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Case report

Vesical clear cell adenocarcinoma arising from endometriosis: A mullerian tumor, indistinguishable from ovarian clear cell adenocarcinoma

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ABSTRACT

Endometriosis is associated with increased rates of ovarian, particularly clear cell, adenocarcinomas. Malignant transformation of ovarian endometriosis is most common but rare cases have been reported in the bladder, abdominal wall, diaphragm, and rectum. We present the case of a 44-year-old female with vesical clear cell adenocarcinoma arising in a background of endometriosis in the absence of other pelvic endometriosis. The malignancy was diagnosed on transurethral resection of bladder tumor and managed with radical surgery. Histology and immunohistochemical findings were consistent mullerian origin and indistinguishable from similar tumors arising in the female genital tract. Extrapolating from the gynecologic literature, the recommendation was made for adjuvant chemotherapy. Further studies are needed to clarify the optimal treatment paradigm for ovarian and bladder clear cell adenocarcinomas.

1. Introduction

Endometriosis, the presence of endometrial glands and stroma at extra-uterine sites, is common among reproductive age women, prevalence ranging 3–15% (Kim et al., 2014). The etiology of endometriosis is unknown but proposed mechanisms include retrograde menstruation, hematogenous or lymphatic dissemination, and coelomic metaplasia. Endometriosis is most frequently identified on the ovaries, rectovaginal septum, and broad and uterosacral ligaments (Loizzi et al., 2015). Endometriosis may also involve extra-pelvic organs including the small and large intestine, abdominal scars, the urinary system, and the lung/diaphragm. The bladder is the most common site of occurrence within the urinary system, though it is involved in less than 1% of extra-ovarian cases (Dadhania et al., 2015; Mann et al., 2012).

Studies report an elevated risk of ovarian cancer in women with endometriosis, rates ranging 0.3–1.6%. Specifically, malignant transformation of endometriosis is associated with clear cell ovarian cancer (Kim et al., 2014). The majority (80%) of malignant transformations are seen in ovarian endometriosis (Heaps et al., 1990). However, clear cell adenocarcinoma (CCA) arising from endometriosis has also been reported in non-gynecologic organs including the bladder, abdominal wall, diaphragm, and rectum (Loizzi et al., 2015; Mann et al., 2012; Heaps et al., 1990; Okazaws et al., 2014). The rate of malignant transformation of extra-ovarian endometriosis is not known. When it occurs, 70% and 4.5% of malignancies are of endometrioid and cell clear histology, respectively (Okazaws et al., 2014). Only 8 cases of CCA arising from vesical endometriosis have been reported in the English literature. We present a case of CCA arising within vesical endometriosis in the absence of ovarian endometriosis.

2. Case report

A 44-year-old para 0, with a history of urge urinary incontinence and recurrent urinary tract infections, presented with urinary frequency, incontinence, and hematuria. In 2008, she was diagnosed with urge incontinence and treated with tolterodine with improvement in symptoms. Multiple urinalyses at that time were positive for blood. The patient was lost to follow up until 2015, when she re-presented with recurrent symptoms. A urinalysis revealed many red blood cells and multiple urine cultures were negative. Patient underwent work-up for cancer including cystoscopy with biopsies and urine cytology which identified a tumor at the bladder neck and atypical cells, respectively. Multiple lines of medical management were employed for symptom management while awaiting radiographic evaluation. CT imaging

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demonstrated an intra-vesical mass. Renal ultrasonography showed normal kidneys and a 3 × 2 × 3 cm heterogeneously echogenic, hypervascular, polypoid mass protruding from the bladder trigone. Following, she underwent a transurethral resection of bladder tumor (TURBT), the pathology of which revealed invasive clear cell adenocarcinoma involving the muscularis propria.

Microscopic examination of the tissue specimen showed a tumor composed of high grade adenocarcinoma with abundant clear cytoplasm, pleomorphic nuclei, and frequent hobnail cells. The tumor cells were arranged in tubulocystic, papillary, and solid patterns and abundant mitotic figures were identified. Several foci of bland cuboidal/columnar cells lined microcysts were seen, consistent with endocervicosis/mullerian rests. Focally, the clear cell adenocarcinoma involved the endocervicosis, raising the possibility of tumor arising from the mullerian rests in the bladder. The urothelial mucosa was unremarkable without evidence of dysplasia or in-situ carcinoma. Immunohistochemically, the tumor cells were positive for AE1/AE3, CK7, CA-125(focal), NAPSIN-A, PAX-8, P-504S, and p16, and negative for CD20, ER, PR, TTF-1, WT-1, CEA-R, p63, Mammaglobin, CDX-2, p53, CD10 and Vimentin (Fig. 1a–d). The immunoprofile itself could not distinguish primary bladder clear cell adenocarcinoma from metastatic clear cell adenocarcinoma from the gynecologic tract.

