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Case Report

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Case Report on the Malignant Transformation of Metastatic Endometriotic Tissue in the Uterus and Para-aortic Lymph Nodes

(Running title: Malignant transformation of endometriosis)

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Abstract

Background: *Endometriosis is a common benign condition affecting 10%-15% of reproductive aged women usually involving intra pelvic organs and sometimes beyond the pelvic organs. Malignant transformation and metastasis of endometriosis is a rare event. We report a case of a patient with a history of severe adenomyosis that led to metastasis of the endometriotic tissue to the para-aortic lymph nodes as well as endometriotic cancer.*

Case Report: *A 48-year-old woman with a long-standing history of pelvic endometriosis, endometriotic cysts and adenomyosis presented to us with severe abdominal cramps and backache. She had regular menstruation. She had magnetic Resonance Imaging (MRI) scan of Pelvis which showed severe pelvic endometriosis, posterior wall adenomyosis and bilateral endometriotic cysts. Her CA125 and CA19-9 were elevated, hence a Computed Tomography (CT) of her abdomen was performed which showed some enlarged aortocaval lymph nodes. The patient underwent total hysterectomy and bilateral salpingoophorectomy (THBSO), para-aortic lymphadenectomy and frozen section of the uterus and lymph nodes. Frozen section pathology examination of the specimen during surgery revealed complex atypical hyperplasia, adenomyosis and benign endometriotic cysts as well as endometriosis of the para-aortic lymph nodes.*

Final histology examination of the specimen revealed two different uterine tumours in a background of complex atypical hyperplasia and microcystic, elongated and fragmented (MELF) respectively and micro-metastases and isolated tumour cells in the para-aortic lymph nodes. A diagnosis of Stage 3C2 endometroid adenocarcinoma was made and she underwent systemic chemotherapy followed by extended field radiotherapy to the pelvic and para-aortic region.

Conclusion: *This case highlights the risks of long term untreated adenomyosis and endometriosis with the rare occurrence of metastatic endometriosis in the para-aortic lymph nodes which ultimately led to the development of cancer in both the uterus and the para-aortic lymph nodes.*

MeSH Keywords: *Adenomyosis, Carcinoma, Endometrioid, Endometriosis, Lymphatic Metastasis.*

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Background

Endometriosis is a common condition affecting 10% to15% of reproductive aged women. [1] It usually involves the ovaries, fallopian tubes, uterus and the tissue lining the pelvis and sometimes, it may spread beyond the pelvic organs. Malignant transformation has also been documented in recent medical literature. In this case report, we present a woman who had severe adenomyosis and later developed metastasis of the endometriotic tissue to the para-aortic lymph nodes as well as development of endometriotic cancer.

Case Report

The patient was a 48 years old married woman who had a long-standing history of pelvic endometriosis, endometriotic cysts and uterine fibroids. She had a history of laparoscopic ovarian cystectomy for benign endometriotic cysts in 2004 and had been undergoing follow-up assessments at another institute for 16 years for uterine fibroids and endometriotic cysts. She has been on regular follow-up as she had declined any surgical intervention.

She complained of severe abdominal cramps and backache for 1 week in June 2020 and she presented to Mount Alvernia Hospital for further management. She had regular menses with normal flow of 1 week. However, she had been experiencing dysmenorrhoea for many years requiring analgesia. She had no bowel or urinary symptoms. She had 2 children by caesarean section and 4 miscarriages. Her pap smear was negative in June 2020. Clinically, she was found to have an enlarged 20 weeks size pelvic abdominal mass. Her cervix looked normal and her per rectal examination revealed thickened uterosacral ligaments and nodular Pouch of Douglas.

