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Case Report

Primary primitive neuroectodermal tumor of urinary bladder in a child: a case report and literature review

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Abstract: Objectives: The present study is to report the clinical and pathological features of the primary primitive neuroectodermal tumor, Ewing's sarcoma (PNET/EWS) of urinary bladder. Methods: A case of PNET/EWS in urinary bladder was reported. The literatures of 14 cases of PNET/EWS were reviewed according to clinical manifestation and pathological characteristics. Results: A 2-year-old boy presented with dysuria was referred to our institution for further management in December 2014. Pelvic computed tomography showed a large intravesical tumor. Cystoscopy showed a large intravesical mass arising from the neck and left side of the bladder, and then biopsy was made. Histopathological examination revealed sheets of uniform, small, round, and oval cells, which presented scarce cytoplasm, hyperchromatic nuclei, inconspicuous nucleoli, and abundant atypical mitotic figures. From the further immunohistochemical characterization, the tumor cells demonstrated strong reactivity to CD99 and Vim. A definitive diagnosis of PNET of the bladder was established. Catheterization was performed, but chemotherapy was refused by the parents, and the patient was discharged according to his parents' will. The patient died 4 months later. Conclusions: Bladder PNET is an extremely rare malignant tumor. The diagnosis is based on histological, immunohistochemical and molecular pathologic findings. It is a kind of highly aggressive tumor and has very poor prognosis. Radical excision combined with adjuvant chemotherapy and radiotherapy appears to be the best treatment.

Keywords: Primary primitive neuroectodermal tumor/Ewing's sarcoma of the urinary bladder, pathology, therapy, prognosis

Introduction

Ewing's sarcoma (EWS) is a kind of rarely seen malignant tumor originated from neural ectoderm. Clinically, EWS is diagnosed as primitive neuroectodermal tumor (PNET) [1]. PNET/EWS is mainly composed of primitive neuroectodermal cells, and possesses the potential of multidirectional differentiation. It can be classified into central type and peripheral type [2]. Peripheral PNET/EWS usually occurs in children and adolescents, with strong invasiveness and poor prognosis. It is commonly observed in bone and cartilage tissues, especially in trunk, limbs, spine, and chest wall [3, 4]. The main clinical manifestations of PNET/EWS include gradually enlarged local masses and mass compression-related symptoms. On computed tomography, PNET/EWS is mainly presented as low density images of circular or irregularly shaped soft tissues [5, 6]. Under electron microscope, PNET/EWS shows tightly arranged small round cells with similar sizes. The cells have high nucleocytoplasmic ratio. The nuclei have dark blue color, and form cord-like, sheet-like or nest-like arrangements. Some areas show fiber component segmentation, and 30-80% cases exhibit Homer-Wright rosettes false characteristic performance [7]. The major treatment method for PNET/EWS is surgical resection supplemented with adjuvant radiochemotherapy. However, radiotherapy is not suitable for patients younger than 2 years old. The prognosis of PNET/EWS is usually poor, with most patients dying within 2-3 years after diagnosis [8]. EWS in bladder is especially rare, which has only been reported in 14 case reports [3, 4, 9-20]. Here, we report a case of bladder EWS occurring in a young child.

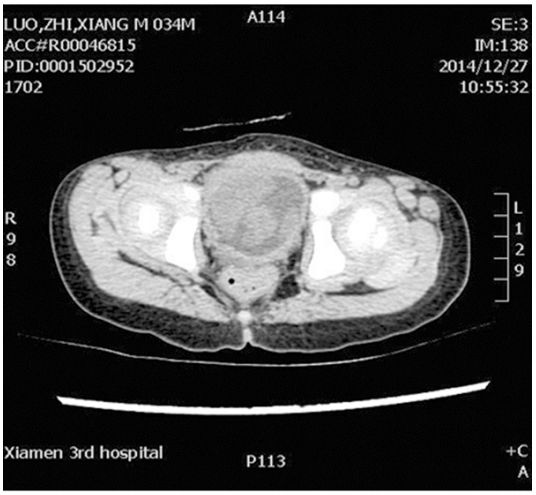

Figure 1. Computed tomography with contrast enhancement for the patient with EWS. The scan showed a large abdominal mass localized in the bladder.

Case report

A child (boy; 2 years and 7 months old) was admitted at our hospital in December 2014 due to dysuria for the past one week. Past medical history was unremarkable. Computed tomography showed that the child had developed bladder occupation 12 days ago. The patient had no fever, emaciation, hematuria, or family genetic history. Body examination showed that the patient was conscious, with normal development both physically and mentally. The sizes of superficial lymph nodes were not large, and the patient had normal movements of trunk and limbs. No weight loss was registered. Routine blood parameters were normal. No distant metastasis was detected by chest computed tomography. Computed tomography revealed a large tumor measuring 7 cm in diameter at the base of the bladder. Enhanced scanning by computed tomography showed that arterial phase was significantly enhanced, and venous phase and muscle equilibrium phase were continuously enhanced (**Figure 1**). Cystoscopy showed a piece of mass on bladder neck and left wall blocked the bladder cavity, and the mass had mucous and smooth surface with grey color (**Figure 2**). Pathological examinations of the mass showed that the tumor cells had diffuse lamellar arrangement, with variable sizes. The cytoplasm was scarce and dyed pink. The nucleus showed round or oval shapes, with dust-like chromatin. Nuclear deviation was observed, the cytoplasm was eosinophilic, and no obvious nucleolus was visualized. In addition, pathological mitotic figures were observed (**Figure 3A**).

