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Endometrioid Carcinoma Arising from an Endometriosis-Associated Abdominal Wall Scar

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF Eduardo Paulino*
ABDEF Andreia Cristina de Melo*
ABDEF Vinicius Freire da Silva*

Departmemt of Gynecology Oncology, Brazilian National Cancer Institute, Rio de Janeiro, Brazil

* All authors contributed equally
Corresponding Author: Andreia Cristina de Melo, e-mail: melo.andreia@uol.com.br
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Patient: Female, 45-year-old
Final Diagnosis: Endometrial cancer
Symptoms: Abdominal discomfort • abdominal distension
Medication: —
Clinical Procedure: Hormone therapy • surgery removal
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Carcinoma arising from an endometriosis-associated abdominal wall scar is a rare entity, with only a few case reports published in the literature. The management is very controversial due to on its own rarity, and there are no specific guidelines. Treatment with a multidisciplinary team is important to achieve the best outcome.

Case Report: We report the case of a 45-year-old woman diagnosed with a growing painless lesion in the right lower quadrant. We decided to perform Tru-Cut biopsy of the abdominal wall lesion, but unfortunately the pathological report was inconclusive at that time. Due to the presence of a highly suspicious lesion, the gynecologic oncologist together with the plastic surgeon and connective tissue surgeon decided to perform a wide resection of the abdominal wall along with hysterectomy and salpingo-oophorectomy. The final pathology report demonstrated endometriosis associated with an endometrioid adenocarcinoma grade II in the abdominal wall tumor. She was restaged with new imaging exams before the definition of the best adjuvant treatment, which showed suspicious bilateral inguinal and right axillary (1.9 cm) lymph nodes, with no other sites of metastatic disease. She was treated with megestrol acetate 160 mg/daily for 8 months, with a partial response.

Conclusions: Carcinoma arising from an endometriosis-associated abdominal wall scar is a rare entity, and there are no no specific treatment guidelines. Such patients must be assessed by a multidisciplinary team for decision making. Options for adjuvant and palliative treatment for endometrial cancer are generally used for the treatment of this entity. The main purpose of this article is to report this rare presentation and perform a review of the literature about diagnosis, clinical presentation, treatment, and prognosis.

MeSH Keywords: Antineoplastic Protocols • Genital Diseases, Female • Genital Neoplasms, Female • Gynecologic Surgical Procedures • Gynecological Examination • Gynecology

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Background

Abdominal wall endometriosis happens mostly after obstetrical and gynecological procedures, and it can be explained by iatrogenic transplantation of endometrial tissue to the wound edge during any surgical procedure. Malignant transformation is very rare (0.3–1%) [1]. The management of the abdominal wall endometriosis malignant transformation is not well established because of its extremely low incidence rate. In this article we discuss this rare disease, from the epidemiological aspects to treatment approach.

Case Report

We report the case of a 45-year-old woman, with 1 child and no previous comorbidities (including past history of endometriosis), who was admitted to our institution in October 2017. She presented with a 1-year history of a growing painless lesion in the right lower quadrant, with a cystic appearance, measuring 10×6 cm, close to an abdominal scar (due to a right hemicolectomy of a benign condition 23 years ago), unrelated to menstruation. A pelvic mass in the contralateral (left) lower quadrant was also noted on her physical exam. No other abnormal findings were observed. A gynecologic evaluation with bimanual exam and colposcopy confirmed this pelvic mass with normal vagina and cervix. An abdominal/pelvic CT scan and thorax X-ray were performed (November/2017) and showed an 18.8-cm enlarged uterus due to presence of many fibroids (some with calcifications) and another 9.8-cm infiltrative mass in the abdominal wall of the umbilical region with no cleavage from the rectus abdominis muscle, as well as prominent (but not suspicious) bilateral inguinal lymph nodes (Figure 1). No metastatic evidence of disease was shown in the thorax X-ray. It was decided to perform a Tru-Cut biopsy of the abdominal wall lesion (December/2017), but the pathological report was inconclusive at that time.

Using a multidisciplinary approach, the gynecologic oncologist, together with the plastic surgeon and connective tissue surgeon, decided to perform a wide resection of the abdominal wall along with hysterectomy and salpingo-oophorectomy. During the surgery, only the abdominal wall lesion and an enlarged uterus were observed, without any other suspicious lesions. The surgery was performed in February 2019 and all macroscopic disease was resected with free margins.