Postoperatively, the patient was referred to gynecology for evaluation of increasingly heavy menses. Her physical exam was unremarkable. An endometrial biopsy demonstrated proliferative endometrium. Transvaginal ultrasonography revealed a 9 × 5 × 6 cm uterus with a 3 × 3 × 4 cm exophytic fundal myoma. A staging CT scan demonstrated diffuse bladder wall thickening and a mural soft tissue mass along the posterior bladder but no evidence of metastatic disease.

Following multi-disciplinary tumor board discussion including urology, medical oncology, and gynecologic oncology, the decision was made to proceed with anterior exenteration, ileal conduit, bilateral salpingo-oophorectomy, and pelvic lymph node dissection. Exam under anesthesia revealed bladder induration palpable along the anterior vagina. Intra-operatively, the bladder and ureters appeared grossly normal. The uterus was small and anteverted with a 3 cm posterior pedunculated fibroid. The adnexa and pelvic peritoneal surfaces were normal. Final pathology revealed rare mullerian rests in the bladder wall, ureters, and the surrounding soft tissue in the form of endometriosis, endocervicosis, or endosalpingiosis (mullerianosis). No residual bladder tumor was identified (Fig. 1e–f). The lack of primary gynecologic tumor and close association with vesical mullerian rests suggest this T2b, N0, M0 (stage II) clear cell adenocarcinoma of the bladder is of mullerian origin.

The patient's postoperative course was complicated by clostridium difficile colitis and right femoral nerve neuropraxia requiring acute rehabilitation at discharge. The patient was readmitted on postoperative day 14 with fever and leukocytosis. CT imaging identified a urinoma, which was managed with intravenous antibiotics and percutaneous drainage. After interdisciplinary meeting, the recommendation for treatment included adjuvant carboplatin and paclitaxel though the patient declined further treatment. She is currently being followed by urology and gynecologic oncology with urine cytology, serum comprehensive metabolic panel, and CT imaging of the chest, abdomen, and pelvis every 3–6 months. Six months postoperatively, she remains without evidence of recurrent disease.

3. Discussion

Eighty-five percent of bladder cancers are transitional cell carcinomas. Adenocarcinomas account for only 0.5–2% of bladder cancers. In all cases of adenocarcinoma, secondary malignancies presenting with metastases from other sites must be ruled out as secondary adenocarcinomas are more prevalent than primary bladder adenocarcinomas. Primary bladder adenocarcinomas demonstrate pure glandular differentiation (enteric, mucinous, signet ring, clear cell, other), yet derive directly from bladder urothelium (Dadhania et al., 2015). Whether clear cell adenocarcinomas (CCAs) of the bladder are of mullerian origin (like CCAs of the female genital tract), of mesonephric origin, or derived from glandular differentiation of the urothelium is of current debate (Oliva et al., 2002).

Vesicular CCA is more common in women than men. They usually arise in the urethra but when found in the bladder, most commonly occur at the trigone or posterior wall. Grossly, the tumor may have a

