

Clinicopathological study of primary renal primitive neuroectodermal tumor

Ruijin Zhou*, Tao Du, Zhonghua Liu, Xiangyang Wang

Henan Provincial People's Hospital, Department of Urology, Zhengzhou, Henan, 450003, China

*Email: zhouruijin@163.com

Abstract: Objective To investigate the clinicopathological feature, immunological phenotype, therapy and prognosis of primary renal primitive neuroectodermal tumor (primitive neuroectodermal tumor, PNET). **Method** To report diagnose and treat condition of a child with renal PNET and review relevant literature. **Result** The male patient aged 13 years old. Color-ultrasound found 3.5 cm × 3.0cm mass of left kidney; CT scan showed edge-cleared equal low density shadows. Before the operation, implement aspiration biopsy under the guidance of CT, and the pathological report showed the Wilms' tumor; implement retroperitoneal left radical nephrectomy. Under light microscope, the formats of oncocyte are consistent that small round or oval shape. The oncocyte was separated into solid sheet or nest by fibrillar connective tissue, form Homer-Wright rosettes and caryokinesis was common. Immunohistochemical markers: CD99, synaptophysin and vimentin were positive, and all diagnosed as PNET. Implement chemotherapy after operation, and followed up for 8 months without recurrence. **Conclusion** Renal PNET is a rare highly aggressive soft-tissue tumor, which has specific clinicopathologic features and expresses MIC2 gene product CD99. Diagnosis is mainly based on pathomorphological features and immunohistochemical markers. Main treat method is the combination of excision with radiotherapy and chemotherapy.

[Ruijin Zhou, Tao Du, Zhonghua Liu, Xiangyang Wang. Clinicopathological study of primary renal primitive neuroectodermal tumor. *Life Sci J* 2014; 11(1): 312-316]. (ISSN:1097-8135). <http://www.lifesciencesite.com> 47

Key words: primitive neuroectodermal tumor; kidney; immunohistochemistry

1. Introduction

Primitive neuroectodermal tumor(PNET) is a cancer that composed by differentiation potential small round cell and stemmed from neuroderm. The disease may occur in all parts of body that more common in chest wall, head and neck, spine and limbs, but may occur in adrenal gland, uterus, ovary and other parts, and rare in urinary system [1]. Among them renal primitive neuroectodermal tumor is relatively common. This paper analyzes the clinicopathology of renal PNET of 1 case patient from our hospital to improve the knowledge of this disease.

2. Case report

The male patient aged 13 years old that had been admitted to hospital without indication in March, 2013 for physical examination found mass in right kidney. B-scan showed the normomorph of right kidney, 3.5cm×3.0cm echo mass in inferior pole of left kidney, and no significant internal blood flow signal. CT scan found tumor located in dorsal inferior pole of left kidney, plain scan showed renal parenchyma equidensity rounded lumps (figure1), enhancement scan showed uniformed low density parenchymatous mass (figure 2).

Preoperative aspiration biopsy pathological reported nephroblastoma, implement retroperitoneoscopy left radical nephrectomy.



Figure 1. CD plain scan of the equally-density mass in dorsal left kidney

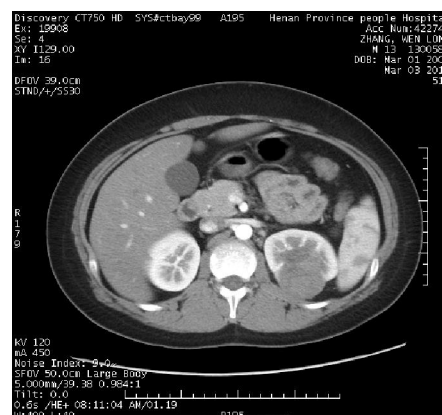


Figure 2. Enhancement scan shows uniformed low density parenchymatous mass in left kidney

3. Postoperative pathology

Generally, tumor tissue specimen sections present gray-white, fish-meat like appearance, clear edge, and brittle texture. Routine HE staining, microscopic appearance is that tumor cell is lamellar growth, separated by thicker fiber, composed by form relatively consistent small round cells that lack cytoplasm, and Homer-Wright rosettes can be seen (Figure 3 and 4). Hyperchromatic nucleus is round. There are pervaded chromatin and micronucleolus within some tumor cell, and mitotic figure. Immunohistochemical phenotype (using the two-step SP) positively express Vimentin (Figure 5), CD99 (Figure 6). Ki67 positive rate is about 40 % (Figure 7), and SYN expresses negatively. Postoperative chemotherapy used Nedaplatin 30mg and etoposide 100mg that five days a course respectively. Treatment last for 6 courses, and no tumor recurrence was found within 6 months' follow-up visit.