After an extensive review by pathologists, the final report demonstrated endometriosis associated with an endometrioid adenocarcinoma grade II in the abdominal wall tumor, with glandular, papillary, and solid patterns, infiltrating the skin and subcutaneous and muscle tissue of the abdominal wall (Figures 2, 3). Immunohistochemical analysis (IHC) showed progesterone receptor (Figure 2) and CD10-positivity in the endometrium. The tumor IHC was positive for cytokeratin 7 (Figure 2) and PAX8, progesterone receptor focally positive, and negative for napsin A, p53, and WT1. The uterine specimen (Figures 2, 3) contained many fibroids (intramural, subserosal, and submucosal, up to 10 cm in size, with infarction and areas of calcification) and complex atypical hyperplasia associated with a superficial endometrioid adenocarcinoma grade 1 (without myometrial invasion).

This patient was again referred to the multidisciplinary team and, because of her delayed surgery (14 months between the first images and the surgery), it was suggested to re-stage the patient with new imaging exams before the deciding on the best adjuvant treatment. Her new images (pelvic, abdominal, and thorax CT scans) now showed suspicious bilateral inguinal and right axillary (1.9-cm) lymph nodes. A fine-needle aspiration of the axillary lymph node was positive for malignant cells suggestive of endometrial origin. Since the patient had oligometastatic disease with no symptoms, we decided to treat this patient with megestrol acetate 160 mg/daily. She

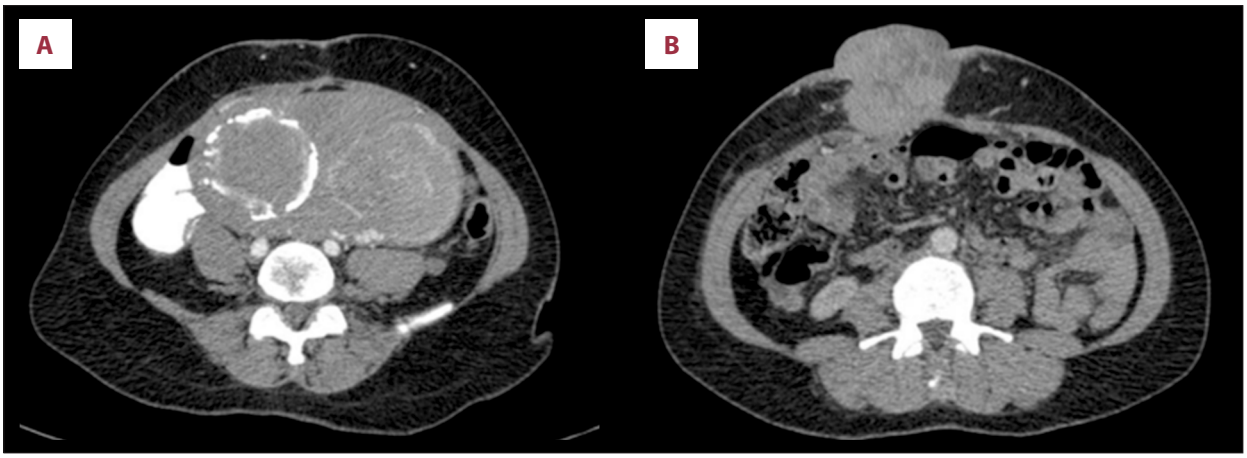

Figure 1. Abdomen and pelvis CT scans showing: (**A**) enlarged uterus due to fibroids (some with calcifications) and (**B**) infiltrative mass in the abdominal wall of the umbilical region.

