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CASE REPORT

Metastatic Low-Grade Endometrial Stromal Sarcoma of Uterus Presenting as Urothelial Tumor: Case Report and Brief Review of Literature

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Abstract

Endometrial stromal sarcoma (ESS) involving the urinary bladder is very rare, with very few reported cases in literature. ESS have indolent clinical course with late recurrences thus warrants long-term monitoring. Here, we report case of 38-year-old woman presenting to department of radiotherapy after TURBT done outside. Block review of TURBT specimen and IHC was asked for final diagnosis. CT urogram revealed large malignant mass involving the vaginal vault with gross infiltration into urinary bladder. She also had history of total abdominal hysterectomy done on 2018. H and E–stained sections from submitted block for review revealed an ill-defined tumor mass composed of uniform, oval to spindle cells arranged in diffuse sheet. Immunohistochemical analysis showed diffuse positivity for vimentin, desmin, ER, PR, BCL-2, CD10, and CD99. Pan CK and SMA were focal and weak positive. WT-1 was nuclear positive. Based on immunohistochemical features, final diagnosis of metastatic low-grade endometrial stromal sarcoma was made. An unexpected extra-uterine location and unusual presentation of ESS may make the diagnosis challenging. Morphological and immunohistochemical features must be combined to render the correct diagnosis.

Keywords Endometrial stromal sarcoma · Urinary bladder · Recurrences · Hysterectomy · BCL-2

Introduction

Secondary neoplasms are uncommon tumors of the urinary bladder and difficult to diagnose, especially when the primary tumor's information is unavailable. Uterine sarcomas arising from uterine musculature and connective tissue are rare tumors that are distinguished from malignant mesenchymal tumors and malignant mixed epithelial-mesenchymal tumors, and it is classified in latest World Health Organization (WHO) classification as leiomyosarcoma, LG-ESS, high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS), adenosarcoma, rhabdomyosarcoma, and malignant-type perivascular epithelioid cell tumor [1].

ESSs have a low risk of becoming cancerous and have an indolent clinical course. Even in patients with stage 1 illness, these tumors are known for late recurrences. More than a third of ESS patients experience a recurrence, necessitating long-term monitoring [2]. Pelvis, abdomen, and, less commonly, lung and vaginal recurrence are the most prevalent sites of recurrence [1].

ESS recurrences presenting as a bladder tumor is extremely rare. Few case reports have been reported in the literature [3]. In this case report, we present a patient presenting with intermittent hematuria, based on a very late recurrence of a formerly undiagnosed low-grade ESS metastasized to the urinary bladder. This case report highlights pitfalls in the diagnosis and discusses the characteristics of this neoplasm with reference to the literature.

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Case Report

A 38-year-old woman presented to department of radiotherapy after TURBT done outside and HPE reported as malignant neoplasm; possibility of sarcomatoid carcinoma can be considered. Block review and IHC was asked for final diagnosis.

Her detailed medical history revealed that she had complaints of intermittent hematuria, passage of clots, and poor urinary stream since 1 year. Her eventual per abdominal examination revealed suprapubic scar. Per vaginal examination, a firm mass was felt through vaginal wall. USG of whole abdomen showed a mass lesion measuring 5.9×5 cm, seen posterior to urinary bladder the region of right VUJ causing hydronephrosis in right kidney. CT urogram revealed large malignant mass involving the vaginal vault with gross infiltration into urinary bladder.

She also had history of total abdominal hysterectomy done on 2018. Histopathological examination was not done. Her blood investigation was within normal limits. Patient underwent TURBT and biopsy was taken from vaginal mass and was sent for HPE. Biopsy from vaginal mass was reported as spindle cell neoplasm with IHC advised for further typing. Patient had uneventful post-operative period. She was referred to higher center for further management.

H and E–stained sections from received block showed unremarkable urothelial epithelium. Subepithelium displayed ill-defined tumor mass composed of uniform, oval to spindle cells arranged in diffuse sheet. These cells have hyperchromatic nuclei, mild to moderate nuclear pleomorphism, inconspicuous nucleoli, and scant to moderate cytoplasm. Many interspersed perivascular tumor cell arrangements are noted. Atypical mitosis and necrosis are not seen. Provisional diagnosis of spindle cell neoplasm was made. (Fig. 1).