Her previous ultrasound scan of pelvis which was performed in another hospital in April and Dec 2019 showed large uterine fibroids measuring 11.6cm and 6.3cm as well as a right 5cm endometriotic cyst and left 1.5cm endometriotic cyst. However, the MRI scan of the pelvis which was performed in June 2020 showed that the uterus was enlarged (19.0 x 9.8 x 16.0cm) with adenomyosis and small adenomyomas as well as bilateral ovarian endometriomas. There was pelvic endometriosis as well and an endometriotic deposit with tethering of the rectum by the endometriosis. There were no enlarged pelvic lymph nodes. Her CA 125 was elevated at 870 U/ml and CA 19-9 was also elevated 102 U/mL. In view of the elevated CA 19-9, a CT scan of her abdomen was performed. Surprisingly, it revealed a few slightly enlarged aortocaval lymph nodes measuring up to 1.9cm. Other than a few benign small liver cysts, the spleen, pancreas and kidneys looked normal. There were no other abnormalities detected.

In view of the severe adenomyosis and endometriomas causing her pain as well as the potential compressive risks by the large uterus and the findings of the enlarged aortocaval lymph nodes, a total Hysterectomy and bilateral salpingo-oophorectomy (THBSO) and frozen section of the uterus and para-aortic lymphadenectomy was recommended to the patient. She underwent the procedure on 8 July 2020 via a midline laparotomy. The surgical finding revealed an enlarged 20- week size adenomyotic uterus with some small fibroids. (See Figure 1).

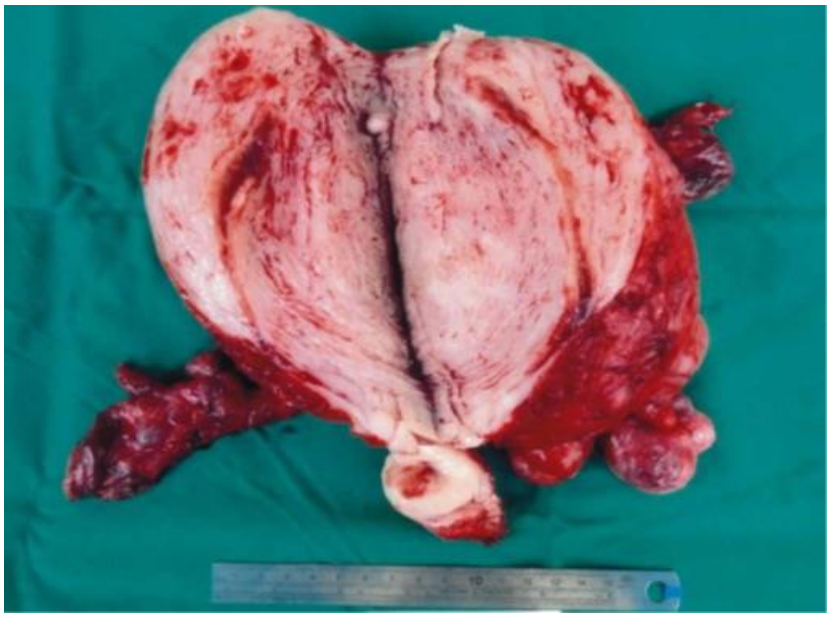

Figure 1: Hysterectomy specimen.

Severe pelvic endometriosis was present and both ovarian endometriomas were plastered to the back of the uterus along with the rectum. There were no enlarged pelvic lymph nodes present. However, there were a few enlarged pigmented para-aortic lymph nodes measuring up to 2cm. (See Figure 2).

