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Presacral Clear Cell Carcinoma of Müllerian Origin 20 Years After Hysterectomy and Bilateral Salpingo-Oophorectomy: A Case Report and Literature Review

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ABSTRACT

Primary presacral clear cell carcinoma (CCC) of Müllerian origin is extremely rare. Malignant transformation of endometriosis is a known phenomenon, though typically involving the ovaries or pelvic peritoneum. Retroperitoneal presentation, especially decades after definitive surgery, is exceedingly uncommon. A 60-year-old woman presented with a large retroperitoneal/presacral pelvic mass leading to hydronephrosis, 20 years after total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. MRI showed a cystic-solid mass with mural nodularity. Surgical exploration revealed dense retroperitoneal adhesions with involvement of the rectosigmoid and the appendix. En bloc resection was performed in posterior exenterative fashion. Histopathology confirmed clear cell carcinoma arising from endometriotic foci, fulfilling Sampson's criteria. Postoperative management included adjuvant paclitaxel-carboplatin chemotherapy. The patient recovered uneventfully and was scheduled for ileostomy reversal. This case illustrates the potential late malignant transformation of endometriosis into Müllerian CCC even decades after hysterectomy and oophorectomy. Endometriosis-associated carcinoma should be considered in the differential diagnosis of retroperitoneal pelvic masses, particularly in women with prior endometriosis.

1 | Introduction

Primary presacral retroperitoneal tumors are rare and may arise from epithelial, mesenchymal, lymphatic, neurogenic or Müllerian origins [1].

Ovarian clear cell carcinoma (CCC) is a rare histological subtype of epithelial ovarian cancer and it accounts for about 5%–10% of all ovarian tumors in western countries [2]. Although endometriosis is a benign disease, it is one of the possible risk factors for malignant transformation in CCC or endometrioid ovarian carcinoma [3].

We present a case of presacral and retroperitoneal CCC of Müllerian origin arising on a background of endometriosis.

Summary

- This clinical case shows the chance of a malignant evolution of endometriosis after a long period from primary surgery and in unusual place like the presacral/retroperitoneum.

2 | Case History

A 60-year-old female presented with a pelvic retroperitoneal mass that involved the sigmoid colon and upper rectum, leading to hydronephrosis of the right ureter. On physical examination, a cystic pelvi-abdominal mass extending to the umbilicus was noted, with limited mobility. The patient had a normal body mass index (BMI) and no previous medical history. She had history of advanced pelvic endometriosis, treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy 20 years before.

2.1 | Imaging Finding

On magnetic resonance imaging (MRI), retroperitoneal masses are evaluated for size, margins, internal characteristics, and their relationship with adjacent organs. Malignant signs include large size, irregular borders, solid-cystic areas, and contrast enhancement. A retroperitoneal origin is suggested by posterior location and anterior displacement of abdominal organs [4].

In our case, imaging studies identified a pelvic mass on the MRI scan that showed a retroperitoneal mass 15.5 cm with internal septations, mild ascites, bilateral hydronephrosis. The case was discussed at the multidisciplinary team discussion (MDT) and imaging suggested the possibility of a retroperitoneal malignant pelvic mass; serum CA125 was 10 U/mL (Figure 1).

2.2 | Surgical Management

The patient underwent an exploratory midline laparotomy. Upon peritoneal opening, a 16 cm left presacral mass was identified, with limited mobility, inseparable from the rectosigmoid colon and upper rectum, involving also the vaginal vault. The appendix appeared grossly normal but was densely adherent to the surface of the pelvic mass. The anatomy of the left pelvic sidewall was distorted by extensive fibrosis, likely related to endometriosis and chronic inflammation. An intraoperative surgical decision was made to proceed with en-block resection of the mass, rectosigmoid colon and appendix was required (Figure 2). The ascending and discending colon were mobilized following Cattel-Braasch and Mattox maneuvers. The pelvic sidewall was accessed, both avascular spaces of pararectal and paravesical were developed. Adhesions between the urinary bladder and the mass were divided with caution, while the bladder was inflated with saline. Full bilateral ureterolysis was performed, and the ureters were slung away in view throughout surgery. Appendicectomy was performed as the appendix was adherent from the mass. The proximal sigmoid was divided using a Gastrointestinal Anastomosis 80 mm–4.8 mm (GIA) stapler. Anterior colpotomy was performed, and the posterior vaginal wall was dissected from rectovaginal septum. The anterior rectal wall was identified at about 8 cm from anal verge.