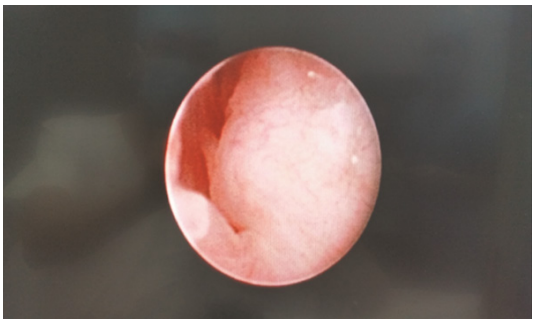

Figure 2. Cystoscopic examination of the bladder mass. Under the cystoscope, a solid smooth and pale tumor with the size of 6.0 cm × 5.5 cm occupied almost the whole bladder cavity.

Immunohistochemistry showed positive expression of CD99 (++) and Vim (**Figure 3B** and **3C**). The pathological diagnosis was small round cell malignant tumor. Morphology observation under light microscope, immunophenotyping and specific staining supported the diagnosis of classical EWS. Catheterization was performed on the patient to relieve dysuria. Chemotherapy was suggested but rejected by the parents of the patient after the condition of the patient was informed to them. Four months later, the patient died.

Discussion

PNET is a kind of malignant tumor in soft tissues and bones that are composed of small round cells. As the development of immunohistochemistry, more and more cases are reported. PNET is also found to occur in internal organs. By December 2014, a total of 14 cases of bladder EWS have been reported. Together with the case reported here, the ages of the 15 bladder EWS patients range from 2 years and 7 months to 81 years (average, 39.1 years). Although PNET/EWS is common in children, 13 out of the 15 cases are older than 14 years. Among the 15 patients, 9 are males and 6 are females. The clinical manifestations of bladder EWS include hematuria (8 cases; 57.1%), dysuria (7 cases; 42.9%), lower urinary tract irritation (2 cases), bilateral hydronephrosis (2 cases), lymphatic edema (1 case), lower abdominal mass (1 case), and lower abdominal pain (1

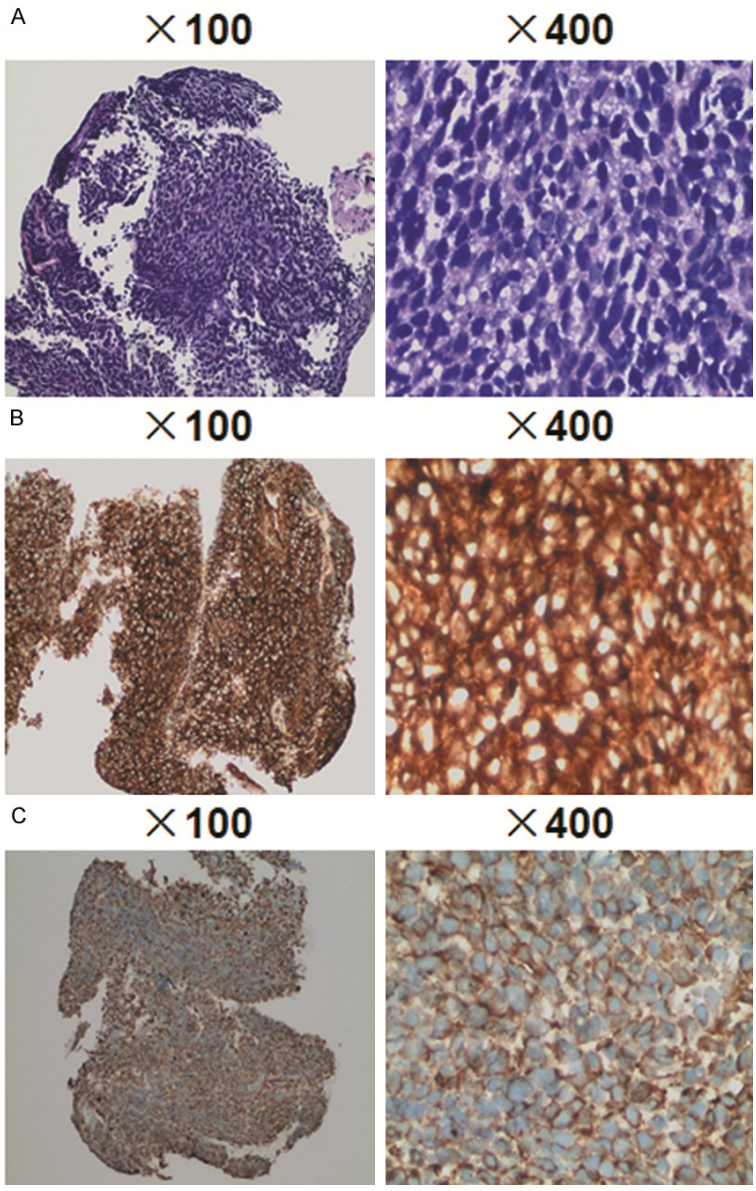

Figure 3. Histopathological examination of tumor tissue biopsy. (A) Hematoxylin and eosin staining showing the presence of sheets of small round blue cells that were separated by minimal desmoplastic fibrous stroma. (B) CD99 and (C) Vim immunostaining showing positive cytoplasmic staining in tumor cells.