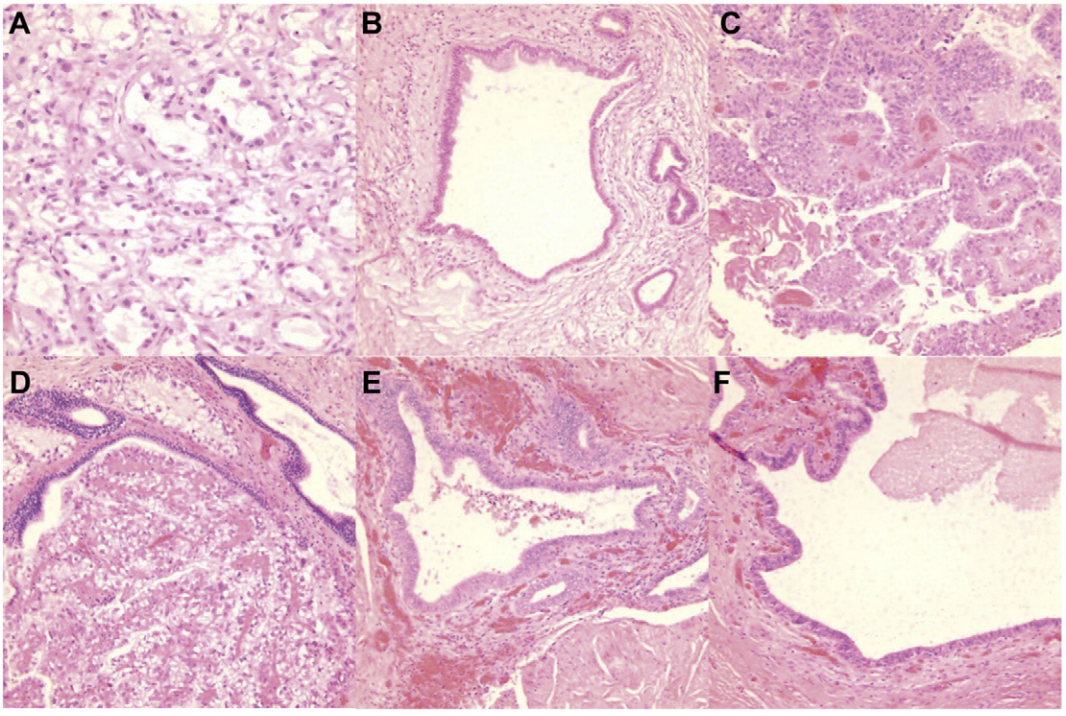

Fig. 1. (A) TURBT – tubulocystic pattern; (B) TURBT – endocervicosis; (C) TURBT – papillary pattern; (D) TURBT – tumor involving mullerian rest; (E) anterior exenteration – trigone, endometriosis; (F) anterior exenteration – trigone, endosalpingiosis.

papillary, exophytic, or polypoid appearance (Roy & Parwani, 2011). Many bladder CCAs are histologically and immunohistochemically similar to CCAs of the female genital tract (Dadhania et al., 2015). Histologically, these tumors demonstrate solid, papillary, or tubulocystic growth patterns, which may be lined by flat, cuboidal or columnar cells with clear or eosinophilic glycogen-containing cytoplasm. Hobnail cells, severe atypia, and frequent mitoses are common (Dadhania et al., 2015; Roy & Parwani, 2011). Immunohistochemistry often demonstrates positivity for CA-125, PAX8, pancytokeratin, and CK7 (Roy & Parwani, 2011). One literature review identified 38 cases of primary CCA arising within the bladder. Surgery was employed in the initial management of 86.8% of cases. Definitive treatment included radical surgery, chemotherapy, and radiotherapy in 18%, 18%, and 21% of cases, respectively (Lu et al., 2012). The role of surgery, chemotherapy, and radiotherapy remains to be delineated for this rare entity.

Current literature suggests an association between CCA and endometriosis; the majority of this data comes from the gynecologic literature as malignant transformation of extra-gonadal endometriosis is rare and only 4.5% of these transformations lead to CCA (Okazaws et al., 2014). Ovarian cancer reportedly occurs in 0.3–1.6% of women with endometriosis. A 2014 meta-analysis reported a relative risk of ovarian cancer of 1.265 (95% CI 1.214–1.318) in women with and without endometriosis. As expected, CCAs were more common (RR 2.606, 95% CI 2.225–3.053) in endometriosis-associated cancers (Kim et al., 2014).

Ovarian CCAs account for 5–25% of epithelial ovarian cancers. Current standards of care include cytoreductive surgery with adjuvant platinum-based chemotherapy. These recommendations are largely extrapolated from studies in serous ovarian cancer. Because it is relatively rare, large prospective trials evaluating this, and other, treatment paradigms have not been performed in ovarian CCA. Retrospective studies suggest that ovarian CCAs demonstrate chemoresistance and may be associated with poorer survival than their serous counterparts (del Carmen et al., 2012). Further investigation is required to delineate the role of multi-modality treatment in ovarian CCA.

Our case raises an interesting question about the role of adjuvant chemotherapy. Urologic literature does not support adjuvant chemotherapy in patients with node-negative transitional cell carcinomas following radical surgery. However, the histology and immunohistochemical profile of this tumor support a mullerian, as opposed to urothelial, origin. In this case, the high grade CCA, arising in background of endometriosis, was indistinguishable from CCAs of the female genital tract. Only eight cases of vesical CCA arising from endometriosis have been previously reported in the English literature. Given the mullerian origin, this case was reviewed by the gynecologic oncology tumor board. Extrapolating from the gynecologic literature, the recommendation was made for adjuvant carboplatin and paclitaxel though the patient declined further treatment. Furthermore, the approach to the adnexa in patients with no adnexal abnormalities needs to be carefully evaluated with each individual patient. Performing bilateral salpingo-oophorectomy (BSO) in patients with endometriosis is considered part of definitive management and is usually standard of care in order to maximally decrease symptoms. BSO may be considered in patients with CCA of the genito-urinary tract, regardless of ovarian involvement. Individual patient factors must be balanced with ACOG recommendations for ovarian preservation during patient counseling. Further studies are needed to clarify the optimal treatment paradigm for bladder clear cell adenocarcinomas. Our case highlights the need for multi-disciplinary approach among urology, medical oncology, and gynecologic oncology in patients with CCAs of the genito-urinary tract. Multi-institutional collaboration will be required to achieve adequate study recruitment.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal, upon request.

Conflict of interest

The authors have no personal or financial affiliations to disclose.

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