Oncology and Translational Medicine
DOI 10.1007/s10330-020-0463-3

Februry 2021, Vol. 7, No. 1, P41–P44

CASE REPORT

Ewing sarcoma/primitive neuroectodermal tumor of the ureter: A case report and literature review

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Abstract

Ewing sarcoma/primary neuroectodermal tumors are rare, invasive, and small round blue cell tumors. There are few reports of its occurrence in the urinary system. Here, we present the first middle-aged female patient whose Ewing sarcoma primary site was in the ureter. The main clinical manifestation was intermittent hematuria. She was in good health after complete surgical resection and adjuvant radiotherapy. To date, there has been no recurrence or metastasis. Accurate early diagnosis and appropriate treatment can help prolong survival. 18F-fluorodeoxyglucose positron emission tomography/computed tomography is expected to be an effective means of evaluating treatment effects and detecting metastasis and recurrence. In this article, besides introducing a case of Ewing sarcoma/primitive neuroectodermal tumor of the ureter, we review the literature to discuss the current status of diagnosis and treatment.

Received: 19 October 2020
Revised: 27 December 2020
Accepted: 15 January 2021

Key words: Ewing sarcoma (ES); primitive neuroectodermal tumor (PNET); ureter; positron emission tomography/computed tomography (PET/CT)

In 1918, Stout described, for the first time, a solid tumor originating from the ulnar nerve, which was later named primitive neuroectodermal tumor (PNET). Subsequently, Ewing discovered a sarcoma he named after himself—Ewing sarcoma (ES)—composed of long bones' undifferentiated cells. In 1973, Hart and Earle proposed that PNET is a malignant small round cell tumor originating from the neural crest [1]. According to the location, PNET can be divided into central PNET and peripheral PNET (pPNET). Because pPNET and ES share the same chromosomal translocation, approximately 85% of ES and pPNET present a specific t(11;22)(q24;q12) balanced translocation, which in 2002, the World Health Organization classified as the ES family of tumors that also includes Askin tumors (ES of the chest wall).

ES/PNET is a highly malignant and extremely rare small round cell tumor, showing varying degrees of neuroectodermal differentiation, which usually occurs in children and adolescents. ES/PNET mainly affects the bones or soft tissues but is not common in the urinary tract. It is mostly reported in case forms, such as in the kidney and bladder, but rare in the ureter. It is challenging to make a preoperative diagnosis and identify other diseases based on clinical symptoms and imaging findings. The diagnosis mainly depends on histological biopsy, immunohistochemistry (IHC), and gene detection. Complete surgical resection combined with adjuvant radiotherapy and chemotherapy is the primary treatment method, whereas a new type of targeted immunotherapy is now being investigated in clinical trials [2].

Case presentation

On July 29, 2019, a 45-year-old woman presented with painless gross hematuria for 3 months. There was no obvious abnormality in patient history, family history, or physical examination. Ultrasound, magnetic resonance imaging, and 18F-FDG PET/CT examination showed that the lower part of the right ureter and bladder triangle was 1.8 cm × 1.5 cm × 0.8 cm, and the presence of a tumor

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was considered (Fig. 1a–1e). The urine smear showed squamous epithelium and lymphocytes; laboratory examination revealed mild anemia (hemoglobin, 101 g/L). After that, the right kidney was removed, and ureterectomy was performed. A lower ureteral neoplasm was observed during the surgery, and lumen stenosis with rough mucosa was found. An intraoperative frozen section evaluation of the ureter suggested invasive urothelial carcinoma (Fig. 2a). The patient recovered well after surgery.

Histological examination of the excised specimen indicated that the right ureteral carcinoma had infiltrated the muscular layer of the wall, but the rest of the tissues were not involved. The tumor was composed of small round blue cells, suggesting the presence of ES/PNET (Fig. 2b). IHC showed that the cells were CD99 diffusely positive, CD117(+), Fli-1(–), cytokeratin (CK, –), desmin(–), chromogranin (CgA, –), synaptophysin (SYN, –), WT-1(–), CD56(–), and S-100(–). These results supported the diagnosis (Fig. 2c). Fluorescence in situ hybridization (FISH) detection revealed a EWSR1 gene (22q12) breakage, consistent with that in ES/PNET. The patient received volumetric modulated arc radiotherapy 1 month after the surgery, with a total dose of 50.4 Gy in 28 fractions at the tumor bed and pelvic drainage area. During the same period, she was simultaneously administered chemotherapy with lobaplatin (40 mg) once a week. After the second administration of chemotherapy, the patient had severe leukopenia and third-degree myelosuppression, which improved after symptomatic support. No severe complications or abnormal lesions were found during the follow-up period. It has been 16 months since the initial diagnosis. At present, the patient receives oral capecitabine maintenance therapy with a