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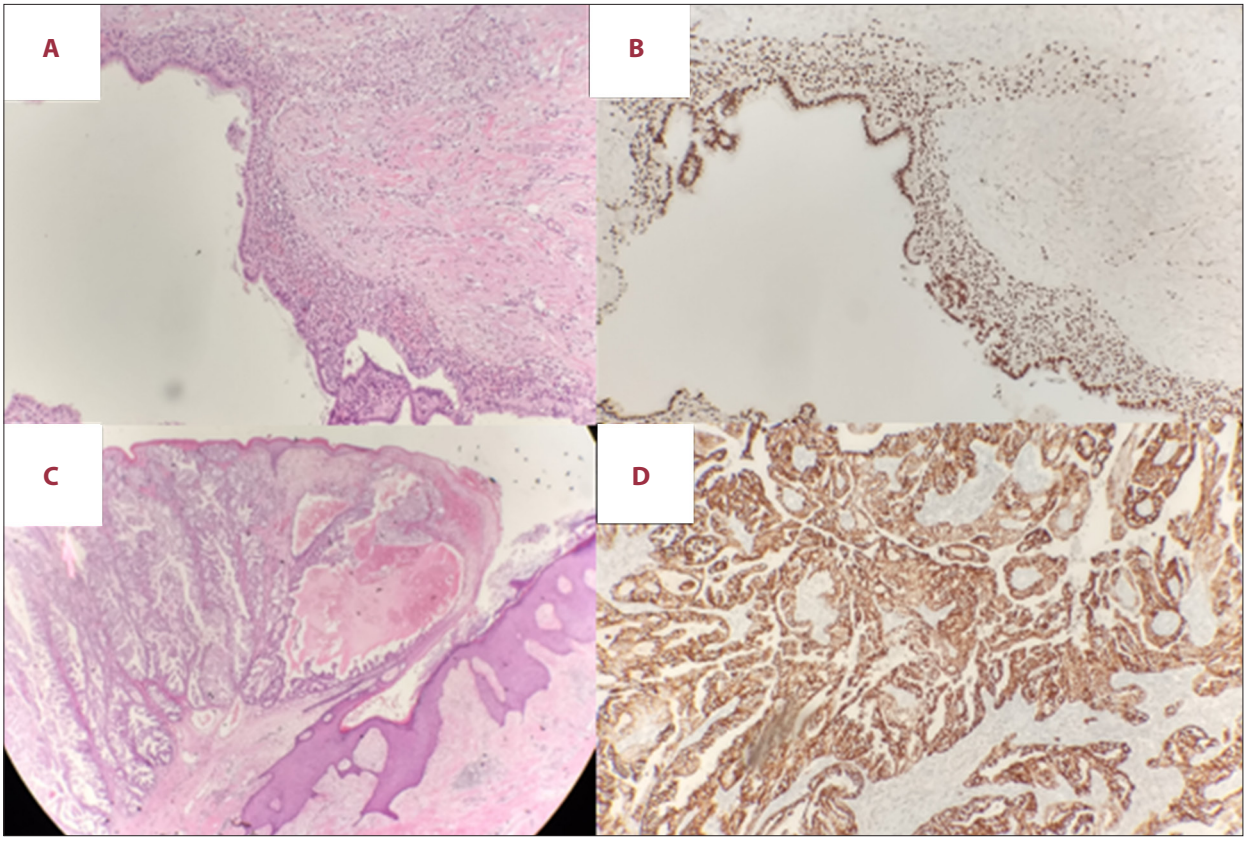

Figure 2. Pathology slides: (**A**) hematoxylin and eosin staining showing endometriosis in the abdominal wall; (**B**) immunohistochemistry positive for progesterone receptor; (**C**) hematoxylin and eosin staining showing adenocarcinoma grade II in the abdominal lesion, with a glandular, papillary and solid patterns, infiltrating the skin, subcutaneous and muscle tissue; with (**D**) immunohistochemistry positive for cytokeratin 7.

has been treated since April 2019, with a good tolerance and partial response.

Discussion

Epidemiology and clinical aspects of abdominal wall endometriosis

Endometriosis was first described by Rokitansky in 1860. It is a benign disease that commonly affects women of reproductive age, and it is defined by the presence of a functioning endometrial gland and stroma outside the uterine cavity. Although the lesions can occur at multiple sites (including the bowel, diaphragm, and pleural cavity), they are typically located in the pelvis [2,3]adhesions, and uterine position in 182 consecutive patients with infertility and endometriosis. The ovary was the most common site of implants with 54.9% having either unilateral or bilateral involvement. This was followed, in order of frequency, by the posterior broad ligament (35.2%. Since endometriosis is an estrogen-dependent and inflammatory disease, the most common symptoms are dysmenorrhea, dyspareunia, chronic pain, and infertility, which can range in intensity from minimal to severely debilitating [4–6].

Abdominal wall endometriosis occurs most frequently after obstetrical and gynecological procedures, and it can be caused by iatrogenic transplantation of endometrial tissue to the wound edge during any surgical procedure [1]. Robert Meyer first described endometriosis in a surgical scar in 1903. The foci of ectopic tissue can arise anywhere in the skin, subcutaneous layer, and fascial tissue, or can even penetrate to the peritoneal cavity. The incidence of endometriosis in abdominal surgical scars is 0.03% to 1.08% after pelvic surgery [1]. Abdominal localizations of these implants typically occur after cesarean section (0.03–0.4%) or hysterectomy, although they have also been reported in association with episiotomy, trocar scars, appendectomy, and hernia repair scars [7–9]. The typical presentation of endometriosis in surgical scars is the presence of a slowly developing, immobile lump in the scar or near it, with swelling and pain during menstruation [7]. Malignant transformation is very rare (0.3–1%) [1].