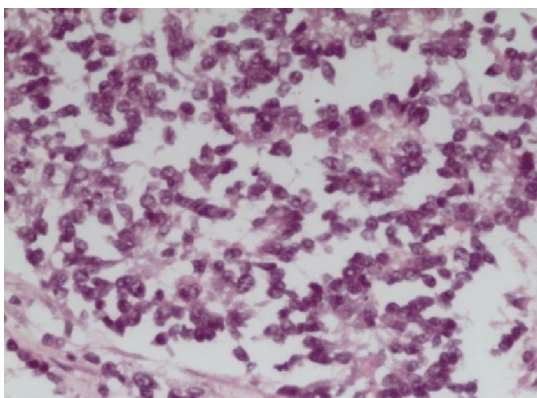


Figure 3. format relatively consistent small round cells and Homer-Wright rosettes HE× 200

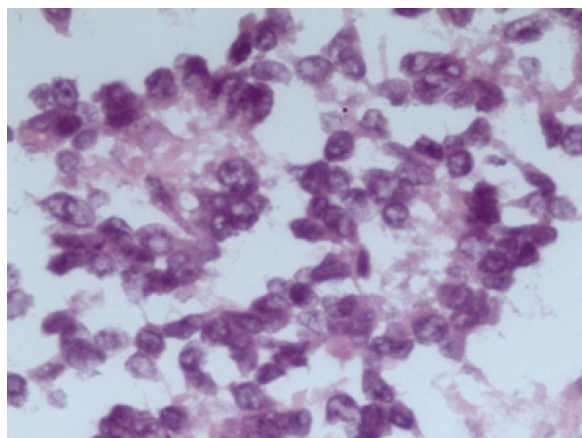


Figure 4. small round cells and Homer-Wright rosettes HE×400

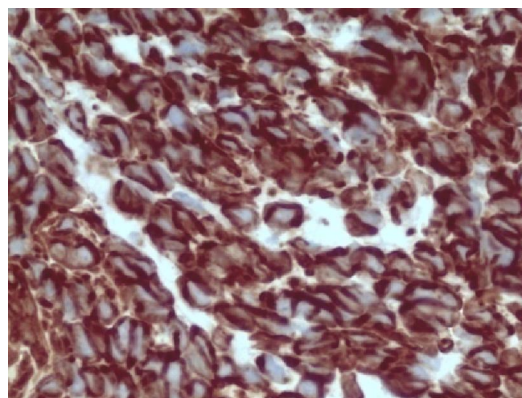


Figure 5. tumor cells vimentin staining were pervaded positive, expression parts were in cell membrane SP×400

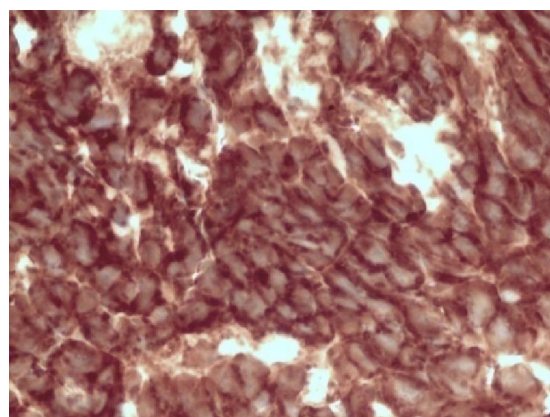


Figure 6. tumor cells CD99 staining were pervaded positive, expression parts were in cell membrane SP×400

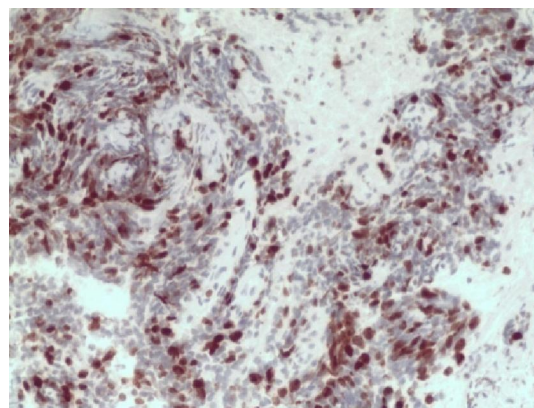


Figure 7. tumor cell nucleus Ki67 staining were positive SP×400

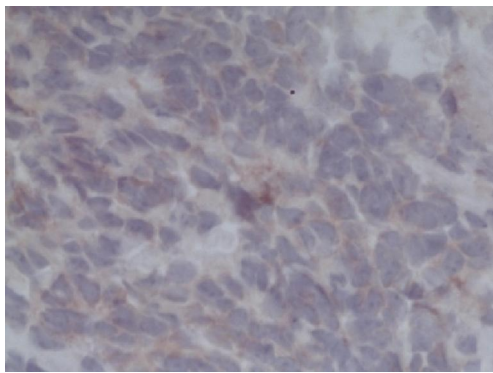


Figure 8. tumor cell SYN staining were positive
SP×400

4. Discussion

Stout firstly reported the case of primitive neuroectodermal tumor in 1918, and the pathology was that the tumor was composed by small round cells and rosettes. Hart and Earle firstly described the definition of primitive neuroectodermal tumor in 1973[2]. PNETs may occur in all age, but more common before 35 years old with an mean age 20 years old that more common in male. This disease, based on different occurrence sites, was divided into central PNET (c-PNET) and peripheral PNET (p- PNET) in which peripheral PNET is more common. In 2007, for morphological and histological similarity, WHO central nervous system tumor classification classified p-PNET and Ewing sarcoma family as one class which was called ESFT or pPNET(Ewing's sarcoma family tumors/peripheral PNET) that including skeletal Ewing sarcoma, extraskeletal Ewing sarcoma, peripheral nerve epithelioma or peripheral primitive neuroectodermal tumor, and Askin tumor[3]. Mainly occur in parts that outside the spinal axis, pPNET is common in buttock and upper leg, shoulders and upper limb. A few pPNET may occur in parenchymal organs, and rare in urinary system. In 1975, the first renal PNET was reported [1]. Then in 1997, vesical pPNET was reported[4]. Followed that, other parts' primitive neuroectodermal tumor of urogenital system were reported, which included kidney, ureter, bladder, testis, penis, etc [5-7].

4.1 Tissue origin and cytogenetics

Currently, the histogenesis of ESFT or pPNET were mainly considered including neural crest cells, original stromal cells, within marrow cavity or commonly considered existing in prepattern interstitial cell of soft tissue. But the origin nature of PNET was that chromosomal abnormality and gene regulation disorder lead to the primitive stem cells differentiate to epithelial tissue and mesenchymal tissue. About 85 percent of PNET has t(11;22)(q24;q12) ectopia, that is EWS gene (located in 22q12, encoding RNA binding domain) 5'end fused with FLI1 gene (located in 11q24, the transcription factor ETS family member of DNA

3'end, thus generated fusion gene EWS-FLI1. Besides, about 10 percent PNET can see t (21; 22) (q22; q12), namely the 5'end of chromosome 22's EWS gene fused with chromosome 21 ERG gene's 3'end. 50 percent of cases detected secondary chromosome mutations which are mainly short arm (1q) of chromosome 1 and chromosome 8, 12's amplification; moreover, there were rare chromosome ectopic t(17;22)(q12;q12)、t(2;22)(q33;q12) and t(7;22)(p22;q12) , that is EWS gene fused ectopically with chromosome 17's E1AF gene, chromosome 2's FEV gene, and chromosome 7's ETV1 gene respectively. The expression products of these fusion genes play important role in the occurrence of PNET. The fusion protein FLI1 of EWS-FLI1 expression was regard as PNET's specific markers, but the literature reports were significantly different. Abnormal genes changes can be confirmed by antisense PCR or FISH. Some scholar believed that the diagnosis of PNET should be reserved, although the fusion gene did not be detected. And the bases were: (1) Thomer, and etc considered that when the detection results of immunohistochemistry and fusion gene were contradictory, the diagnosis based on immunohistochemistry was superior to genetic phenotypes. (2) Mhaweche-Fauceglia, and etc also believed that when CD99 or FLI1 was positive, but fusion gene was not detected, the diagnosis of PNET should still be reserved; and only when CD99 or FLI1 was negative and fusion gene was not detected, PNET can be excluded.

4.2 Clinical manifestation and imaging feature

The age of onset of renal PNET is younger that often occurred in children and teenager, and 75 percent was 10-39 years old [1]. Based on the different occurrence site, tumor size, whether invaded the surrounding organ, and whether transfer, the common clinical manifestation of renal PNET is waist and abdominal pain and the patients involved the collecting ducts are gross hematuria visible. This case of patient was accidentally found by physical examination for fever. CT plain scan showed edge clear or not clear equidensity shadow or equal low density shadow; MRT plain scan showed that T1WI presented equal signal or low signal, T2WI presented high signal or heterogeneous high signal, the substantial part that had enhanced scan presented significant strengthening.

4.3 Pathological features

Although PNET and Ewing sarcoma had same call morphological feature, their neural differentiation degrees were essentially different that PNET expresses at least 2 kinds of neural differentiation antigen, but Ewing sarcoma is rarely express. The pathological features of PNET were that massive format consistent primitive small round cells; hyperchromatic nuclei, easily found mitotic figure, obvious atypia; the cells were round, oval, or short

shuttle-like, and cytoplasm less. Small focal necrosis and laminar necrosis could be seen in some tumor. There were abundant of fibrovascular intervals. Around the blood vessels, the tumor cells presented false rosettes, and intimal boundary or basement membrane. The center of the cells was filamentous fibers, no cavity, blood vessel or sphacelus of oncocyte, that were Homer-Wright rosettes which were characteristic features of PNET. Immunohistochemistry was the main means of PNET's confirmation. The diagnostic criteria were CD99 expressed positive, and more than two kinds of different neural markers' (like NSE, Syn, Vim, EMA, etc) express. Based on statistics, 30% to 70% percent patients appeared Homer-Wright rosettes, thus the diagnosis of PNET could not only based on Homer-Wright rosettes under light microscope, but combine with immunohistochemical examination.

4.4 Differential diagnosis

The histology manifests of PNET were small round cell tumors, lacking specificity, thus need to make identification with a series of morphology similar small round cell malignant tumors. (1) Small cell neuroendocrine carcinoma: the tumor cells presented ovoid or short shuttle-like morphology, less cytoplasm, hyperchromatic nuclei, coarse chromatin, common mitotic figure, common extrusion, rosettes structures were also visible. It is the very one of tumors that need to be identified with PNET. The immunohistochemical expression neural marker CD99 expressed positive occasionally, but weaker than PNET, and CK, TTF-1 positive, diffuse infiltrative growth pattern and etc can facilitate the identification with PNET. (2) Lymphoma: it is primarily identified with lymphoblast type. It was round or oval, diffuse distribution, less cytoplasm, nucleus round or distorted, small nucleoli seen; immune markers: tumor cells LCA, TdT positive, CD3 or CD20 and others positive; neural markers negative can be identified with PNET. (3) Neuroblastoma: it was common among children, and often occurred in the adrenal gland, sympathetic ganglion, and posterior mediastinum. The tumor cell was small round, the nucleus was round or oval, chromatin was rough blocks, and rosettes were visible. The neural markers were positive, CD99 and vimentin were negative. (4) Rhabdomyosarcoma: tumor cells were composed by small myoblast cells in different developmental stages, some areas of the cells may occur muscle differentiation, nuclei hyperchromatic and deviation. Myogenic markers desmin, MyoD1, myoglobin and actin positive and neural markers s-100 and NSE negative can be identified. (5) Malignant melanoma: tumor cells were diffuse distribution, diverse shapes; within the cells can have rich pigment or no pigment. HMB45 and melan-A was positive, neural markers were negative. Examination by electron microscope can

see that melanosome in different developmental stages. (6) Desmoplastic small round cell tumor: small round cells were nested distribution, surrounded by apparent hardening of fibrous interstitial septation; immunohistochemical epithelial, muscular, neural markers Vimentin, CK, EMA, Desmin, NSE expressed positive, and t (11; 22) (p13; q12) chromosome ectopic was the cell cytogenetic features [11]. (7) Nephroblastoma: under the microscope, the tumor had three main basic ingredients: undifferentiated germ tissues, mesodermal interstitial and epithelial components. The undifferentiated germ tissues mainly were small round cells, which with less and transparent cytoplasm; the cells arranged in variety ways: diffuse, nodular, ribbon-like and basal cell sample arrangement. Some cells showed the kind of neuroblastoma rosettes like arrangement, and some showed tubular cells arrangement in a single layer. This patient was pathologically diagnosed nephroblastoma by preoperative aspiration biopsy, and PNET postoperatively. From above showed PNET is difficult to diagnose, especially the biopsy specimens that need to do variety of immune markers and fusion gene detection. This tumor will be considered after the exclusion of other malignant tumors, and it can be finally confirmed after surgical specimens.

