

Original Article

Clinical features of 12 cases with peripheral primitive neuroectodermal tumors of soft tissue

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Abstract: Objective: To clarify the clinical characteristics including basic data, imaging, and pathological features of peripheral primitive neuroectodermal tumors (pPNETs) in patients. Methods: A retrospective analysis was conducted on the clinical data of 12 pathologically-confirmed pPNETs patients treated in the Affiliated Hospital of Jining Medical University from January 2012 to December 2017. All the patients were examined by CT and MRI imaging, and the imaging findings were evaluated. The pooled tumor specimens were subject to routine H&E staining and immunohistochemical staining for observation of pathological features. Nine patients who had received surgical resection were followed for 1 year and their rates of tumor recurrence and metastasis were assessed. Results: Twelve enrolled patients had a mean age of 22.2 years (range, 8-50 years), with much more males than females (at a ratio of 2 to 1). The tumors were all pPNETs of soft tissue. The manifestations of pPNETs on computed tomography (CT) images showed uneven density nodules with necrosis and cystic changes, and heterogeneous enhancement mass. On MR images, the tumors were isointense or hypo-intense on T1-weighted image (T1WI), and isointense or hyper-intense on T2-weighted image (T2WI). The regions with tumor cystic degeneration or necrosis showed hypo-intense on T1W images and hyper-intense on T2W images. Typical Homer-Wright rosette forming was noted by H&E staining. The results of immunohistochemical staining demonstrated that the positive rates of CD99, neuron-specific enolase (NSE), Vimentin, synaptophysin (Syn), and S-100 proteins were 100%, 50%, 33.3%, 58.3% and 16.7%, respectively. After one-year follow-up, the recurrence rate of pPNETs was 33.3% and the metastasis rate was 25% in patients with surgical resection of pPNETs. Conclusion: pPNETs of soft tissue were not specific on CT and MRI images, and the definitive diagnosis was still dependent on pathological examination.

Keywords: Primitive neuroectodermal tumor, peripheral type, computed tomography, magnetic resonance imaging

Introduction

Peripheral primitive neuroectodermal tumor (pPNET) is a clinically rare malignant tumor of the nervous system, and a group of highly malignant small round cell tumors arising from neural crest cells beyond the central system and the sympathetic nervous system [1, 2]. The tumor is characteristic of potential multi-directional differentiation, invasive growth, poor prognosis, and recurrent tendency [3]. Clinical epidemiological studies demonstrate that pPNET accounts for approximately 4% of soft tissue sarcomas, with a 5-year survival rate of 45%, and a mortality rate of over 70% in patients [4]. Children and adolescents are at high risk for the disease. The majority of pa-

tients are confirmed by pathologic examinations [5]. Patients with pPNETs often present with atypical manifestations, so they are prone to be misdiagnosed as other tumors before surgery. Recently, pPNET is primarily diagnosed by analyses of CT or MRI images, but it still needs confirmation by pathologic examinations due to the diverse and complex imaging manifestations [6, 7]. Nevertheless, few reports have so far stated pPNETs, and some reports have merely analyzed the examination results of individual cases or even small samples [8-11]. Of note, the CT and MRI findings of pPNETs are still unclear. As a result, they are not conducive to improving diagnosis of the tumor, and cannot provide imaging evidence for surgical resection.

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Therefore, in order to further investigate the characteristics of CT and MRI studies regarding pPNETs, in the present study ranging from January 2012 to December 2017, a retrospective analysis was made to elucidate the clinical features of 12 patients with pPNETs confirmed by pathologic examinations in The Affiliated Hospital of Jining Medical University. The goal was to provide more clinical evidence for the clinical diagnosis and treatment of the tumor in patients.

Materials and methods

Study participants

All the enrolled patients in this study provided written informed consent, and this study was approved by the medical ethics committee of The Affiliated Hospital of Jining Medical University. From January 2012 to December 2017, 12 patients with pPNETs admitted to The Affiliated Hospital of Jining Medical University were recruited in this retrospective study, and their conditions were confirmed by surgical resection or biopsy. The patients ranged in the course of disease from 1 week to 1 year (mean, 5.2 ± 1.6 months). The major findings showed one case of abdominal pain and distention, 2 cases of pelvic swelling, 4 cases of superficial soft tissue masses, 2 cases of chest tightness and pain, and 3 cases of progressive local pain and tumor compression without evident incentives. Nine patients were treated with surgical resection followed by adjuvant chemotherapy or radiotherapy. Three patients who could not undergo surgical resection received chemotherapy or radiotherapy. Chemotherapy utilized a cyclophosphamide plus doxorubicin-based regimen, while radiotherapy adopted three-dimensional therapy or intensity-modulated conformal radiation therapy.

Imaging examination

Plain CT scanning and enhanced scanning were carried out using a 64-row spiral CT scanner (Philips, the Netherlands). The parameters of the 64-row spiral CT scanner were tube voltage 120 kV, current 250 mA, acquisition matrix $256 * 256$, slice thickness and gap 4-8 mm, and reconstructed slice thickness 2.5 mm. The scanning range exceeded the superior and inferior borders of the lesions, and enhanced CT scanning was performed subsequent to plain

scanning. Prior to enhanced scanning, non-ionic iodine contrast agent (80-100 ml) was injected at an injection speed of 3 mL/s via the cubital vein using a double cylinder high-pressure injector for all the patients. A dual-phase CT scan was conducted, namely arterial phase (30 seconds after contrast injection) and venous phase (70 seconds after contrast injection).