Immunohistochemical analysis showed diffuse positivity for vimentin, desmin, ER, PR, BCL-2, CD10, and CD99. Pan CK and SMA were focal and weak positive. WT-1 was nuclear positive. S-100, cyclin D1, CK7, CK20, P40, MyoD1, HMB45, CD34, H-caldesmon, LCA, synaptophysin, inhibin, and ALK-1 were negative in tumor. Ki67 labeling index was low (1–2%). Based on immunohistochemical features, final diagnosis of metastatic low-grade endometrial stromal sarcoma was made (Figs. 1 and 2).

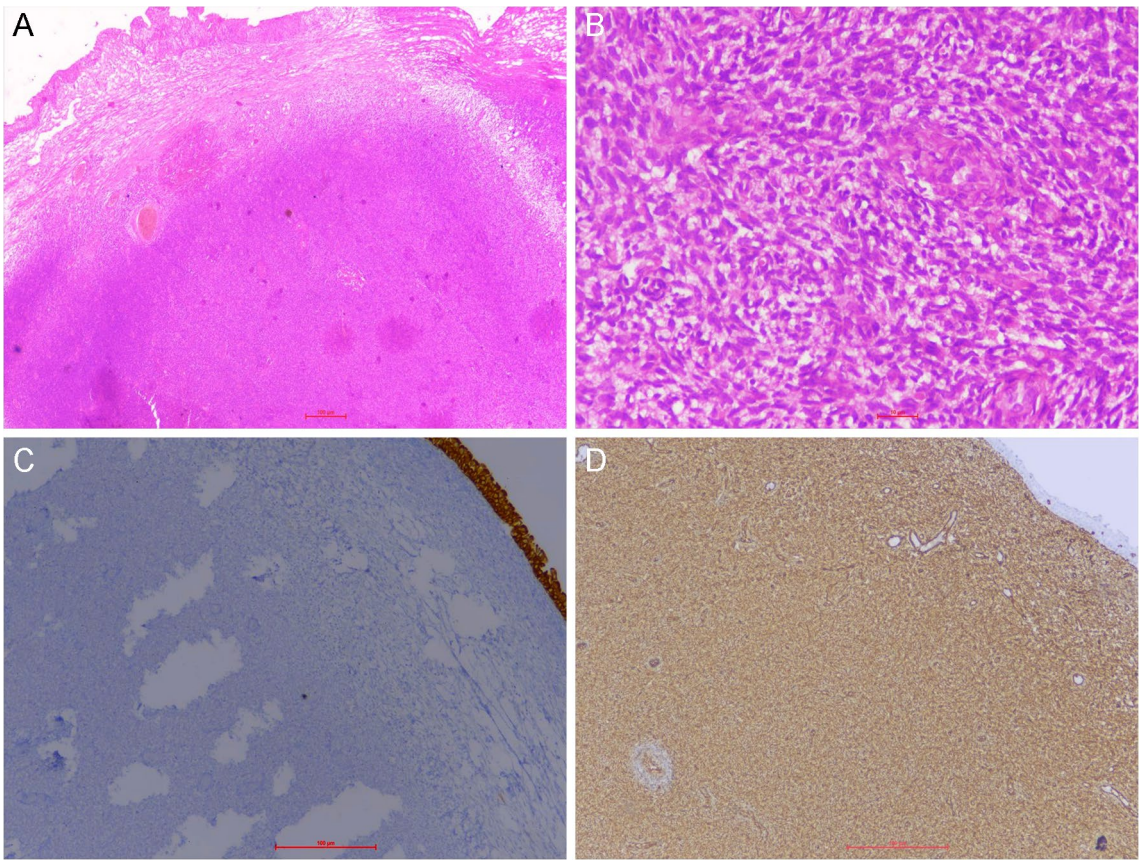

Fig. 1 **A** A poorly circumscribed, infiltrative tumor mass in the lamina propria of urinary bladder (H&E: ×40). **B** Monotonous tumor arranged in diffuse sheets and in perivascular pattern, composed of oval to spindle cells with minimal cytologic atypia, vesicular chromatin, and scant cytoplasm (H&E: ×400). **C** Tumor cells are immunonegative for CK-7 (IHC: ×100). **D** Tumor cells are diffuse immunopositive for vimentin (IHC: ×100)

