EDORIUM Journals

J Case Rep Images Pathol 2021;7(2):14–17.
www.ijcripathology.com

CASE REPORT PEER REVIEWED | OPEN ACCESS

Adenocarcinoma arising from isolated endometriosis of umbilicus

Chelsea Milito, Xi Wang

ABSTRACT

Introduction: The reported incidence of abdominal wall endometriosis (AWE) ranges from 0.03% to 1.08%. A slightly more than 50 cases of abdominal wall endometriosis-associated adenocarcinoma have been reported; commonly clear cell carcinoma, followed by endometrioid adenocarcinoma and serous papillary carcinoma. All of these patients had a history of gynecological or obstetric surgery some time prior to the diagnosis of carcinoma.

Case Report: Here we report a case of a 39-year-old G0P0 female with no history of abdominal/pelvic surgery, who presented with isolated umbilicus endometriosis and an incidental finding of 2 mm adenocarcinoma associated with the endometriosis. Thorough systemic exam was non-eventful, other than a germline variant of the ATM gene of unknown significance.

Conclusion: Our case is unique as it is an isolated sporadic event of malignant transformation of endometriosis, without history of gynecological or obstetric surgery.

Keywords: Abdominal wall endometriosis, Clear cell carcinoma, Endometrioid adenocarcinoma, Malignant transformation of endometriosis

How to cite this article

Milito C, Wang X. Adenocarcinoma arising from isolated endometriosis of umbilicus. J Case Rep Images Pathol 2021;7(2):100056Z11CM2021.

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Received: 16 June 2021
Accepted: 01 October 2021
Published: 01 December 2021

Article ID: 100056Z11CM2021

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doi: 10.5348/100056Z11CM2021CR

INTRODUCTION

Endometriosis is a common chronic disorder, affecting approximately 10–15% of all women of child-bearing age. It is characterized by uterine endometrial glands and stroma located outside of the uterus. The pelvis is the most common location of endometriosis, especially the ovaries, but it can be found in extra-pelvic locations such as the bowel, lungs, kidneys, or anterior abdominal wall. The reported incidence of abdominal wall endometriosis (AWE) ranges from 0.03% to 1.08%, and is most commonly associated with a history of gynecological/obstetric surgery [1, 2]. Malignant transformation of endometriosis is rare and affects less than 1% of the patients with this condition, with ovary as the most common site (80% of cases) [3]. Slightly more than 50 cases of abdominal wall endometriosis-associated adenocarcinoma (AWEAA) have been reported; most commonly clear cell carcinoma, followed by endometrioid adenocarcinoma and serous papillary carcinoma [4–7]. All of these patients had a history of gynecological or obstetric surgery some time prior to the diagnosis of AWEAA. Here we report a case of adenocarcinoma arising from isolated AWE with no history of abdominal/pelvic surgery and a germline variant of the ATM gene of unknown significance.

CASE REPORT

A 39-year-old female patient (G0P0) presented with an abdominal wall mass that she had first noticed more than a year ago. Her medical history includes uterine fibroids, depression, G6PD deficiency, and previous umbilical piercing. She did not recall any other trauma to this area and had no abdominal/pelvic surgical history. The mass did not change in size with her menstrual cycle, but did cause some mild waxing and waning discomfort. She had no personal or family history of cancer. On physical exam,

the mass was 2 centimeters (cm) in greatest dimension, firm, immobile, and located just superior to the umbilicus. A separate keloid within the umbilicus corresponding to the patient's previous piercing was also identified as well as a small umbilical hernia. The patient underwent an uncomplicated surgical procedure to remove the mass and repair the umbilical hernia. It was found during the surgery that the mass was arising from the umbilical stalk and adherent to the fascia.

