumour board, and the decision was made for complete cytoreductive surgery, in the absence of distant metastasis.

Madam XY was optimized for surgery, and her Hb was topped up to 8.9g/dl. She underwent a laparotomy, and intra-operative findings included a large intra-abdominal tumor with haemoperitoneum arising from the mid jejunum. The mass was adherent to the sigmoid, descending colon, uterus and left ovary. In addition, multiple small tumor nodules was found scattered on the surrounding small bowel mesentery, limited to a 29 cm section of the small bowel. Frozen section diagnosis was that of a poorly differentiated tumour, and scattered spindle cells were also observed. She underwent an en bloc resection of the large tumor mass and small bowel mesenteric nodules that necessitated a high anterior resection, left salpingo-oophorectomy, omentectomy and small bowel resection.
Figure 1 Large intra-abdominal mass with mural involvement of multiple small bowel loops

Figure 2 Left adnexal mass which appears inseparable the mass
Histology of the small bowel, omental, descending colon tumor all returned with the diagnosis of high grade endometrial stromal sarcoma. Numerous scattered endometriotic foci was found adherent to the left ovary, fallopian tube, colon and small bowel. Replacement of endometrial like stromal cells by malignant stromal cells was appreciated. While tumor deposits found on the surface of the left ovary were ESS, a discrete, well-circumscribed 1.6cm nodule was found within the ovarian stroma. The latter had features consistent with clear cell carcinoma of the ovary.

Microscopic sections of the tumor showed a range round to oval to spindle-shaped cells arranged in sheets (Figure 3). Within these sheets of tumor cells were multiple foci of benign looking strips and glands of epithelium. A high mitotic count (>20/10 HPF) was noted. On immunohistochemical staining, tumor cells showed diffuse immunoreactivity to CD10 and cyclin D1. They were negative for estrogen and progesterone receptors, cytokeratin, CD-117, S-100 protein, CD 34, smooth muscle actin (SMA), and beta-catenin.

All resection margins were free of tumor cells.

Madam XT’s postoperative recovery was uneventful and she was discharged well on post operative day 5. Given the unusual situation of a dual malignancy, the choice of adjuvant therapy posed a challenge. While the optimal treatment of clear cell carcinoma of the ovary is taxane or platinum-based adjuvant chemotherapy, this was of questionable benefit in the management of ESS. Radiotherapy and hormonal therapy was offered for the management of high grade ESS but only in the context of a clinical trial. The patient however declined all adjuvant therapy.
Discussion

Endometriosis is a relatively common gynecological condition and is known to be associated with infertility as well as gynecological complaints such as dysmenorrhea, menorrhagia and dyspareunia. Even though a benign clinical course is often predicted, it is estimated that up to 1% of women with endometriosis will develop endometriosis-associated malignancy. ESS represents one of the rare histopathological subtypes of malignancy arising from endometriosis.

In previously reported case reports, the age at diagnosis ranged from 31 to 75 years [4,18-21]. Presenting symptoms were varied but the most common complaint was that of vague abdominal pain, followed by per rectal bleeding and difficulty in defecation. The sigmoid colon and rectum are areas of the gastrointestinal tract with the highest incidence of endometriosis, and hence the most commonly reported sites of ESS. In Mdm XY, ESS arose mainly from the endometriotic foci deposited on small bowel, and as such she did not present with colorectal related symptoms. She also did not experience any per- vaginal bleeding. This posed a diagnostic challenge.

ESS is a malignancy of the endometrial stromal cells of a normal proliferative endometrium. Microscopic features include: invasive ‘tongues’, short regular fasicles or sheets of monomorphous plump oval to spindle cells admixed with scattered prominent arterioles [3,14,22]. A possible differential diagnosis in the presence of spindle cells is gastrointestinal stromal tumor (GIST). Immunohistochemical staining is useful in differentiating these two entities. GISTs are strongly and diffusely for CD117 (c-KIT) while ESS often stains positive for vimentin, CD10, Estrogen(ER) and Progesterone receptors (PR). In our case, tumour cells stained positive for CD10 and cyclin D1; and were negative for ER, PR and c-KIT. The surrounding entrapped epithelium was positive for Cytokeratin 7(CK7), Epithelial Membrane Antigen (EMA), Beta-Catenin and negative for CK20. This was suggestive of cells of Mullerian origin.

In Mdm XY, a dual pathology was present: disseminated high grade ESS and clear cell carcinoma of the left ovary. Endometriosis is present in up to 30% of women with ovarian cancer [23]; when they co-exist, there are 2 possibilities: (1) malignant transformation of benign endometriosis into ovarian cancer, and (2) de-novo development of carcinoma with incidental findings of endometriosis [24,25]. In our patient, histological findings suggest that the clear cell ovarian carcinoma arose from endometriosis, as did the ESS. A case of 2 distinct malignancies developing from endometriotic foci has not been reported in literature.

The cornerstone for treatment of ESS is complete cytoreductive surgery (CRS). In patients with low grade ESS, radical surgery has yielded good outcomes in most of the reported cases. Some authors propose that a combination of surgery and adjuvant radiotherapy resulted in the lowest recurrence rates while others report superior overall survival rates with the use of adjuvant hormonal therapy [19,26,27]. Radiotherapy may provide local control in the setting of uterine ESS, however, the same may not be applied to extra-uterine foci of ESS developing from endometriosis. As such, no absolute treatment protocol has been established for the management of extra-uterine ESS. Furthermore, reported prognosis of high grade ESS is dismal even with the use of adjuvant therapies [28,29]. CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) has been adopted as a modality of treatment for peritoneal dissemination from colon, ovarian and primary peritoneal malignancies [30-32]. Its use has also been reported in high grade uterine sarcomas with peritoneal dissemination [33]. In Mdm XY, ESS arising from endometriotic foci was found scattered throughout the abdominal cavity, and represent a form of ‘peritoneal sarcomatosis’. In the absence of improved outcomes with traditional adjuvant therapy, CRS/HIPEC could be considered as an option in selected patients.
Conclusion

Our case represents a highly rare event where there was development of multiple high-grade ESS from disseminated endometriotic foci in the abdominal cavity. A high index of clinical suspicion is required, especially in women with known histories of endometriosis for the early detection of malignant transformation of this supposedly benign gynecological condition. Due to the rarity of such tumors, no gold standard management option exists. This draws importance to the need for various specialist centers worldwide to share their experience so that further progress may be made to optimize therapeutic options for patients with this rare disease.

References

17. Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. *Am J Pathol*. 1927, 3:93-110.43
32. Bakrin N, Cotte E, Golffier F, Gilly FN, Freyer G, Helm W, Glehen O, Bereder JM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent