

## Case Report

# Primitive neuroectodermal tumor of the posterior urethral: a case report and literature review

Xinming Hu<sup>1</sup>, Xianping Che<sup>1</sup>, Jingzhu Xiao<sup>1</sup>, Zhihua Wang<sup>2</sup>, Hui Zhu<sup>3</sup>, Zhiquan Hu<sup>2</sup>

<sup>1</sup>Department of Urology, Hainan Provincial Nongken General Hospital, Haikou, PR China; <sup>2</sup>Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, PR China;

<sup>3</sup>Department of Urology, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH

Received May 27, 2016; Accepted August 3, 2016; Epub September 15, 2016; Published September 30, 2016

**Abstract:** Primitive neuroectodermal tumor in adults is extremely rare. It belongs to the Ewing's sarcoma family that usually occurs in children and adolescents with a predilection for the truncal and axial soft tissue. Primitive neuroectodermal tumor of the posterior urethra is even less common with no prior reported cases in the English-language literature. We reported here a case of primitive neuroectodermal tumor of the posterior urethra with local bladder wall invasion and distant pulmonary metastasis in a 49-year-old man. The patient's treatment and clinical outcome were examined with literature review for the management of primitive neuroectodermal tumor in general with emphasis on its management in the genitourinary tract.

**Keywords:** CD99/CD56, Ewing's sarcoma, urethral, diagnosis, treatment

## Introduction

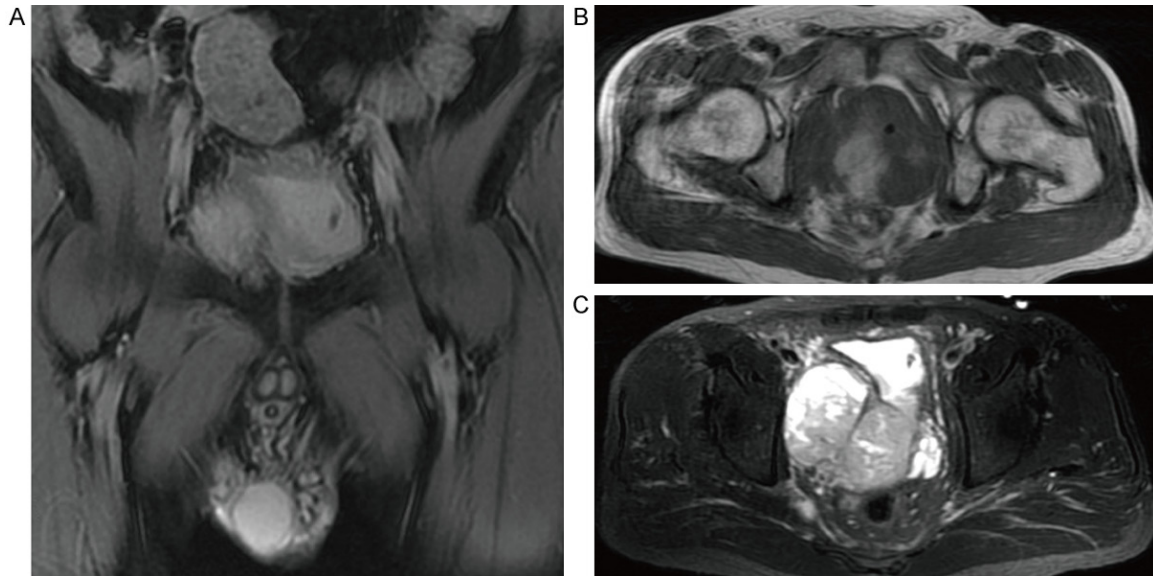
Primitive neuroectodermal tumor (PNET) is a rare cancer in general. It is a neural crest tumor that belongs to the Ewing's sarcoma (ES) family and usually occurs in children and adolescents with a predilection for the truncal and axial soft tissue. Primitive neuroectodermal tumor occurs even less frequently in adults [1]. Until now, only sporadic cases have been reported to occur in the lung, posterior mediastinum, and other extra-thoracic localizations such as the breast or the pancreas. Only case reports have been published for its occurrence in the genitourinary tract. On the other hand, the primary tumors arising from the posterior urethra are also rare, and most of them are urothelial or squamous cell carcinomas in nature. In fact, no primitive neuroectodermal tumor of the posterior urethra had even been reported in the English-language literature according to our recent Medline search. In this case report, we reported an adult case of primitive neuroectodermal tumor arising from the posterior urethra with both bladder wall invasion and distant pulmonary metastasis. The patient's clinical out-

comes to cyclophosphamide, adriamycin, and vincristine/ifosfamide-etoposide (CAV/IE) chemotherapy was examined with a literature review on its management in general. Special emphasis was put on its clinical presentations and management in the genitourinary tract.

## Case report

The patient was a 49-year-old man with family history significant for prostate cancer was admitted because of hematuria, dysuria, and the pain on right lower limb. Prior to the admission, he had undergone cystoscopy examination twice and a transurethral resection of a urethral tumor at a local hospital about one year earlier. The histopathology examination at the local hospital suggested inflammatory granuloma arisen from the prostatic posterior urethral according to the pathology report.

Upon admission, the patient's serum lactate dehydrogenase (LDH) and neuron-specific enolase (NSE) levels were markedly elevated to 347.0 U/L and 18.96 ug/L, respectively. His serum alkaline phosphatase, prostate specific

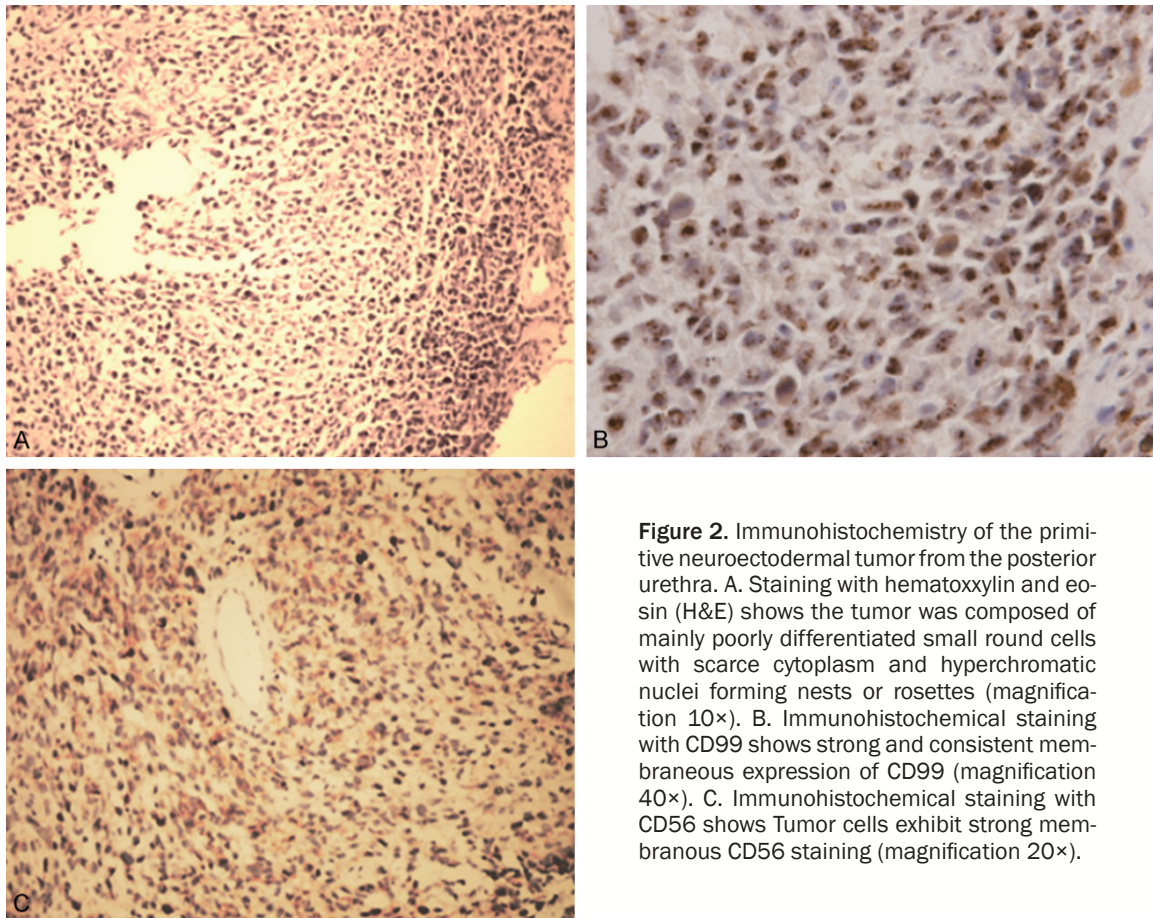


**Figure 1.** As shown from (A to C), this tumor expressed intermediate or high signal intensity in both T1- and T2-weighted images, while the wall of bladder and prostatic urethra expressed intermediate intensity on the T1-weighted MR images and high intensity on the T2-weighted ones. (A) Coronal thin-slice MRI reconstruction demonstrates a large pelvic mass of 9 cm×6 cm in the maximal dimensions arising from the posterior urethra with infiltration to the posterior wall of the bladder. (B) Axial T1 weighted MRI shows an lesion near to bladder, which heterogeneously expressed high signal intensity while the wall of bladder and prostatic urethra expressed intermediate intensity. (C) Axial T2-weighted MRI shows the lesion expressed high intensity.

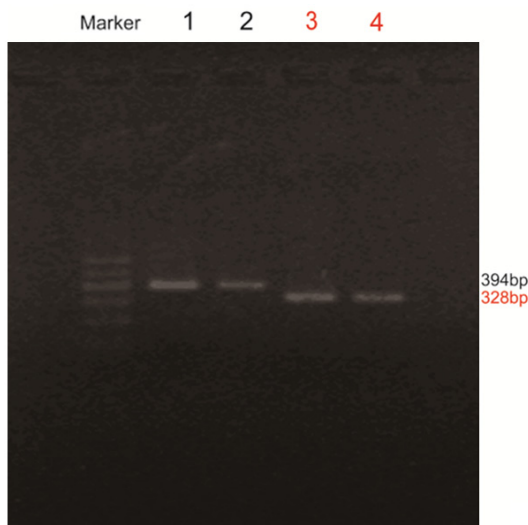
antigen (PSA), alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA) levels were within normal limits. The magnetic resonance imaging (MRI) of the abdomen and pelvis revealed a large pelvic mass of 9 cm×6 cm in the maximal dimensions arising from the posterior urethra with infiltration to the posterior wall of the bladder (**Figure 1**). In addition, both the bladder and the prostatic urethral walls were noted to be thickened. No lymphadenopathy was noted in the pelvis and inguinal region. His bone scintigraphy revealed no distant metastasis. His computed tomography of the chest demonstrated multiple lesions involving both lungs with the maximum dimension up to 1.5 cm, which were consistent with metastatic disease radiographically. However, no histological examination of the pulmonary lesions was obtained because the patient refused lung biopsy. The patient subsequently underwent transurethral resection of the posterior urethral tumor in order to control the hematuria, relieve the bladder outlet obstruction, and obtain specimen for pathological diagnosis. The histological examination of the acquired specimen with H&E stain revealed that the tumor was composed of mainly poorly differentiated small round cells with scarce cytoplasm and hyperchromatic

nuclei forming nests or rosettes (**Figure 2A**). Immunohistochemical staining of the specimen showed strong and consistent membranous expression of CD99 and CD56 and strong cytoplasmic staining for vimentin (**Figure 2B, 2C**). The staining for CgA, PCK, CK5/6, CK7, CEA, Syn and PSA were largely negative with the exception of the CgA staining, which was weakly positive in some of the tumor cells. The radiological and pathological examinations, including the immunohistochemical findings, led to the diagnosis of a primitive neuroectodermal tumor of the posterior urethra. To confirm this diagnosis, a EWS-FLI-1 fusion transcript was detected by nested reverse transcription polymerase chain reaction (RT-PCR) in the formalin-fixed and paraffin-embedded tumor tissues (**Figure 3**). In brief, total mRNAs were firstly extracted according to the method published in Stanta and Schneider [2], which was then reverse-transcribed into cDNA. Nested PCR was performed as QI-XING GONG et al. described [3]. The positive results confirmed the diagnosis of PNET/ES arising from the posterior urethra.

Based on the pathological diagnosis and clinical staging, the patient was initially treated with



**Figure 2.** Immunohistochemistry of the primitive neuroectodermal tumor from the posterior urethra. A. Staining with hematoxylin and eosin (H&E) shows the tumor was composed of mainly poorly differentiated small round cells with scarce cytoplasm and hyperchromatic nuclei forming nests or rosettes (magnification 10×). B. Immunohistochemical staining with CD99 shows strong and consistent membranous expression of CD99 (magnification 40×). C. Immunohistochemical staining with CD56 shows Tumor cells exhibit strong membranous CD56 staining (magnification 20×).



**Figure 3.** The analysis of PNET/ES by Reverse transcription polymerase chain reaction (RT-PCR). A EWS-FLI-1 fusion transcript was detected by reverse transcription polymerase chain reaction (RT-PCR). A 394 base pair (bp) and 328 bp product are detected, corresponding to fusion transcripts of EWS-FLI1 gene (lane M size marker, lanes 1 and 3 current case, lanes 2 and 4 Ewing cell line as a positive control).

4 cycles of chemotherapy using alternating Vincristine-Adriamycin-Cyclophosphamide and Ifosfamide-Etoposide according to the framework of the Indiana University Ewing tumor studying [4]. Briefly, cyclophosphamide 1200 mg/m<sup>2</sup>, adriamycin 75 mg/m<sup>2</sup>, and vincristine 2 mg were administered intravenously on the first day. They were then alternated with ifosfamide 1.8 g/m<sup>2</sup> for 5 days plus etoposide 100 mg/m<sup>2</sup>. Each course would take three weeks to complete. After three cycles of administration of CAV/IE, the patient developed new onset of pain on right lower limb and dysuria again. MRI and CT scan showed local disease recurrence and metastasis to the brain. The patient underwent hospice care and expired from respiratory failure two months later.

## Discussion

Primitive neuroectodermal tumor is a neuron-derived small round-cell tumor and belongs to the Ewing's sarcoma family [5]. Ewing sarcoma, which primarily occurs in bones, is an uncommon neoplasm in soft tissues. It had been



reported that only approximately 20 new cases are registered per year in Japan [6]. Primitive neuroectodermal tumors, which develop in the soft tissues, are therefore more rarities. Currently, only a few cases of soft tissue primitive neuroectodermal tumors had anecdotally been reported. Moreover, among these reported cases, most of them were between 10 and 30 years old and usually occurred in the chest wall, para-vertebral muscles, the buttocks muscles, and the retroperitoneal space. To our knowledge, no case of posterior urethral primitive neuroectodermal tumors was reported (last search Medline on Apr 5, 2011). It is therefore highly remarkable for a 49-year-old patient to develop primitive neuroectodermal tumor of the posterior urethra.

Because the primitive neuroectodermal tumor develops in soft tissues away from critical organs, thus the symptoms often appear late in the course of the disease, and are frequently not specific. This may account for the often delayed diagnosis of primitive neuroectodermal tumor. The CT and Magnetic Resonance Imaging (MRI) can be helpful to the diagnosis and staging of the primitive neuroectodermal tumor through their anatomical findings. In CT scan, the primitive neuroectodermal tumor usually has a large soft-tissue component without calcification and lymphadenopathy and the soft-tissue component generally tends to displace, rather than encase, the adjacent organs [7, 8]. In addition, the primitive neuroectodermal tumor usually shows non-enhancing necrotic areas and has only moderate enhancement after intravenous contrast administration [7]. The magnetic resonance imaging usually demonstrates a mass with high signal intensity on T2-weighted images, and intermediate or high signal intensity on T1-weighted images [7].

The definitive diagnostic method for primitive neuroectodermal tumor is usually obtained through excisional biopsy. Histologically, the primitive neuroectodermal tumor appears as a highly cellular tumor composed of sheets of uniform small round. The tumor cells frequently express CD99, a glycoprotein expressed on the cell surface, which is the product of the MIC2 gene. It is considered to be a marker for the diagnosis of primitive neuroectodermal tumor [9]. Likewise, CD56, a neural cell adhesion molecule, is also frequently expressed at a high level on most of the tumor cells. It has also

been suggested that PNET is expressed at a high level for tumors with positive CD56 expression, especially among adult patients [10]. In addition, because the nonrandom chromosomal translocations and gene rearrangements between the *ews* gene on chromosomes 22q12 and 11q24 occurs in approximately 80% of the primitive neuroectodermal tumors, EWS-FLI1, the fusion protein, can be used as a clue to diagnosis of the primitive neuroectodermal tumor [11]. The patient's immunohistochemistry staining revealed heterogeneously positive results for both the CD56 and CD99, as shown in **Figure 2**. These results, together with the presence of the fusion protein EWS-FLI1 confirmed by RT-PCR, were consistent with the diagnosis criteria for primitive neuroectodermal tumor. Because of its rarity, the pathology was probably misdiagnosed initially at the local hospital with the typical "small round cells" confused as "the white cell".

As a member of the Ewing's sarcomas' family, the primitive neuroectodermal tumor is an extremely aggressive tissue neoplasm and surgical resection is considered to be the only definitive treatment [12]. Once the tumor recurrence or metastasis occurs, most patients die within one year. Though a standardized treatment strategy for the primitive neuroectodermal tumor has not been established, accumulated data had showed that intensive chemotherapy combined with local tumor control can contribute to improved survival [13]. Some had reported that the international chemotherapy protocol with CAV/IE for primitive neuroectodermal tumor could improved the outcome of localized unresectable primitive neuroectodermal tumor arising from the bone or soft tissues [4]. However, in our present case, the palliative resection combined with chemotherapy regimen failed to control the progression of disease.

Till now, no more than 100 cases of genitourinary PNETs, involving kidney, bladder, prostate, ureter, and seminal vesicle, have ever been reported (last search Medline on Apr 5, 2011). None of them involved urethra. According to the literature, the clinic presentations of genitourinary PNETs were highly variable and not always specific to voiding symptoms, such as gross hematuria or urinary retention. However, the reported treatment strategies for genitourinary PNETs were similar and mainly consist of a

combination of surgery for local control and chemotherapy for metastatic diseases. Radiotherapy is reserved for inoperable tumors or those not responsive to neoadjuvant chemotherapy

In summary, primitive neuroectodermal tumor is an extremely aggressive cancer. Once it can not be fully resected surgically, the outcome would expect to be poor even with extensive chemotherapy.

## Acknowledgements

This work was supported by the Natural Science Foundation of China (No. 81200353).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Zhiquan Hu, Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China. Tel: +86-13971656164; Fax: 089866808281; E-mail: huzhiquan2000@163.com

## References

- [1] Borden EC, Baker LH, Bell RS, Bramwell V, Demetri GD, Eisenberg BL, Fletcher CD, Fletcher JA, Ladanyi M, Meltzer P, O'Sullivan B, Parkinson DR, Pisters PW, Saxman S, Singer S, Sundaram M, van Oosterom AT, Verweij J, Waalen J, Weiss SW and Brennan MF. Soft tissue sarcomas of adults: state of the translational science. *Clin Cancer Res* 2003; 9: 1941-1956.
- [2] Adams V, Hany MA, Schmid M, Hassam S, Briner J and Niggli FK. Detection of t(11;22) (q24;q12) translocation breakpoint in paraffin-embedded tissue of the Ewing's sarcoma family by nested reverse transcription-polymerase chain reaction. *Diagn Mol Pathol* 1996; 5: 107-113.
- [3] Gong QX, Fan Q, Zhang Z and Zhang W. Detection of EWS-FLI1 fusion transcripts in paraffin embedded tissues of peripheral primitive neuroectodermal tumors by nested reverse transcription polymerase chain reaction. *Chinese Journal of Clinical and Experimental Pathology* 2005; 21: 4.
- [4] Ehrlich Y, Beck SD, Ulbright TM, Cheng L, Brames MJ, Andreoiu M, Foster RS and Einhorn LH. Outcome analysis of patients with transformed teratoma to primitive neuroectodermal tumor. *Ann Oncol* 2010; 21: 1846-1850.
- [5] Scurr M and Judson I. How to treat the Ewing's family of sarcomas in adult patients. *Oncologist* 2006; 11: 65-72.
- [6] Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. *Jpn J Clin Oncol* 2007; 37: 79-89.
- [7] Hari S, Jain TP, Thulkar S and Bakhshi S. Imaging features of peripheral primitive neuroectodermal tumours. *Br J Radiol* 2008; 81: 975-983.
- [8] Li X, Zhang W, Song T, Sun C and Shen Y. Primitive neuroectodermal tumor arising in the abdominopelvic region: CT features and pathology characteristics. *Abdom Imaging* 2011; 36: 590-5.
- [9] Okada Y, Kamata S, Akashi T, Kurata M, Nakamura T and Kihara K. Primitive neuroectodermal tumor/Ewing's sarcoma of the urinary bladder: a case report and its molecular diagnosis. *Int J Clin Oncol* 2011; 16: 435-8.
- [10] Nagaya T, Tanaka N, Kamijo A, Joshita S, Nakazawa K, Miyabayashi H, Yoneda S, Ito T, Komatsu M, Tanaka E and Kitano K. Primitive neuroectodermal tumor as a differential diagnosis of CD56-positive tumors in adults. *Intern Med* 2009; 48: 1267-1272.
- [11] Bernstein M, Kovar H, Paulussen M, Randall RL, Schuck A, Teot LA and Juergens H. Ewing's sarcoma family of tumors: current management. *Oncologist* 2006; 11: 503-519.
- [12] Ellinger J, Bastian PJ, Hauser S, Biermann K and Muller SC. Primitive neuroectodermal tumor: rare, highly aggressive differential diagnosis in urologic malignancies. *Urology* 2006; 68: 257-262.
- [13] Masui F, Ushigome S, Kamitani K, Asanuma K and Fujii K. Chondroblastoma: a study of 11 cases. *Eur J Surg Oncol* 2002; 28: 869-874.