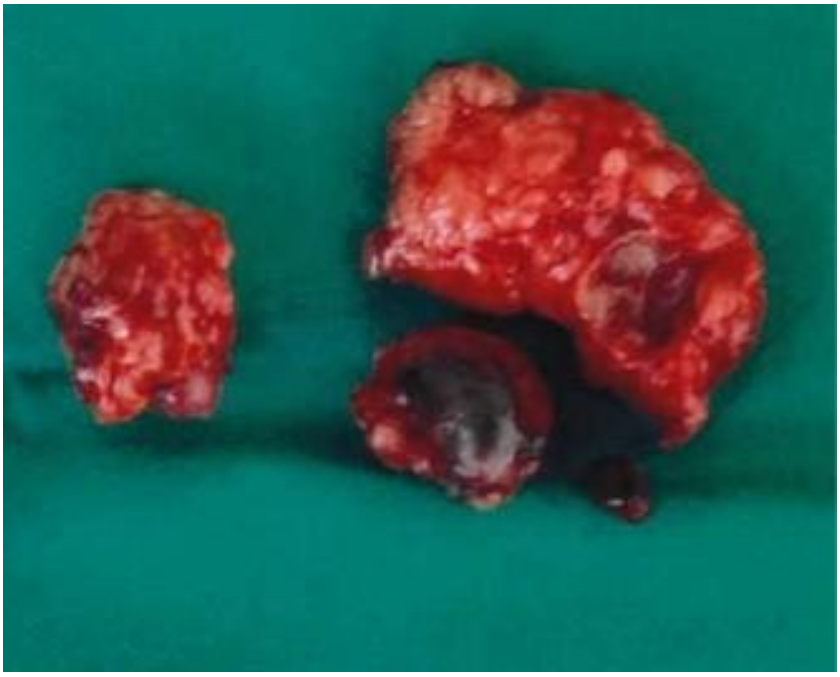

Figure 2: Pigmented para-aortic lymph nodes.

The uterine cavity looked smooth and the cervix looked normal. The subdiaphragmatic surfaces were smooth and intraperitoneal survey was normal.

Intraoperative frozen section of the uterus and the lymph nodes revealed complex atypical hyperplasia and bilateral endometriotic cysts as well as endometriosis of the lymph nodes.

However, the final histology after thorough sampling revealed extensive adenomyosis of the uterus and involvement by two different uterine tumours. Tumour 1 was an endometrioid carcinoma, grade 1 arising in a background of complex atypical hyperplasia (CAH) and confined to the endometrium. (See Figure 3).

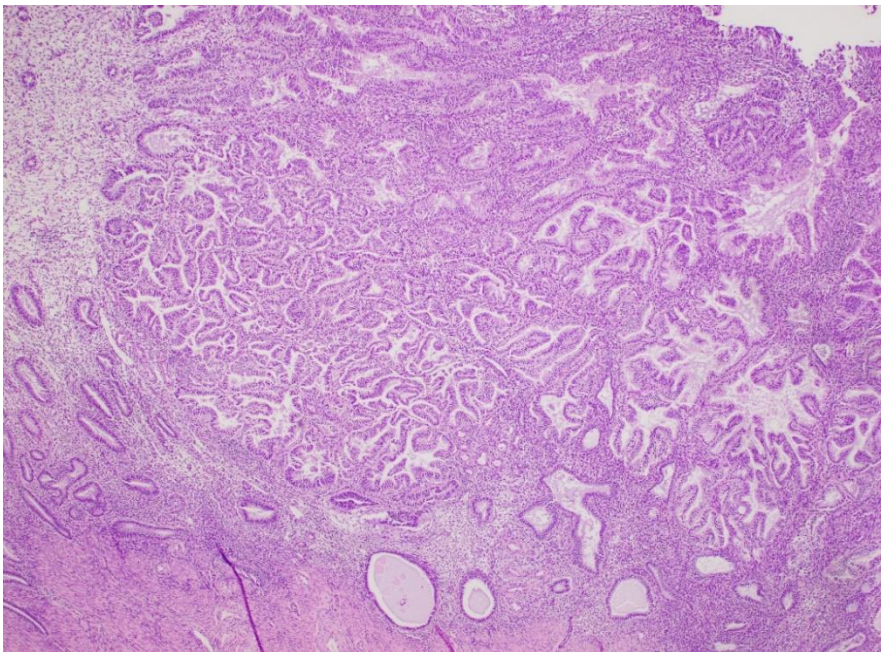

Figure 3: Endometroid carcinoma, grade 1, composed of fused and focally-confluent, complex glands that are confined to the endometrium. (Actual magnification, x40).