A distal bowel transection was performed using Contour rectal transector and the specimen was delivered. The vaginal vault was closed with interrupted Vicryl 1 sutures. A primary end-to-end bowel anastomosis was performed using an End-to-End Anastomosis (EEA) circular stapler. An under-water air-leak test was performed and was negative. A de-functioning loop

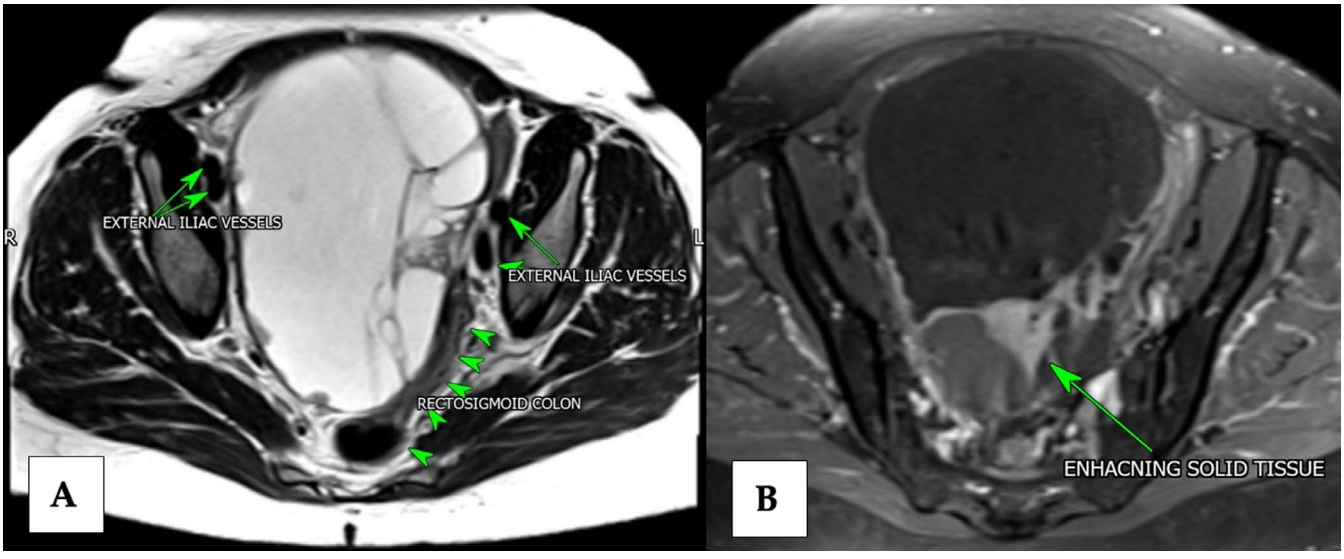

FIGURE 1 | (A) Axial T2-weighted MRI showing a 15.5 cm retroperitoneal mass with internal septations (arrow), displacing adjacent pelvic structures. Note mild ascites and right sided hydronephrosis. (B) Axial post-contrast T1-weighted fat-suppressed MRI image demonstrating a hyper enhancing mural nodule (green arrow) arising from the posterior aspect of a large retroperitoneal pelvic mass.

