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Pregnancy Complicated by Inflammatory Myofibroblastic Tumor: A Case Report

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Abstract: *Inflammatory myofibroblastic tumors (IMTs) are solid mesenchymalspindle cell tumors with malignant potential. Primary genitourinaryIMT is rare. We present a case report of pregnancy complicated by IMT and review the literature for the manegment of such rare tumors.*

Keywords: *Pregnancy, inflammatory myofibroblastic, tumor*

1. Introduction

Inflammatory myofibroblastic tumors (IMTs) are solid mesenchymal spindle cell tumors with malignant potential. Primary genitourinary IMT is rare, has the same morphological and molecular characteristics as other malignant spindle cell sarcomas, and is often misdiagnosed as other bladder tumors in the early stage.

2. Case Report

A 24 years old pregnant female (18 weeks gestation, Gravida 2 - Para 1) referred to urology from the obstetrics department for the evaluation of bilateral hydroureteronehrosis with renal failure (creatinine 500 umol/L). She presented with pyelonephritis, flank pain, and fever; with history of frequency, poor urine stream and intermittency for four months and recurrent UTI for 5 years. There was no history of TB, shistosomiasis, hematuria, renal stones or pervious surgical or urological interventions. Clinical examination was unremarkable apart form a palpable cervical mass. She was catheterized with a 16 Foley catheter after which her creatinine normalized. Evaluation for bladder outflow obstruction has been carried out including examination under anesthesia, cystoscopy and MRI pelvis. The findings showed a large infiltrative mass (8 x6 cm) involving the vagina and cervix circumferentially, abutting the posterior aspect of the urinary bladder and urethra and pushing the rectal wall with loss of fat cleavage with no gross lymphadenopathy. Cystoscopy showed normal bladder with congested urethra and bladder neck, posterior wall of bladder above trigone is plugging and elevated by the underlying mass, normal left ureteric orifice but right orifice is slit like and pushed by the mass. Random biopsies taken from bladder, vagina and cervix. The histopathology was confirmative for the diagnosis of inflammatory myofibroblastic tumour.

The patient was managed with bilateral insertion of double J-stent and the decision was taken to treat her conservatively till she delivers. Her renal function normalized and she had occasional UTI. She delivered a healthy full term baby by cesarean section and the stents removed 3 months after delivery. She remained asymptomatic with normal renal function for 1 year and an MRI pelvis showed disappearance of the pelvic mass seen during pregnancy. Unfortunately, two years later she presented again with left flank pain and pyelonephritis. Evaluation showed she had left hydroureteronephrosis and a stent inserted again in the left side. Further evaluation including cystoscopy and MRI pelvis was carried out with the following findings: The previously described ill-defined pelvic mass previously seen circumfrentially encasing the uterine cervix shows notable regression in the size. However, the distal end of the left ureter is still seen encased with a double-J ureteric stent seen in place. There is mild to moderate left-sided hydroureteronephrosis. The aforementioned

mass lesion is seen abutting the distal right ureter, however no significant hydronephrotic changes could be detected. Both ovaries display normal size and follicular activity. Average filling of the right bladder with no evidence of invasion noted. No sizable myometrial uterine masses with normal endometrial complex. The cystoscopy showed plugging of the floor of the bladder above and medial to the left ureteric orifice and biopsies taken with similar histopathological findings. A decision was taken to repeat tissue biopsy from the mass looking for ALK positivity to consider her for Crizotinib treatment and if not responding to consider Pelvic exploration and excision of the mass with or without partial cystectomy.