Tumour 2 comprised of occult atypical glands consistent with microcystic, elongated and fragmented (MELF) pattern of an endometrioid carcinoma, invading the outer half of the myometrium, interspersed between foci of adenomyosis, and not breaching the uterine serosa. (See Figure 4 and 5) of the 10 excised para-aortic lymph nodes examined, 2 had micro-metastases and 1 had isolated tumour cells. (See Figure 6).

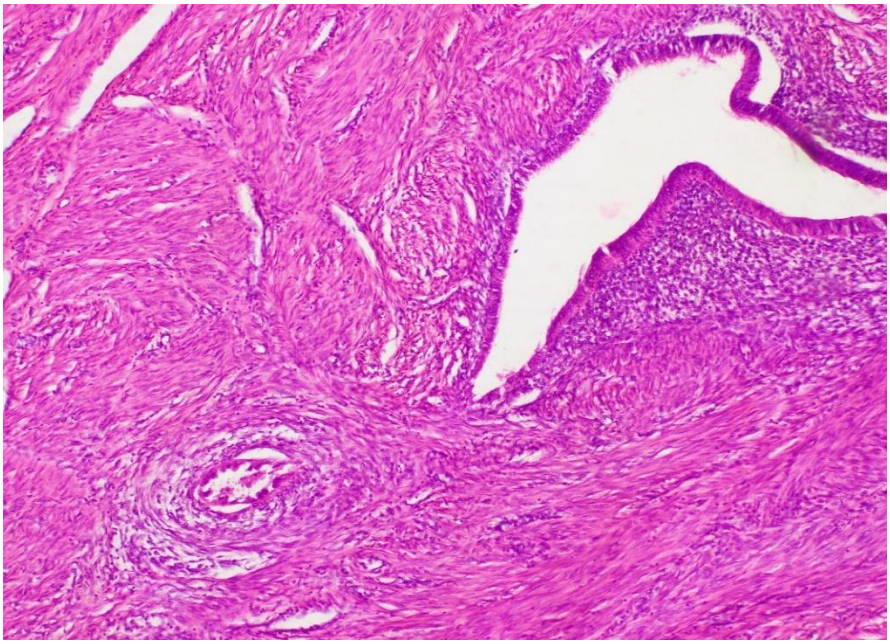

Figure 4: Endometriosis at upper right field comprising a large endometrial gland surrounded by a cuff of cellular endometrial stroma. A smaller malignant MELF-type gland composed of eosinophilic cuboidal cells which are fragmented and frayed, surrounded by a loose fibrotic stroma. (Actual magnification, x100).