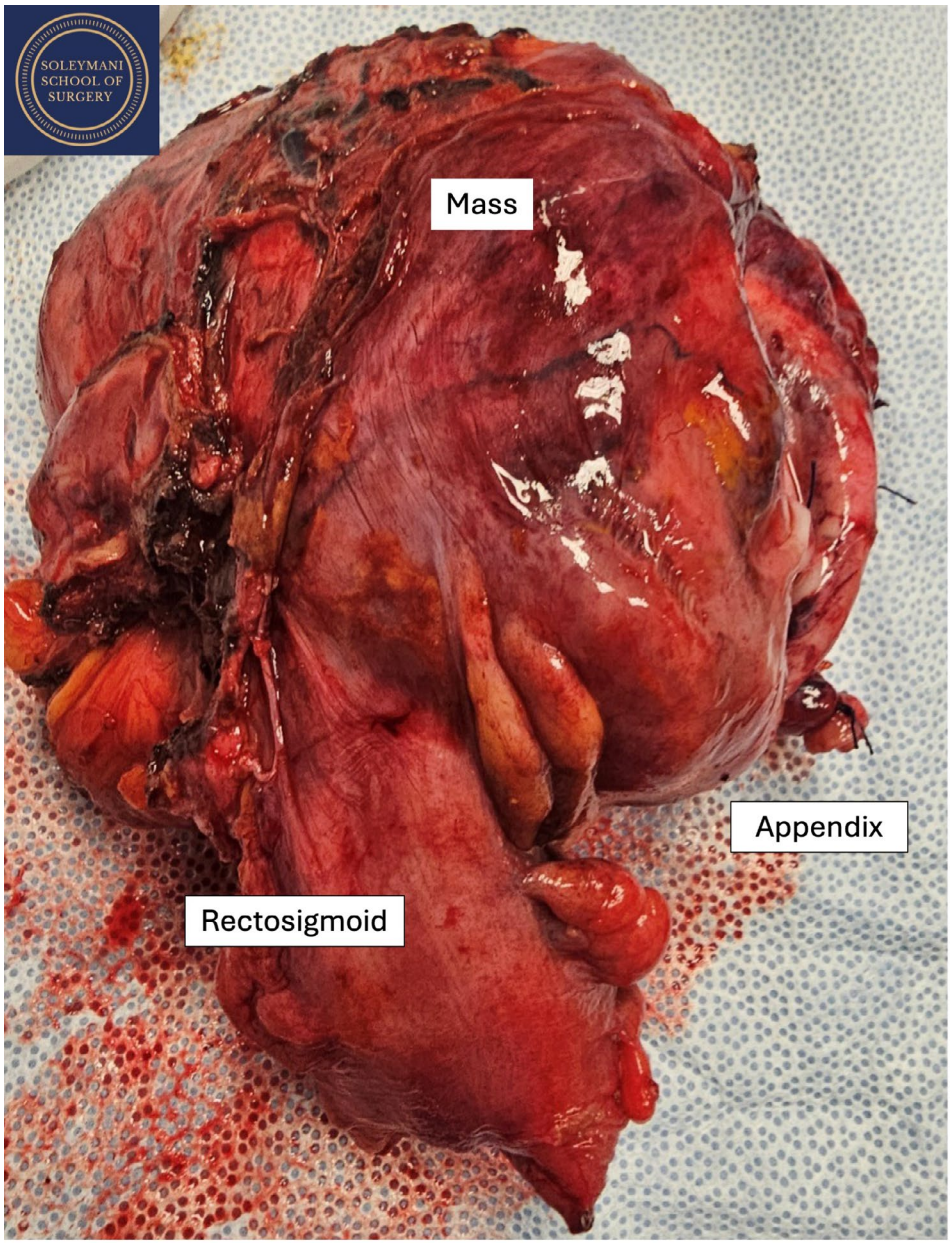

FIGURE 2 | Intraoperative specimen after en-bloc resection, showing the rectosigmoid, the appendix, and the tumor mass.

ileostomy was created approximately 20 cm away from the ileocecal junction, with proximal limb eversion and spouting. Blood loss was estimated at 600 mL.

The patient had an uneventful recovery and was discharged home Day 6 post-surgery.