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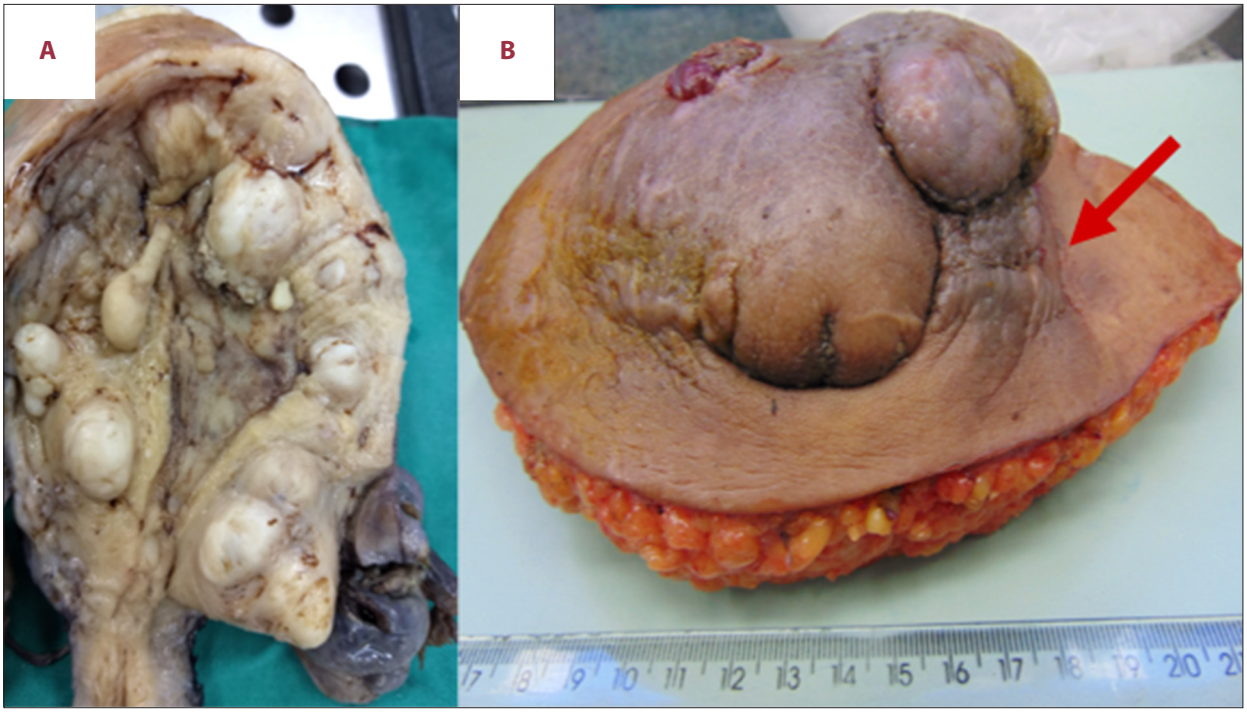

Figure 3. Macroscopy of: (**A**) uterus with many fibroids and (**B**) abdominal wall lesion attached to a previous scar (red arrow).

Pathological aspects of carcinoma arising from endometriosis-associated abdominal wall scar

In 1925, Sampson proposed 3 criteria for the diagnosis of malignancy arising in endometriosis: demonstration of both benign and neoplastic endometrial tissues in the tumor, histology compatible with endometrial origin, and no other primary tumor sites found [10]. Later, Scott introduced a fourth criterion: metaplasia between endometriosis and carcinoma [11]. In one study, 66% of the patients had the coexistence of benign endometriosis with cancer [12]. Another study, by Modesitt et al., showed the presence of "transition points" in many of these tumors, where a benign endometriotic glands was observed to merge with atypical and overtly malignant glands [13]. These findings support the idea that endometriosis can undergo malignant transformation rather than simply being a coexisting diagnosis.

About 80% of endometriosis-associated malignancies are found in the ovary, whereas 20% are localized in extra-gonadal sites such as the intestines, rectovaginal septum, abdominal wall, and pleura [14]. Numerous reports have established that abdominal wall endometriosis-associated malignancies often show clear cell or endometrioid histopathology, with CCC being the most common (63% of the patients), followed by EC (22% of patients) [12,15].