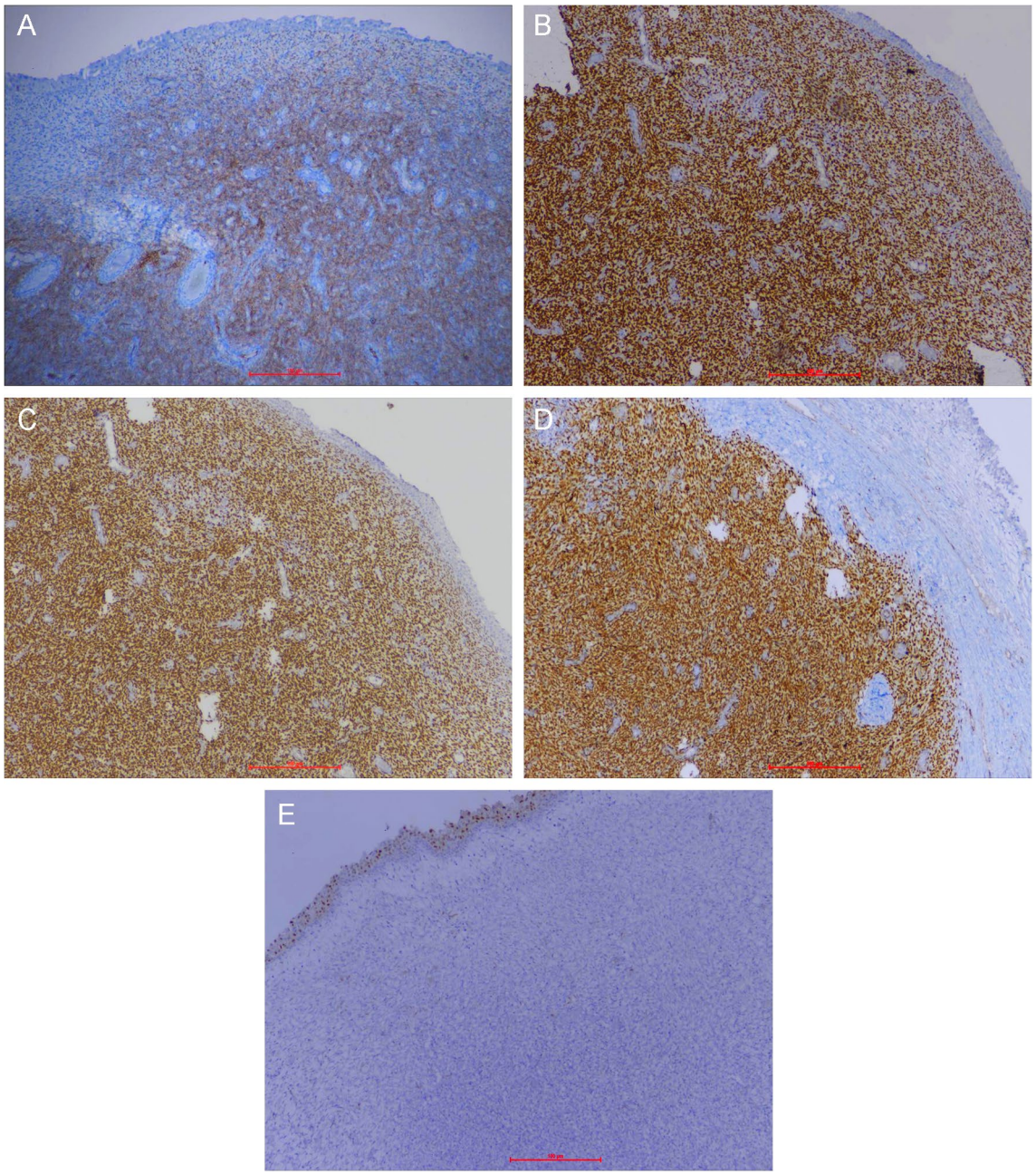

Fig. 2 **A** Tumor cells are immunopositive for CD 10 (IHC: × 100). **B** Tumor cells are immunopositive for estrogen receptor (IHC: × 100). **C** Tumor cells are immunopositive for progesterone receptor (IHC: × 100). **D** Tumor cells are immunopositive for WT1 (IHC: × 100). **E** Tumor cells are immunonegative for cyclin D1 (IHC: × 100)

Discussion

Secondary neoplasms of the urinary bladder are rare and can arise as tumor extension from an adjacent organ, such as the prostate, gynecologic tract, colon, or ureter, or as a result of metastasis through blood and lymphatic channels [4, 5].

ESS involving the urinary bladder is extremely rare and has previously only been described in a few case reports. Tian et al. reported case series of low-grade ESS involving the bladder. Out of 6 cases, one patient presented with bladder involvement at initial diagnosis of ESS. In rest 5 cases, patients presented with bladder involvement after 7 to 30 years (mean 18 years) after a known diagnosis of ESS ($n = 2$) or after a remote history of hysterectomy with an uncertain diagnosis ($n = 3$). Approximately 50% of endometrial stromal sarcomas (ESSs) occur in premenopausal

women and the majority is detected at stage I of the International Federation of Gynecology and Obstetrics (FIGO) [6].