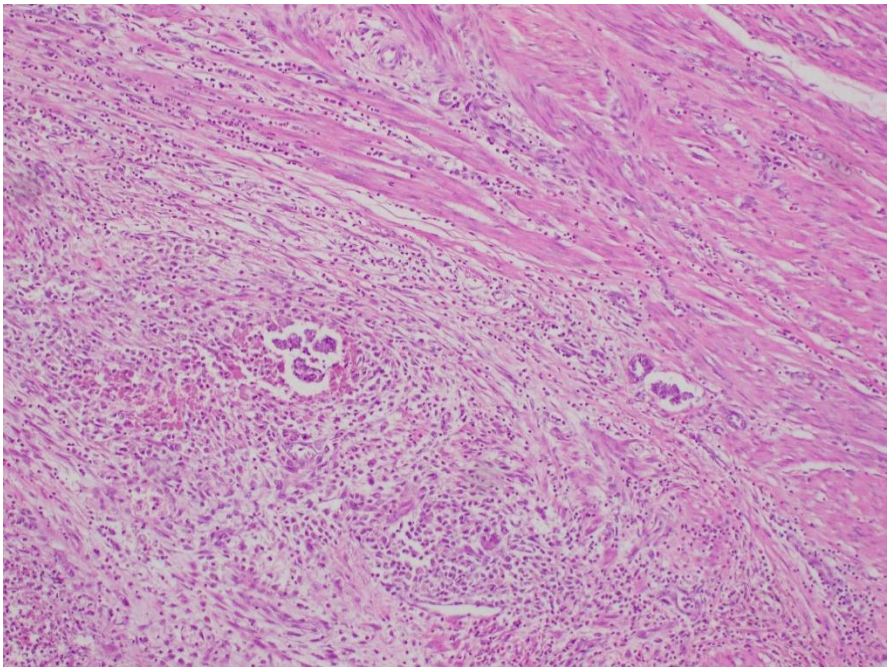

Figure 5: Two microscopic foci of fragmented MELF-type malignant glands surrounded by loose fibroblastic stroma. (Actual magnification, x100).

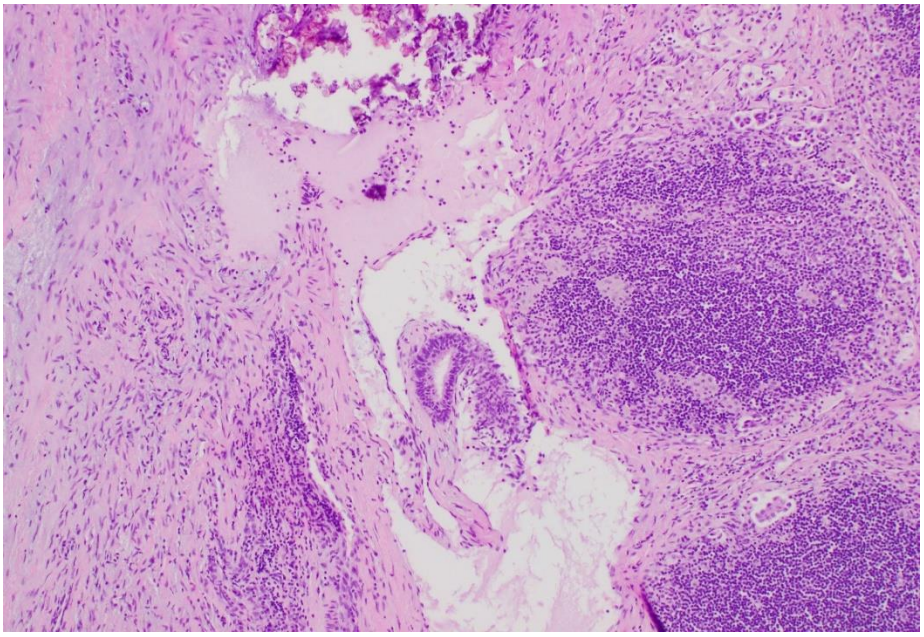

Figure 6: A lymph node showing an endometriotic gland at the centre field. Microscopic micropapillary clusters of metastatic tumour cells surrounded by stromal retraction spaces in the upper and lower right fields. Focal dystrophic calcifications at top centre field. (Actual magnification, x100).

She was assigned to have a Stage 3C2 endometroid adenocarcinoma and she underwent systemic chemotherapy followed by extended field radiotherapy to the pelvic and para-aortic region. She completed her treatment in March 2021 and is on close clinical follow up currently.

Discussion

Endometriosis is found in up to 30% of women complaining of severe menstrual pain. However, as endometriosis may present with unrelated symptoms to periods or minimal discomfort, it is often under diagnosed. According to case reports, the natural risk of endometriosis can include its metastasis to distant organs and lymph nodes [2]. Numerous case reports also show the large range of possibilities in metastatic transformation of endometriosis to different types of cancer [3], stressing the importance of being thorough in one's evaluation of endometriosis and early treatment.