5. Treatment and Prognosis

For renal PNET is extremely rare, its treatment always refer to Ewing's sarcoma. At present, the main treatments were radical resection, radiotherapy and/or chemotherapy. PNET was highly invasive, easy to recurrence and metastasis. Like other sarcomas, the metastasis of PNET was hematogenous metastasis, and metastasis was more common in bone, lung, and liver. Approximately 25%-50% cases had distant metastasis when have the initial diagnosis, which resulting in significant shorter of survival time, 5-year survival rate <25%, while ≤70% patients with localized lesions get cured. Rodriguez-Gatindo etc. [11] believed that the kidney PNET and extrarenal PNET have poor prognosis, and renal PNET with tumor thrombus in vessel has a worse prognosis. Gao Qiqi etc. [12] reported two cases of renal PNET, respectively dead after operation 14 months and 6 months. As clinical stages were the main prognostic factor, screening metastases in bone, lung, and liver will facilitate the determining patients' prognosis and confirming treatment options.

In short, PNET is a rare highly invasive tumor, and particularly rare seen in the kidney. The clinical presentation has no specificity, and diagnosis is mainly dependent on the pathological, immunohistochemical, and fusion gene detection. At present, the treatment is mainly treated with operation and chemoradiotherapy, but the prognosis is not optimistic.

***Corresponding Author:**

Ruijin Zhou,
Department of Urology,
Henan Provincial People's Hospital,
Zhengzhou, 450003, Henan, China
Email: zhouruijin@163.com

Reference:

- [1] Ellinger J, Bastian PJ, Hauser S, et al. Primitive neuroectodermal tumor: rare, highly aggressive differential diagnosis in urologic malignancies. *Urology*, 2006, 68:257-262.
- [2] Hart MN, Earle KM. Primitive neuroectodermal tumors of brain in children. *Cancer*. 1973, 32: 890-897.
- [3] Kampman WA, Kros JM, De Jong TH, et al. Primitive neuroectodermal tumors (PNETs) located in the spinal canal, the relevance of classification as central or peripheral PNET: case report of a primary spinal PNET occurrence with a critical literature review. *J Neurooncol*, 2006, 77:65-72.
- [4] Banerjee SS, Eyden BP, McVey RJ, et al. Primary peripheral primitive neuroectodermal tumour of urinary bladder. *Histopathology*, 1997, 30: 486-490.
- [5] Song HC, Sun N, Zhang WP, et al. Primary Ewing's sarcoma/primitive neuroectodermal tumor of the urogenital tract in children. *Chin Med J* 2012; 125(5): 932-936.
- [6] Kong LF, Liu ZG, Liu X, etc. Peripheral primitive immune phenotypic neural ectoderm tumor morphology and clinical prognosis. *Chinese journal of clinical oncology*. 2003, 30(9): 627-630.
- [7] Al-Najar A, Siggelkow M, Naumann CM, et al. Ewing's sarcoma of the urogenital tract. *Int Urol Nephrol* 2009; 41: 13-17.
- [8] Lopez-Beltran A, Pérez-Seoane C, Montironi R, et al. Primary primitive neuroectodermal tumour of the urinary bladder: a clinico-pathological study emphasising immunohistochemical, ultrastructural and molecular analyses. *J Clin Pathol*, 2006, 59: 775-778.
- [9] Angel JR, Affred A, Sakhuja A, et al. Ewing's sarcoma of the kidney. *Int J Clin Oncol*, 2010, 15: 314-318.
- [10] Sen s, Kashyap s, Thanikaachalam s, et al. Primary Primitive neuroectodermal tumor of the orbit. *J Pediatr Ophthalmol Strabismus*. 2002, 39(4): 242-244.
- [11] Zhou RJ, Liu ZH, Ji TY, etc. Clinicopathologic analysis of retroperitoneal promoting fibrous tissue proliferative small round cell tumor. *Chinese Journal of Urology*. 2002, 23(2): 108-110.
- [12] Rodriguez-Gatindo C, Marina NM, Fletcher BD, et al. Is primitive neuroectodermal tumor of the kidney a distinct entity? *Cancer*, 2000, 79: 2243-2250.
- [13] Gao QQ, Xiang H, Zheng YL, etc. Clinicopathologic analysis of urinary system of primary primitive neural ectoderm tumor. *Chinese Journal of Urology*. 2011, 32(7): 463-466.

1/20/2014