The specimen consisted of a 2.7 × 1.4 cm skin ellipse with a depth of 2.4 cm and a separate soft tissue fragment (2.2 × 1 × 0.7 cm). Sectioning of the skin ellipse revealed an ill-defined, firm, tan-white ovoid lesion (2.2 × 1.7 × 1.6 cm) with fibrous and cystic cut surfaces. Sectioning of the separate soft tissue fragment showed a tan-white fibrotic cut surface. Microscopically, the majority of the ill-defined lesion showed the changes of endometriosis (Figure 1A and B). However, on one section, there was a 2 millimeter (mm) region of adenocarcinoma mixed with the endometriosis. It was composed of crowded small glands with round enlarged nuclei, high nuclear to cytoplasmic ratio, prominent nucleoli, and active mitotic rate (Figure 2A and B). Immunohistochemical (IHC) stains were performed. The tumor cells were positive for CK7, Pax8, and vimentin, while negative for CK20, CDX2, GATA3, and TTF-1, similar with the adjacent endometriosis glands. Interestingly, the tumor cells were also negative for HNF1b, ER, and PR, different from the adjacent endometriosis glands (Figures 1C, D and 2C and D). Nevertheless, in view of the morphology, association with the endometriosis, and the overall IHC pattern, an endometrioid adenocarcinoma was favored. The separate soft tissue fragment showed dense fibrosis, but was otherwise unremarkable.

The patient underwent an additional surgery involving total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and re-excision of the abdominal wall. Microscopic examination showed residual endometriosis

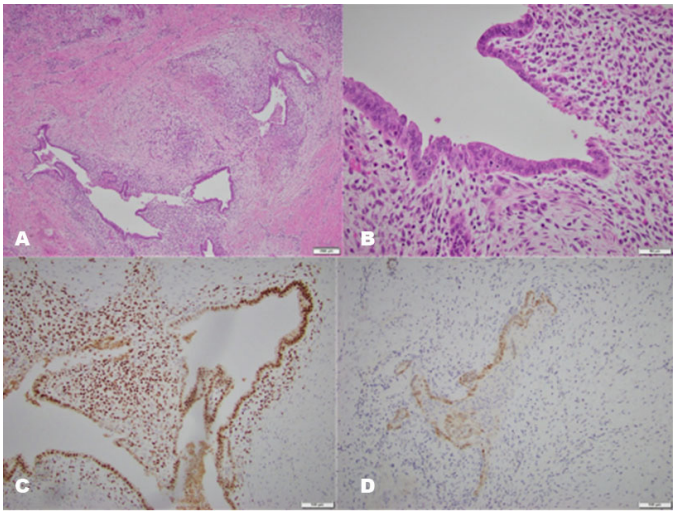

Figure 1: Endometriosis. (A) H&E, low-power view (4×); (B) H&E, high-power view (20×); (C) IHC staining for ER (10×); (D) IHC staining for HNF1b (10×).

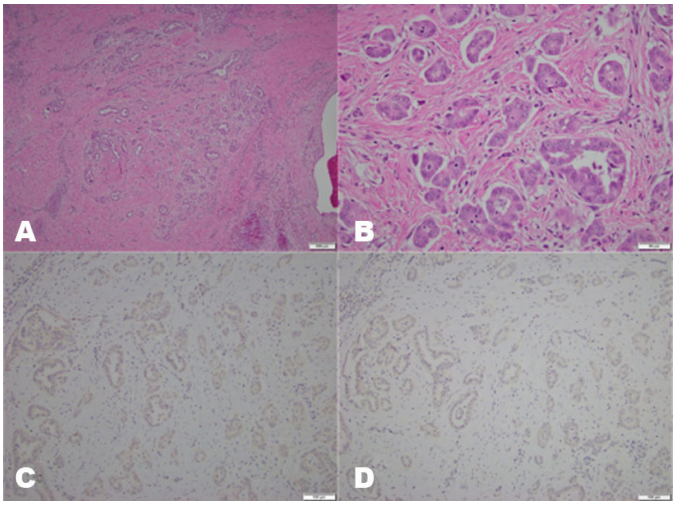

Figure 2: Adenocarcinoma. (A) H&E, low-power view (4×); (B) H&E, high-power view (20×); (C) IHC staining for ER (10×); (D) IHC staining for HNF1b (10×).

in the umbilicus and a large leiomyoma (up to 11.5 cm) of the uterus. No additional focus of adenocarcinoma was identified. No pelvic or ovarian endometriosis was identified. The uterine endometrium showed exogenous hormone effect (intrauterine device in place). Genetic testing revealed heterozygosity for a variant of the ATM gene (c.5675-10T>G) with unknown significance, which is a gene associated with an autosomal dominant predisposition to endometrial, breast, pancreatic, and colorectal cancers.