2.3 | Histopathological Report

The histology results confirmed a clear cell carcinoma of gynecological/Müllerian origin, with no invasion of the bowel, appendix, or vaginal wall, albeit dense adherence to these structures. Foci of endometriosis and CCC were identified in the peritoneal surface of the mass raising the possibility of stage FIGO IIB ovarian neoplasm (Figures 3 and 4). There was also an incidental finding of low-grade mucinous appendicular neoplasm (LAMN).

Sections from the pelvic mass showed an adenocarcinoma with a tubulocystic and papillary architecture. The tumor cells showed high-grade nuclear atypia and contained clear cytoplasm. In some areas the cells had a hobnail arrangement and were associated with hyaline stromal cores.

Immunohistochemistry showed that the tumor was diffusely positive for PAX8 and focally positive for Napsin A. There was no loss of staining for the mismatch repair proteins MSH2, MSH6, MLH1 and PMS2. Additional immunohistochemistry showed that the tumor was also positive for CK7 and AMACR and negative for CAIX, CD10, RCC and WT1. There was a wild-type pattern of staining for p53. The stroma surrounding the tumor was weakly positive for WT1 and negative for ER and PR.

The morphological and immunohistochemical features were those of a clear cell carcinoma of gynecological/Mullerian

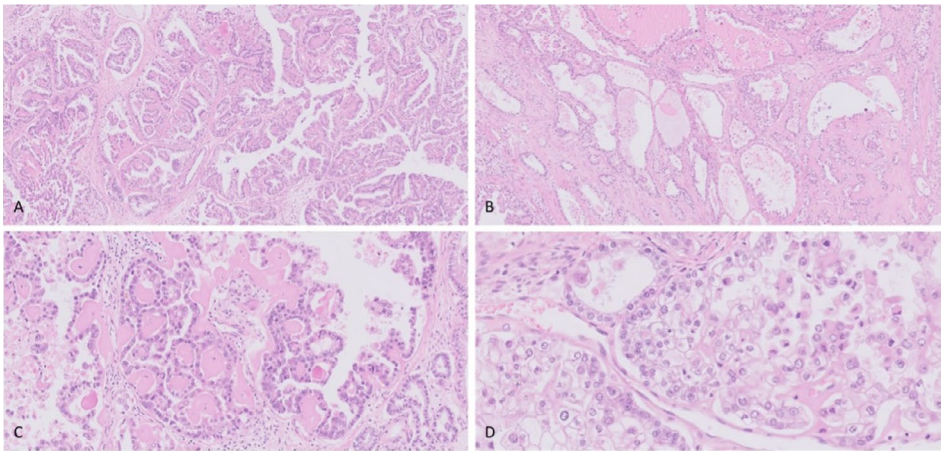

FIGURE 3 | Histological examination of the pelvic mass shows features of a clear cell carcinoma. (A) Papillary pattern (H&E, 100×); (B) tubulocystic architecture (H&E, 100×); (C) stromal hyalinization (H&E, 200×); (D) clear cytoplasm and atypical nuclei (H&E, 400×).