3. PATHOLOGY

Anterior vaginal wall biopsy: multiple fragments of hyperplastic glycogenated stratified squamous epithelium and fragment of dense fibrous tissue lined by similar epithelium. The stroma is infiltrated by chronic inflammatory cells. There is no evidence of dysplasia or malignancy. Cervical biopsy: fragments of fibrous tissue lined by stratified squamous epithelium. The larger piece is polypoid. The squamous epithelium is histologically unremarkable. The stroma is oedematous and contains scattered spindle shaped cells, variably sized blood vessels and a patchy lymphocytic infiltrate. Some blood vessels show a mild perivascular hyaline change. The spindle shaped stromal cells stain positively with ER and PR and negatively with SMA, desmin, CD34, S100, melanA, PanCK, MNF116, BCL2, CD117 and CK7. Ki67 shows proliferative activity in less than 2% of cells. CD34 highlights the vascular proliferation. CD99 immunostain is difficult to evaluate due to background staining. Posterior fornix biopsy: fragments of tissue lined by glycogenated stratified squamous epithelium. The stroma is oedematous and contains scattered chronic inflammatory cells. Bladder biopsy: fragments of fibrous tissue and a fragment of bladder tissue. The bladder tissue shows oedema of the lamina propria and infiltration by chronic inflammatory cells. The urothelium is histologically unremarkable. The two pieces of fibrous tissue show a dense infiltrate of lymphocytes, plasma cells, histiocytes and eosinophils, associated with scattered stromal spindle shaped and stellate cells and collagen fibers. Some of these stromal cells contain enlarged vesicular nuclei with small nucleoli. The stromal cells stain negatively with ER, PR, ALK1, CD34, PanCK, MNF117, MelanA, BCL2 and CK7. CD117 is positive in some cells. CK7 immunostain highlight an epithelial lining in the two pieces of fibrous tissue with the spindle cell lesion, confirming that these two pieces are also from the bladder. There is a vascular proliferation with perivascular condensation of inflammatory cells. Occasional mitotic figures are present. There is no evidence of necrosis. The Ki67 stain shows high proliferative activity, but some of this activity is probably in the inflammatory cells, although many large stromal cells also stain positively **(Figure 1).**

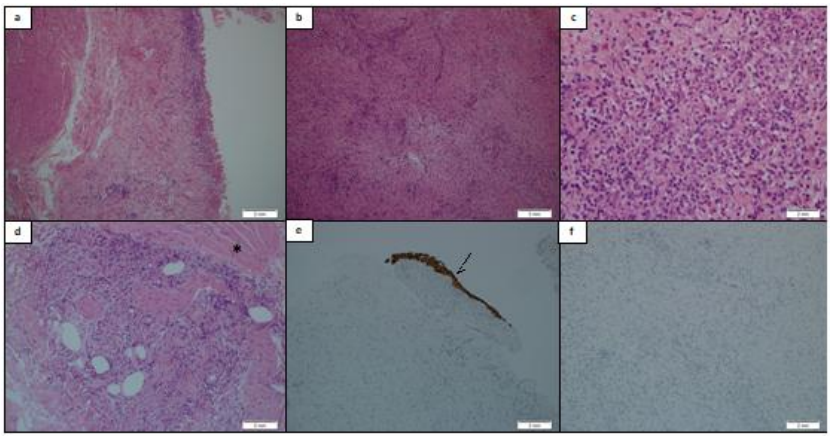

Figure 1. *Image **a** shows bladder mucosa lined by normal urothelium (H&E, 20X). Image **b** shows lamina propria expanded by a bland yet cellular spindle cell proliferation (H&E, 40X). Image **c**: an inflammatory component including eosinophils and plasma cells (H&E, 40X). Image **d**: the lesion extends into muscularis propria (asterisk) and is in close proximity to nerves (H&E, 40X). Image **e**: tumor cells are negative for pan-cytokeratin with positive internal control (arrow). Image **f**: tumor cells are negative for ALK.*

4. DISCUSSION

An inflammatory myofibroblastic tumor (IMT) was first reported in a lung lesion in 1973. [1] and pseudosarcomas of the genitourinary tract were first described in 1980. [2] These tumours are known by many different names in the

literature including: nodular fasciitis, pseudosarcomatous myofibroblastic tumor, fibromyxoid pseudotumor, pseudo-malignant spindle cell proliferation, inflammatory myofibroblastic tumor, and inflammatory pseudotumor. [3] IMTs are classified as tumours of intermediate biological potential by WHO, due to a tendency for local recurrence and a small risk of distant metastasis. [4] The recurrence rate varies by anatomical site, from 2% for tumours confined to the lung to 25% for extrapulmonary lesions. Distant metastasis of IMT is rare, occurring in 5% of cases. [4] Histologically, IMTs are characterized by a variably cellular spindle cell proliferation in a myxoid to collagenous stroma with a prominent inflammatory infiltrate composed primarily of plasma cells and lymphocytes, with occasional admixed eosinophils and neutrophils. [5] By ultrastructural analysis, IMTs are composed predominantly of myofibroblasts with a smaller fibroblastic component. [6] Chronic infection has been regarded as an important factor in the pathogenesis of IMTs, and the microorganisms that have been isolated from IMT lesions include mycobacteria, corynebacterium, Epstein-Barr virus and human papilloma virus. [7] Chromosomal translocations leading to activation of the ALK tyrosine kinase can be detected in approximately 50% of IMTs. [8]