DISCUSSION

Abdominal wall endometriosis (AWE) is a rare condition with the incidence rate ranging from 0.01% to 1.08% [1, 2]. It is often associated with a history of gynecologic or obstetric surgery in the area, such as cesarean section (C-section). The pathophysiology for this occurrence is believed to be the direct implantation of endometrial tissue during the surgery. Less commonly, sporadic AWE in patients without previous surgery has been identified. It is reported that these patients usually present with concurrent pelvic endometriosis [8]. A lymphatic or hematogenous dissemination is hypothesized as the pathogenesis in this situation. However, the endometriosis in our case was an isolated sporadic process, with no concurrent pelvic endometriosis or previous gynecologic/obstetric surgery. Other theories, such as embryonic cell rest, stem cell origin, and metaplastic transformation could be considered as the potential pathogenesis for our case.

Malignant transformation of endometriosis (MTE) is a rare event. In 1925, Sampson et al. proposed three criteria for this diagnosis: (i) the endometriosis is closely associated with the neoplasm; (ii) the histology is compatible with

endometrial origin; and (iii) no other primary tumors are found [9]. A fourth criterion was added later by Scott [10]: Histological proof of transition from benign changes in endometriosis to malignant changes in cancer. The 2 mm adenocarcinoma in our case was intimately mixed with endometriosis; the morphology and IHC pattern were that of müllerian origin; and a thorough imaging, surgical sampling, and microscopic examination were undertaken and no additional malignancy was identified. We conclude that this is a primary adenocarcinoma arising from endometriosis. However, there was no definitive "atypia" identified in the epithelial cells of the adjacent endometriosis which showed an IHC staining pattern of normal/benign endometrium (ER/PR positive). To the best of our knowledge, virtually all of the reported adenocarcinomas arising from AWE are associated with a prior surgical history, mostly C-section. Our case is the first one that presented as an isolated sporadic event.

The risk factors for the malignant transformation of endometriosis have been extensively studied, including molecular events such as loss of heterozygosity (LOH) and genetic instability, excessive estrogen effect, and alterations in micro-environment [11]. Interestingly, women with endometriosis-associated ovarian carcinomas (EAOC) are on average five to ten years younger than the patients with non-endometriosis associated ovarian cancers [3], further indicating that endometriosis could have served as a local promoting factor for the carcinogenesis. The average age for the patients with AWEAA is 45.88 years [4], similar with the EAOC patients. Our patient is 39 years old at presentation, younger than the average age. Her genetic testing showed a variant of ATM gene of unknown significance, a gene associated with an autosomal dominant predisposition to endometrial, breast, pancreatic, and colorectal cancers [12, 13]. It is not clear if the germline susceptibility played any role in the malignant transformation. Further study in this field will be interesting.

The differential diagnosis in this case would include clear cell carcinoma, which is the most common type of carcinoma associated with abdominal wall endometriosis, especially when the tumor cells in our case were negative for ER and PR. However, the H&E morphology and negative IHC staining for HNF1b did not support clear cell carcinoma. Although uncommon, ER/PR negativity has been reported in endometrioid adenocarcinomas in the uterus, even in the low grade endometrioid adenocarcinomas and is considered to be a poor prognostic factor [14, 15]. It is challenging to say, at this moment, if ER/PR negativity in the endometrioid adenocarcinoma associated with AWE implies a more aggressive behavior, given the scarcity of cases and lacking the information on their ER/PR status. However, in general, AWEAA is considered as an aggressive disease with poor five years survival [7, 16], even though most of these cases are clear cell carcinoma.

CONCLUSION

We reported a unique case which presented as an isolated sporadic event of malignant transformation of endometriosis in the abdominal wall, without concurrent pelvic endometriosis or previous gynecologic/obstetric surgery.

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Author Contributions

Chelsea Milito – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Xi Wang – Conception of the work, Design of the work, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.