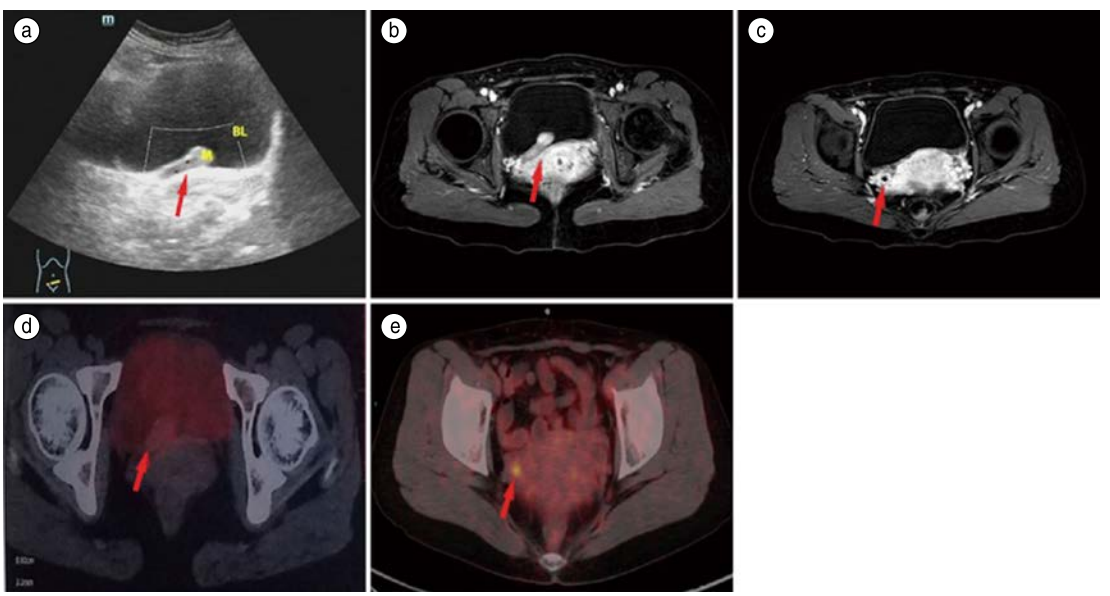

Fig. 1 US, MRI and PET/CT images of tumor. (a) US image shows hypoechoic nodule can be seen in the triangle of the bladder, with regular shapes and clear boundaries; (b, c) Enhanced axial MRI images show abnormal signal shadow in the bladder triangle, thickening of the ureteral wall with dilation; (d, e) 18F-FDG PET/CT images show solid nodules in the right ureter and bladder triangle with increased radioactivity uptake. US, ultrasound; MRI, magnetic Resonance Imaging; 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography

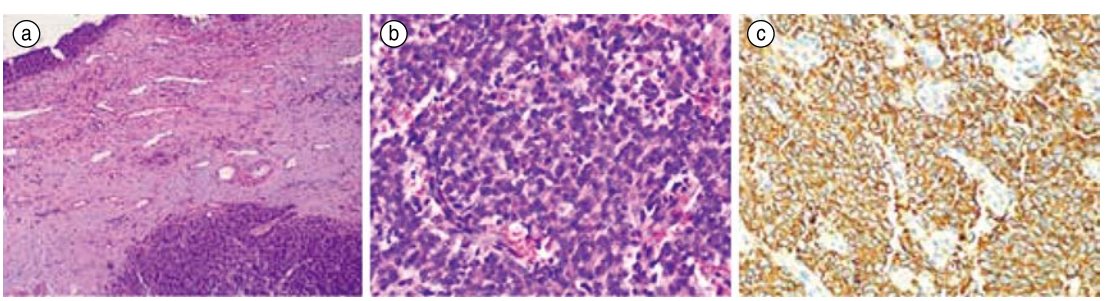

Fig. 2 Histologic and immunohistochemical images of tumor. (a) Cancer cells in the interstitium showed invasive growth (× 100); (b) Microscopically, histologic analysis of hematoxylin and eosin staining (× 200) revealed that the tumor was composed of small blue round cells; (c) Immunohistochemical staining showed positive expression for CD99 (× 400)

good mental state, appetite, and sleep state and is being closely followed up.

Discussion

Principal findings

The clinical and imaging findings of urinary ES/PNET are not specific, and most of the symptoms are related to the involved site; thus, a direct diagnosis is difficult, and ES/PNET is easily misdiagnosed as other common space-occupying diseases. Extraosseous ES is highly malignant, aggressive, and easily metastasizes or recurs in the early stage. Although patients show obvious local clinical signs, occult metastases may also exist in most localized diseases, resulting in a short survival period; the 5-year disease-free survival rate is approximately 45% to 55%, and the 3-year survival rate is 60%. Histopathologically, ES/PNET is mainly characterized by small round blue cells of equal size, evident nucleoli, fine nuclear chromatin, and sparse or vacuolar cytoplasm. IHC and molecular genetics play an essential role in diagnosis and differentiation. CD99 (MIC-2 gene product) and FLi-1 are sensitive indices for diagnosis, but their specificity is not high; they can also be expressed in small round cell tumors such as lymphoma and rhabdomyosarcoma and can be distinguished by combining with other biomarkers such as neuron-specific enolase (NSE), vimentin, desmin, CK, CgA, SYN, and S-100. EWS dual-color, breakable-apart rearrangement probe FISH detection is a highly sensitive and specific diagnostic technique, which combined with CD99 is the preferred diagnostic method, and the combination of CD99 and FLi-1 can improve specificity.