IMTs develop at any age, but commonly arise in children and young adults, particularly in females. [9] Patients generally present with a mass or nonspecific symptoms, including vague abdominal pain or gastrointestinal complaints for intraabdominal lesions, and cough, chest pain, or, less often, haemoptysis for pulmonary tumours. A constitutional syndrome consisting of fever, weight loss and malaise is seen in 15–30% of patients, and laboratory evaluation may reveal microcytic anaemia, a raised erythrocyte sedimentation rate, thrombocytosis, and/or polyclonal hypergammaglobulinaemia. [5]

Inflammatory myofibroblastic tumor of the urinary bladder is a rare mesenchymal tumor with uncertain malignant potential. It often mimics soft tissue sarcomas both clinically and radiologically. As such, preoperative differentiation from sarcomas is of utmost importance to avoid radical surgeries. Surgical resection in the form of partial cystectomy or transurethral resection remains the mainstay of treatment. [10] The lung is the most common site, although IMT has been reported in the head and neck, gastrointestinal tract, retroperitoneum, breast, and central nervous system. In the genitourinary tract, the urinary bladder is the most common site, although IMT has been reported in the kidney, ureter, prostate, urethra, uterus, and paratesticular tissue. [11]

Coffen et al. [5] reported their experience with 84 cases occurring in the soft tissues and viscera of 48 female patients and 36 male patients between the ages of 3 months and 46 years (mean, 9.7 years; median, 9 years). A mass, fever, weight loss, pain, and site-specific symptoms were the presenting complaints. Laboratory abnormalities included anemia, thrombocytosis, polyclonal hypergamma globulinemia, and elevated erythrocyte sedimentation rate. Sites of involvement included abdomen, retroperitoneum, or pelvis (61 cases); head and neck, including upper respiratory tract (12 cases); trunk (8 eases); and extremities (3 cases). The lesions ranged in size from 1 to 17 cm (mean, 6.4; median, 6.0). Excision was performed in 69 cases. Other reported associations with IMT were: a case report of IMT associated with Mycobacterium tuberculosis infection; [12] a case of a 13-year-old boy with a pelvic mass diagnosed as IMT underwent malignant transformation and metastasized to the liver; [13] and a case report describing an inflammatory tumor of the urinary bladder along with left renal cell carcinoma. [14]

Differential diagnosis of IMT includes benign diseases such as leiomyoma, postoperative spindle cell nodule, nodular fasciitis, and neurofibroma and malignant diseases such as leiomyosarcoma, embryonal rhabdomyosarcoma, and sarcomatoid carcinoma. Immunohisto chemistry remains the cornerstone for diagnosis of IMT with positive stain for vimentin (95% to 100%), desmin (5% to 80%), smooth muscle actin (48% to 100%), muscle-specific actin (62%), and keratin (10% to 89%) and negative stains for epithelial membrane antigen, myogenin, p53, and h-caldesmon. [15] ALK stains positive in approximately half of these tumors and is a promising marker for differentiation of IMTs from other lesions.[11]

Radical resection is the preferred method of treatment for IMTs of the bladder [16]. The choice of partial resection of the bladder or transurethral resection of a bladder tumor depends on the depth of the tumor invasion. For large tumor masses, treatment of the patients with celecoxib and prednisone is attempted first [17] and then partial resection of bladder is performed if the tumor has narrowed. Atrial of Crizotinib treatment for disease regression has been advocated [18]. For advanced bladder IMT

with ALK (+), neoadjuvant therapy with lorlatinib has been used when surgical intervention fails, and partial cystectomy is considered if there is a significant therapeutic response. [19]

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