Our case had history of hysterectomy without histopathological examination of the specimen, and hence with uncertain diagnosis. Two years after hysterectomy she presented with urinary symptoms and vaginal mass. Low-grade ESS is known to cause direct extension of tumor. However, in this case, immunohistochemical analysis was important as previous history was unclear and there was long-list differential diagnosis which needed to be ruled out including synovial sarcoma, solitary fibrous tumor (SFT)/hemangiopericytoma, carcinoid tumor, large nested variant of urothelial carcinoma, and endometriosis. Since, we received only one block for review, whole tumor morphology was unknown and thus all spindle cell neoplasm in urinary bladder was considered and leiomyoma was closest differential. SMA and H-caldesmon negativity ruled out leiomyoma.

LG-ESSs have same morphological characteristics in both uterine and extrauterine locations, consisting of sheets of oval to fusiform cells with scant cytoplasm, which resembles stromal cells of normal proliferative-phase endometrium, interspersed with small vessels resembling spiral arterioles of the endometrium. Mild atypia is noted. The presence of nuclear grooves is common in these lesions. Mitotic activity is low (median mitotic index: 3 mitoses per 10 high power fields), in general. ESS infiltrates into myometrium as a tongue-like pattern of invasion and is frequently associated with lymphatic invasion, but this pattern of invasion may be absent at extra-uterine sites [7]. Pathologists considering the diagnosis of bladder involvement by ESS cannot always rely on a clinical history of uterine ESS. Histologic features, immunophenotypes, along with previous history of hysterectomy are keys to arrive at the diagnosis of ESS.

The monotonous spindle-shaped cell along with presence of rich collagen elevates the possibility of a misdiagnosis between SFT and synovial sarcoma. However, numerous vessels in ESS resembling spiral arterioles in proliferative phase endometrium, in contrast to the dilated staghorn vessels in SFT, are an important differentiating feature. However, the presence of ER and PR with a negative CD34 ruled out SFT and synovial sarcoma [3]. However, ER, PR positivity with negative CD34 ruled out possibility of SFT and synovial sarcoma.

The bland short spindle to oval cells with pale to clear cytoplasm and finely stippled chromatin without conspicuous nucleoli may resemble carcinoid tumor [8]. Synaptophysin negativity ruled out possibility of carcinoid.

ESS with tumor nests penetrating the bladder wall might be mistaken for infiltrative urothelial carcinoma, particularly the large nested variety, which has bland histologic characteristics and low mitotic activity [9]. In comparison to ESS, urothelial carcinomas exhibit more defined cytoplasmic boundaries and have more abundant cytoplasm [3]. Mucosal precursor lesion can help confirm the diagnosis; many cases have no in situ lesion, which may mimic secondary involvement by ESS. With antibodies to GATA-3, the difference between the two tumors can be easily distinguished immunohistochemically. Low-grade urothelial carcinoma has been found to be positive for GATA-3 (100%) and thrombomodulin (68%) in studies, whereas ESS is negative for both markers [10, 11].

LG-ESSs are genetically diverse, with a high number of chromosomal translocations that result in gene fusions. However, only around one-third of these tumours have genetic fusions. The most common gene fusion is JAZF1-SUZ12, which is seen in about half of the cases and is linked to the cytogenetic hallmarks of ESN and LG-ESS. Other gene fusions seen in LG-ESS patients include EPC1-PHF1, MEAF6-PHF1, JAZF1-PHF1, MBTD1-CXorf67 (MBTD1-EZHIP), BRD8-PHF1, JAZF1-BCORL1, and EPC2-PHF1. MEAF6-PHF1 has recently been discovered in ESNs [12].

The first-line treatment for LGESS is hysterectomy and adnexectomy surgery. The advantages of lymphadenectomy and tumor debulking are not well understood. For individuals with advanced stages of the disease, endocrine therapy with gestagens and aromatase inhibitors is being considered an adjuvant treatment. Because radiation only provides locoregional control, and because patients with LG-ESS usually have a good prognosis, the advantages must be balanced against the risks. Recurrence surgery is the first option in the event of a recurrence [13].

Conclusion

ESS involving the bladder is highly unusual, with a prolonged interval between onset and bladder involvement. In patients without a known history of ESS, distinguishing primary bladder cancer from metastatic sarcoma to the bladder might be difficult. ESS should be included in the differential diagnosis of low-grade spindle cell lesions involving the bladder in female patients.

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Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Taken.

Conflict of Interest The authors declare no competing interests.

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