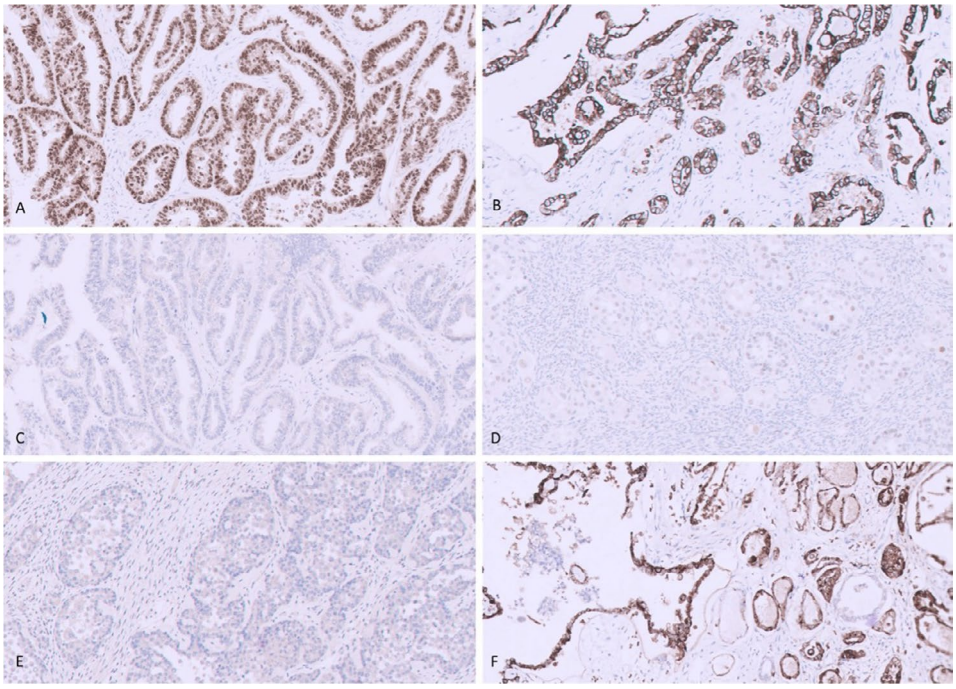

FIGURE 4 | Immunohistochemistry shows that the tumor is positive for PAX8 (A) and CK7 (B) and negative for ER (C). p53 shows a wild-type pattern of staining (D). WT 1 is negative (E) and Napsin A is positive (F).

origin. The surrounding stroma in places had a spindled appearance which resembled ovarian stroma, suggesting a possible ovarian origin (Table 1).

Alternatively, the tumor may be arising from endometriosis within the pelvis as there were small foci of endometriosis in the surrounding tissues.

The tumor did not involve the capsular surface of the mass. The non-peritonealised surface was also free of tumor. The mass was adherent to the bowel. There was fibrosis and focal endometriosis at the site of attachment but no evidence of invasion of tumor into the bowel. The mass was adherent to vagina macroscopically but there was no tumor involvement of the vaginal tissue histologically. The tumor was adherent to the appendix but did not invade into it. The lumen of the appendix at the tip was dilated and filled with mucin. The appendiceal mucosal epithelium showed focal stratification and it directly abuts the muscularis propria, without any involvement of the lamina propria. Mucin does not extend beyond the muscle layer. These features were those of a LAMN.

2.4 | Follow-Up

The patient had an uneventful recovery and with no complications. The definitive histopathological report was debated at MDT and six courses of adjuvant chemotherapy (Paclitaxel 180 mg/m^2 and Carboplatin AUC 6 mg/mL × min) at 3-week intervals were prescribed. The patient tolerated the adjuvant

TABLE 1 | Showing the immunohistochemistry (IHC) and its diagnostic implication.

Marker	Result	Diagnostic implication
PAX8	Diffusely positive	Supports Müllerian (gynecologic) origin
Napsin A	Focally positive	Suggestive of clear cell histology
CK7	Positive	Commonly positive in epithelial tumors of Müllerian origin
AMACR (P504S)	Positive	Often expressed in CCC; supports diagnosis
WT1	Negative	Helps exclude high-grade serous carcinoma
ER/PR	Negative	Suggests clear cell over endometrioid carcinoma
p53	Wild-type pattern	Rules out high-grade serous carcinoma
WT1 (stroma)	Weakly positive	May suggest ovarian stromal component

treatment, with tolerable adverse symptoms. Following that, another CT scan and MDT discussion were planned with the final decision to dispense maintenance treatment with 18 cycles of bevacizumab. Reversal of ileostomy was planned by surgical team after the end of maintenance therapy.