Endometriosis has long been established to be premalignant. This likelihood of endometriosis to undergo malignant transformation is described first by Dr. Sampson in 1925 as a rare occurrence, affecting approximately 1% of ovarian endometriomas. [4] Amongst the many cancers that endometriosis risks malignant transformation to, a meta-analysis revealed that patients with endometriosis had an increased risk of ovarian cancer [RR 1.964; 95% CI (1.685, 2.290)], a non-substantially higher risk of endometrial cancer [RR 1.176, 95% CI (0.878, 1.575)] and no association with an increased risk for cervical cancer (CC) [RR 0.670, 95% CI (0.537, 0.838)]. [5] Around 80 % of endometriosis associated malignancies are in the ovary while 20 % are localized to extragonadal sites like intestine, rectovaginal septum, abdominal wall, pleura and others. [3] It is hence unsurprising that increased risk of malignancy of ovarian cancer is most reported in association with endometriosis in epidemiological studies. Additionally, several studies revealed an association between endometriosis and other cancers such as endometrial cancer, breast cancer, colorectal cancer, non-Hodgkin lymphoma and others. [6]

Malignant transformation to endometrioid carcinoma such as in this case however has still been notable in other studies. [7] In this case, although no definitive mass lesion is located despite thorough sampling of the uterus, it is postulated that the primary site may be an occult focus of adenomyosis with malignant change. An observation that supports this hypothesis reveals that a hyperestrogenic state could be common in the pathogenesis of adenomyosis and endometrial cancer, increasing the risk malignant transformation. [8] Other theories have hypothesised genetic alterations as the culprit for the pathogenesis of malignant transformation in endometriosis. Although the exact mechanisms remain unknown, researchers have identified recurrent oncogenic mutations in KRAS and ARID1A in cases of deep-infiltrating endometriosis [9], as well as other mutations in genes known to suppress tumours, such as PTEN, p53, bcl, and TP53, in both ovarian tumours and endometriotic lesions [10].

Endometriosis has been recognised to have similar behaviour to cancer although this behaviour is rare in occurrence. There have been many theories attempting to explore the underlying mechanisms of the migration of endometriosis cells, but in all studies, malignant behaviour such as metastasis to distant organs and lymph nodes is established. [11] Endometriosis has a pathogenesis that still remains unknown although many theories have been proposed. It has been theorised that the presence of endometrial and/or endometriotic tissue in lymphatic

vessels, lymph nodes, and rare sites, as well as high recurrence rates following treatment can be explained by the lymphatic dissemination theory. [12] The presence of endometriosis in the para-aortic lymph nodes in this case supports this theory that endometriosis travels lymphatically and not just by locoregional spread. [13] Another theory is The Stem/Progenitor Cell Theory which hypothesises that endometrial stem cells in the basalis layer of the endometrium can implant endometriotic cells in ectopic sites through reflux. [14] Lymphagionic factors enhance this process where lymphangionic growth factors stimulate the differentiation of endometrial stem cells. [15] Interestingly enough, this theory is opposed by the presentation of this case where the endometriotic cells were found in the myometrium instead of the basalis layer. Metastasis and malignant transformation of adenomyosis could be an area to be researched further as its pathogenesis is still unclear [8]. The presence of MELF pattern of endometrioid carcinoma is also noted to increase likelihood of lymph node metastasis and lymphovascular space invasion in patients with endometrial carcinoma. [16] Hence, it could be favoured that the metastatic tumour in the para-aortic lymph nodes is derived from the MELF pattern carcinoma rather than of a serous origin.

Although rare for endometriosis to metastasise and for malignant transformation to occur, it is highly possible for lymph node infiltration to occur in particular with MELF pattern tumours. Vigilance is key in preventing rare complications of endometriosis. Tumour markers such as CA-125 and CA19-9 appear to be useful adjuncts in the diagnosis and treatment planning. The approach of using multiple diagnostic modalities only serves to maximise diagnostic accuracy and should be implemented with attentiveness.

Conclusion

This case highlights the risks of long term untreated adenomyosis and endometriosis with the rare occurrence of metastatic endometriosis in the para-aortic lymph nodes which ultimately led to the development of cancer in both the uterus and the para-aortic lymph nodes.

Acknowledgements-NA

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