There is no standard treatment guided by evidence-based medicine. Usually, a comprehensive treatment mode of surgery is adopted, supplemented by radiotherapy and chemotherapy, and the most commonly used chemotherapy regimens are VCD + IE (VCD: vincristine+cyclophosphamide+doxorubicin; IE: ifosfamide+etoposide). Some studies have proposed that sandwich therapy (neoadjuvant chemotherapy+surgery+adjuvant chemotherapy) can be used for ES/PNET, and radiotherapy can be used as a postoperative adjuvant or an alternative in locally advanced disease that is not amenable for surgery [3]. Thorough surgical resection is important for the control of local diseases. The 2-year overall survival rate of patients undergoing surgery is approximately 80%, whereas the survival rate of patients who do not undergo surgery is 30%. Despite the aggressive treatment strategy, the prognosis of ES/PNET is still frustrating, with a median overall survival of approximately 26.5 months. Kuroda *et al*[4] have pointed out that the average age at the time of diagnosis is 27.7 years, and whether metastasis is present at the time of diagnosis is a critical factor influencing prognosis. The 5-year survival rates of metastatic and localized diseases are 22% and 55%, respectively. Young age may be a protective factor. Some studies have shown that the prognosis of adults is worse than that of children, and this difference may derive from the dose of chemotherapy drugs and the duration of local treatment [5]. In addition, the tumor size and location of the central axis are also adverse prognostic factors. At present, there are no definite protocols for the follow-up period. The authors believe that if conditions permit, the follow-up period should be extended to monitor the changes in the disease or even carry out a lifetime follow-up.

A case of a middle-aged woman with ureteral ES/PNET is presented for the first time in this article. Thus far, only five cases of ureteral ES/PNET have been reported in the English literature [6–10] (Table 1). These patients were treated for abdominal pain or hematuria. Among them, three minor patients underwent surgery and chemotherapy, and two of them could be traced to follow-up; the longest disease-free survival time was 8 years. An adult male relapsed twice after surgery and radiochemotherapy and died of disseminated disease. Another elderly female patient only underwent surgery, and there was no obvious abnormality in the examination at 6 months follow-up. Our patient was in good condition

Table 1 Characteristics of 5 patients with ureteral ES/PNET

Case No.	Gender	Age (years)	Location	Symptoms	Treatment	Prognosis
1	Female	17	Right ureter	Right flank pain and hematuria	Surgery+ chemotherapy	None
2	Male	45	Left ureter	Painless hematuria	Surgery+ chemotherapy+ palliative radiotherapy	Relapsed 3 years after the first operation, relapsed 7 years after the second operation, and died of metastasis 2 years later
3	Male	12	Right ureter	Abdominal pain	Surgery+ chemotherapy	Disease-free survival 8 months after surgery
4	Male	12	Right ureter	Abdominal pain	Surgery+ chemotherapy	Disease-free survival for 8 years without recurrence
5	Female	69	Left ureter	abdominal pain and hematuria	Surgery	Followed up for 6 months without recurrence and metastasis

ES/PNET, Ewing's sarcoma/primary neuroectodermal tumor

after complete surgical resection and radiotherapy, and there was no recurrence or metastasis 11 months after the completion of treatment. Unfortunately, our patients did not receive standard systemic chemotherapy because of long-term leukopenia. Currently, only maintenance monotherapy is administered, which requires close observation and follow-up. This patient underwent a systemic PET/CT scan before surgery to rule out other possible lesions. Some studies [11] have pointed out that this examination can also be carried out during follow-up to evaluate treatment response, distant metastasis, and recurrence.

Conclusion

Urinary tract ES/PNET is a rare disease. The most fundamental challenge is an accurate preliminary diagnosis, combined with active systematic treatment and close follow-up to improve the prognosis and survival time. With the increasing application of IHC markers, the regulation of tumor transformation, growth, and metastasis is becoming increasingly sophisticated, and potential therapeutic targets and diagnosed cases will increase. The establishment of a global database for these rare malignant tumors will also contribute to improving treatment strategies.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-020-0463-3
Cite this article as: Zhou Q, Du GB, Tang J, *et al*. Ewing sarcoma/primitive neuroectodermal tumor of the ureter: A case report and literature review. Oncol Transl Med, 2021, 7: 41–44.