case). These phenomena are local irritation and oppressive symptoms caused by rapid growth of the mass. At the time of diagnosis, 5 cases already have metastasis into external tissues of the bladder, such as prostate, seminal vesicle gland, uterus, and rectum. Two cases have ureteral obstruction induced by compression. Only one case has shown distant metastasis in the lungs. Four cases have radical total resection of bladder, three cases have partial resection of bladder, four cases have received transurethral resection of bladder tumor and 9 cases have undergone chemotherapy (vincristine + doxorubicin + cyclophosphamide and ifosfamide + etoposide). Among the reported 14 cases, 8 cases were followed up. The follow-up results show that one case has survived for 3 years and is still alive [14], and two cases have survived for 18 months. Among the remaining 5 patients, two cases died 2-3 weeks after diagnosis due to metastasis [10, 12], one case died 2 weeks after transurethral resection of bladder tumor and bilateral nephrostomy [13], one case died 4 months after diagnosis [19], and one case died 22 months after total resection of bladder [16].

The cells of PNET have round or oval shapes, with mitotic phase being easily observed. PNET tumor cell types are uniform, the cytoplasm is scarce and basiphilic, and nucleolus is blurry or absent. The arrangement of the cells is nest or leaf shape, which is separated by fibrous tissue vessels, and the center of the cells is usually necrotic region [3, 4, 13]. These histological shapes are difficult to be distinguished from those of other small cell malignant tumors, and immunohistochemistry is usually necessary for the diagnosis. The immunohistochemical staining of PNET shows positive CD99, vim and CD177 expression. Sometimes, PNET tissues are accompanied by local focus positive expression of cytokeratin AE1 or AE3. However, negative expression of smooth muscle actin, chromogranin, epithelial membrane-like antigen, desmin, and leukocyte antigen antibody [14]. These manifestations can help distinguish PNET cells from neuroendocrine carcinoma, lymphoma and melanoma [21]. Although the positive immuno-

histochemical expression rate of CD99 in PNET is more than 95% [22], its expression is not specific for PNET. Some lymphoblastic lymphoma, poorly differentiated synovial sarcoma and rhabdomyosarcoma also have positive expression of CD99 [23].

Cell biology and molecular genetics studies show that the occurrence of PNET/EWS is closely associated with chromosomal translocations, with more than 85% showing t [11, 22] (q24;q12) abnormal karyotype, which is the result of the fusion of EWS gene (located at 22q12) with FLI-1 gene (located at 11q24). In addition, about 10% NET/EWS cases show t [21, 22] (q22;q11) karyotype, which is the result of the fusion of EWS gene with Ets-related gene [24]. Fusion genes produced by chromosome translocations have stable structures, and tumor specificity. Therefore, EWS translocation gene test combined with FLSH is of great value in the clinical diagnosis of PNET/EWS [25].

Currently, surgical resection is the primary method for the treatment of PNET/EWS. Patients with tumor foci that can be completely resected should receive the surgery. Early and complete resection of the tumor can reduce local recurrence and metastasis, eliminate drug-resistant tumor cells, and help to enhance the effectiveness of postoperative chemotherapy. Chemotherapy is a supplementary treatment in addition to surgery for adults, but is debatable for child patients. The efficacy of chemotherapy for PNET/EWS is already proven, and novel adjuvant chemotherapy can increase resection rate. In a case report, the size of bladder mass on a ten-year-old patient was decreased from 14 cm × 13 cm × 13 cm to 4.7 cm × 3.4 cm × 3.3 cm after three courses of novel adjuvant chemotherapy (vincristine + doxorubicin + cyclophosphamide and ifosfamide + etoposide), after which the mass in bladder was resected [20]. Recent studies show that EWS/FLI-1 can cause abnormal activation of cyclin dependent kinase and the deactivation of its inhibitors, which may be a key reason for the uncontrolled proliferation of EWS cells. It is already proven that inhibition of cyclin dependent kinase can induce the apoptosis of tumor cells and thus, cyclin dependent kinase may become a potential target in the treatment of EWS [26]. In conclusion, bladder EWS is a kind of rare malignant soft tissue tumor that occurs in neural ectoderm of bladder. Preoperative diagnosis is dependent on histological, pathological and immunohistochemical examinations, especially the determination of EWS translocation gene. Complete resection, accompanied with chemotherapy and radiotherapy, may prolong the survival duration of patients with EWS.

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Disclosure of conflict of interest

None.

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