Potential mechanisms for transformation of endometriosis to carcinoma

Current knowledge links endometriosis malignant transformation to pathways or networks related to inflammation, oxidative stress, and hyperestrogenism. In ovarian endometrioma, inflammation evokes high levels of proinflammatory cytokines (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor-α, and tumor necrosis factor-β) that play a vital role in cell proliferation, angiogenesis, and production of reactive oxygen species. These microenvironmental changes induce tumor invasion and metastases. Hyperestrogenism has been associated with the malignant transformation of endometriotic cysts and the microenvironment created by endometriosis, with higher aromatase activity, which facilitates the accumulation of excess estrogen.

Some molecular events might be involved in the transformation, such as: loss of heterozygosity (LOH) and genetic instability [16], (b) p53 mutation [17,18], (c) PTEN and K-ras mutation [19,20], HNF-1B [21], and overexpression of VEGF [22], interleukin, and interferons [23].

Clinical presentation, imaging studies, and differential diagnosis of carcinoma arising from endometriosis-associated abdominal wall scars

The typical presentation is a mass in the abdominal wall, usually adjacent to a scar from a previous surgery, with a cyclical pain correlated with the menstrual cycle [24]. In a review

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by Taburiax et al., the median age of patients was 47 years and 100% of patients had a mass in the surgical scar, usually associated with cyclic or continuous pain (88% of patients). The most common histologic type was clear cell in 63% and endometrioid in 22% [12]. In the largest systematic review to date (48 patients), the mean age at diagnosis was 46 years, the median period from the first surgery to diagnosis of malignancy was 19 years, and median diameter was 7 cm; the most common histology was clear cell (66%) followed by endometrioid (14%) [25]. In a study evaluating 15 years of experience at a large Taiwanese academic institution, 6 patients with clear cell histology were treated. The mean age was 52 years, mean BMI 22.6 kg/m^2, and clinical presentation was a mass near the surgical scar (mean of 10.1 cm). In this institutional review, the mean time from the most recent gynecologic obstetrical surgery to the malignant diagnoses was 20.2 years [26]. Clinical history with emphasis in previous gynecological surgeries is very important. Imaging techniques are very useful; soft-tissue ultrasound is recommended, complemented, if necessary, with ultrasound-guided fine-needle aspiration of the mass. An MRI/CT scan is sometimes needed to provide additional information.

The clinical differential diagnosis of palpable masses in the abdominal wall includes hernia, hematoma, lymphadenopathy, lipoma, abscess, subcutaneous cyst, neuroma, soft tissue sarcoma, desmoid tumor, and metastasis [1].

Surgical approach and adjuvant treatments

The management of abdominal wall endometriosis malignant transformation is not well established because of its extremely low incidence rate. In the review by Mihailovici et al., all patients received wide local excision, with 47%, 47%, and 25% also undergoing hysterectomy, salpingo-oophorectomy, and omentectomy, respectively [25]. Adjuvant treatment was mainly based on chemotherapy with a platinum-based therapy (60%). Twenty-one patients (43%) also received radiotherapy after surgery and chemotherapy.

In the Taiwanese study, with 6 patients in 15 years of experience, the authors recommended wide complete tumor resection with cystectomy and resection of any macroscopic intrabdominal disease when feasible, with or without bilateral inguinal lymph node dissection. After surgery, they also recommend adjuvant chemotherapy [26].

It is important to note that treatment of these patients must be discussed by a multidisciplinary team of radiation oncologists, medical oncologists, and gynecologic oncologist to select the best approach for each individual.

Prognosis

In the largest review to date, the 5-year OS was about 40% and the median OS was 42 months [25]. Univariate analysis showed a trend toward worse outcomes for patients with clear cell histology, tumor larger than 8 cm in non-clear cell histology, and more than 18 months after diagnosis, but the differences were not statistically significant. Taburiax et al. reported the median survival was 30 months, but because of the low number of patients it was not possible to form any strong conclusions [12]. They also found that ovarian endometrioid malignant transformation usually affected young patients who presented with low-grade tumors and had a better prognosis than those with endometriosis-associated abdominal wall carcinoma.

Conclusions

Our case presents the difficult aspects of carcinoma associated with endometriosis located in an abdominal wall scar and the importance of treatment involving a multidisciplinary team. Surgical resection followed by adjuvant treatment with radiation and chemotherapy appears to be effective in treatment of localized disease.

Conflicts of interest

None.

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