3 | Discussion

Endometriosis is a common disease in which functioning endometrial tissue (stroma and glands) is present outside the uterine cavity, or myometrium. The reported incidence is between 7% and 10%. Pelvic organs are the most common targets for endometriosis (including the ovaries, pelvic cul-de-sac, and broad ligament, and so forth). In addition, it has been described in numerous other locations in the pelvis and abdomen. Tumorigenesis of endometriotic spots is initiated by genetic mutation of the AT-rich interactive domain containing protein 1A (ARID1A) tumor suppressor gene, and driver genes including phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and Kirsten rat sarcoma viral oncogene homologs (KRAS). The risk factors for this process include prolonged exposure to unopposed estrogen and obesity, even after a definitive surgery. For this reason, combined estrogen-progesteron therapy has been recommended after hysterectomy in patients with suspected residual endometriosis [5, 6].

The differential diagnosis of a presacral retroperitoneal mass in postmenopausal women is broad and includes both primary retroperitoneal neoplasms and metastases. Among primary tumors, sarcomas such as liposarcoma and leiomyosarcoma are the most common, typically presenting as large, deep-seated masses with variable imaging characteristics depending on their histologic subtype [7]. Lymphoma, particularly non-Hodgkin's type, should be considered, especially when masses are multifocal or associated with lymphadenopathy, benign neural tumors (e.g., schwannomas) may also mimic malignant masses, though the former often encases rather than displaces adjacent structures [8]. Metastatic disease from gynaecologic primaries (especially ovarian or endometrial clear cell carcinoma) should be suspected in patients with prior pelvic malignancies [1]. Imaging modalities such as MRI and contrast-enhanced CT are critical for characterization, while tissue biopsy is often necessary for definitive diagnosis.

Malignant transformation of endometriosis is an uncommon event. Clear cell and endometrioid carcinoma are the most common histopathological types of cancer reported in women with ovarian endometriosis. Histopathological criteria to define a malignant transformation of endometriosis rely on Sampson's discovery [9].

In literature there are many case reports regarding CCC of Müllerian origin arising from endometriosis of the bladder [10–14] and the colon [15]. Many others are reported in the work of Gadducci et al. [2].

Regarding the retroperitoneal onset, we found only two case reports on Pubmed [16, 17]. In the first case [16] the patient had a previous hysterectomy and bilateral adnexectomy for benign indication, and after 19 years she presented with a left-sided pain strictly linked to the presence of a pelvic mass on that side. In this case, the histopathological report showed a retroperitoneal müllerian carcinosarcoma. The second case [17] showed an endometrioid carcinoma arising in the retroperitoneum from an endometriosis lesion of the ureter.

To our knowledge, the case that we have presented is the first case showing a clear cell carcinoma arising in the presacral/retroperitoneum from an endometriosis lesion.

Although malignant transformation of endometriosis is a rare event, these cases represent a warning whenever an unusual mass is detected not only at sites of previously treated endometriosis, but also in locations where no macroscopic disease had been detected.

4 | Conclusions

Malignant transformation of endometriosis is an uncommon but clinically relevant event. Our case highlights how the differential diagnosis of Presacral and retroperitoneal lesions can be particularly challenging, as it does not allow clinicians to rule out even rarest possibilities. Early recognition and multidisciplinary

team management are cardinal to ensure timely treatment and to maximize patients' outcomes.

Author Contributions

Alaa Elzarka: investigation, methodology, validation, visualization, writing – original draft, writing – review and editing. **Jacopo Conforti:** validation, writing – review and editing. **Sabina Ioana Nistor:** investigation, visualization. **Mahmoud Awaly:** investigation, visualization. **Andreas Zouridis:** investigation, visualization. **James Tak-kwan Fung:** investigation, visualization. **Priyanka Reddy:** visualization, investigation. **Stephen Damato:** visualization, investigation. **Sunanda Dhar:** visualization, investigation. **Hooman Soleymani majd:** conceptualization, investigation, methodology, project administration, visualization.

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Ethics Statement

The authors have nothing to report.

Consent

Written consent form was signed by the patient to collect anonymously her data for research and publications according to Wiley Clinical Case Report journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available following reasonable request to protect patient's privacy.

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