MRI examination was performed for scanning the transverse, sagittal, and coronal planes of the lesion sites using a GE 1.5-T MR system (USA). Conventional magnetic resonance examinations were performed on T1-weighted images (T1WI) and T2-weighted images (T2WI). TR of T1WI in spin echo sequence was 530 ms and TE was 15 ms. TR of T2WI in spin echo sequence was 4800 ms, and TE was 120 ms; slice thickness was 4 mm; slice gap was 1.5 mm. As contrast agent of enhanced scan, Gd-DTPA was injected via the antecubital vein at a dose of 0.1 mmol/kg and at a rate of 2.5 ml/s.

Pathological examination

Nine patients received surgical resection, and 3 patients underwent biopsy. H&E-stained sections and immunohistochemistry stained sections of tumor tissue were examined for diagnosis. The neuronal markers used in immunohistochemistry included CD99, neuron-specific enolase (NSE), vimentin, S-100 protein, and synaptophysin (Syn). The criteria for diagnosing pPNETs were microscopically typical undifferentiated small round cells with less cytoplasm, hyperchromatic nuclei, and a high nucleo-cytoplasmic ratio, visible nuclear division with or without visible rosette formation or expression of two or more positive neuronal markers.

Follow-up

Nine patients who had undergone surgical resection were followed for 1 year by means of clinic appointments and telephone calls. Imaging examinations were performed at 3, 6 and 12 months postoperatively.

Statistical analysis

All the data were analyzed using the SPSS software, version 17.0. Measurement data are described as mean \pm sd, while count data are expressed as percentages. $P < 0.05$ was considered significantly different.

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Table 1. Basic patient data

Case	Age (year)	Sex	Size (cm ³)	Site
1	17	Male	4.2 * 3.5 * 5.1	Right chest wall
2	21	Female	11 * 8 * 9	Left ovary
3	8	Male	7 * 5 * 4	Left chest wall
4	38	Male	12.3 * 8.6 * 7.5	Left thigh
5	12	Female	5.5 * 6.3 * 3.7	Right ovary
6	15	Male	5.2 * 4.8 * 5.8	Prostate
7	36	Male	8 * 9 * 12	Pelvic cavity
8	50	Male	11 * 12 * 7	Right lung
9	16	Female	15*20*13	Abdominal cavity
10	19	Male	7 * 8 * 13	Right thigh
11	11	Female	8 * 11 * 6	Left lung
12	23	Male	6 * 4 * 10	Pelvic cavity

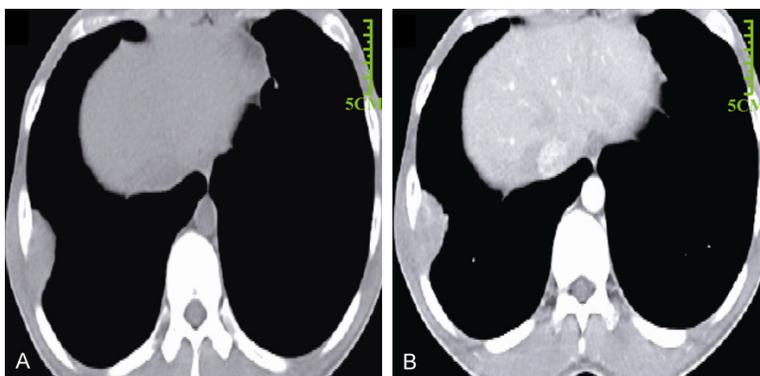


Figure 1. Plain CT and contrast-enhanced CT images of pPNET of the right chest wall. The soft tissue intensity opacities and swollen surrounding tissue with uneven intensity were visualized in the right chest wall on the CT images. Enhanced scanning revealed separations, with heterogeneous enhancement. A: Unenhanced CT scan; B: Contrast-enhanced CT scan.

Results

Basic data of patients

Of the 12 enrolled patients, 8 were males and 4 were females, with an age ranging from 8 to 50 years. The smallest nodule was 4.2 * 3.5 * 5.1 cm³ in diameter, whereas the largest nodule was 15 * 20 * 13 cm³ in diameter. The pPNET lesions were located in lower extremities (2 cases), pelvic cavity (5 cases), abdominal cavity (1 case), the lung (2 cases), and the chest walls (2 cases), respectively. All nodules were of soft-tissue type, as shown in **Table 1**.

CT and MRI findings

CT scan showed heterogeneous density in the tumor with necrosis and cystic changes, but no

calcification. The tumor foci were heterogeneous after enhancement scan. They were moderate or showed significant heterogeneous enhancement in the arterial phase, and maintained incremental homogeneous enhancement in the parenchymal phase (**Figure 1**). The lesions in the chest wall (2 cases) invaded the surrounding ribs, which gave rise to hyperplasia and sclerosis of ribs. The lesions in the lung (2 cases) led to ipsilateral compression to the lung that was incomplete dilation. The lesions in the abdominal cavity (1 case) and in the pelvic cavity (5 cases) with clear boundary resulted in displacement and compression to the surrounding organs, which included the spleen, pancreas, kidney, rectum, and uterus, but no invasion.

MRI scans revealed isointense or hypo-intense opacities on T1WI, and isointense or hyper-intense opacities on T2WI. The regions with tumor cystic degeneration or necrosis showed the tumor was hypo-intense on T1W images

and hyper-intense on T2W images. Contrast-enhanced MRI scans demonstrated moderate or significant enhancement in the arterial phase and sustained homogeneous or heterogeneous enhancement in the parenchymal phase (**Figure 2**).

Pathological examination

The lesions demonstrated diversified lobulated or nodular masses in volume. Between the tumor margins and surrounding tissue, vague boundaries were noted and affected the surrounding bone. The cut surface of pPNETs was fish-like, grayish-white, or gray-yellow, and tenacious, with local visible necrosis. Under a light microscope, the tumor cells were small and uniform in size, with less cytoplasm, hyperchromatic nuclei, and apparent nuclear division

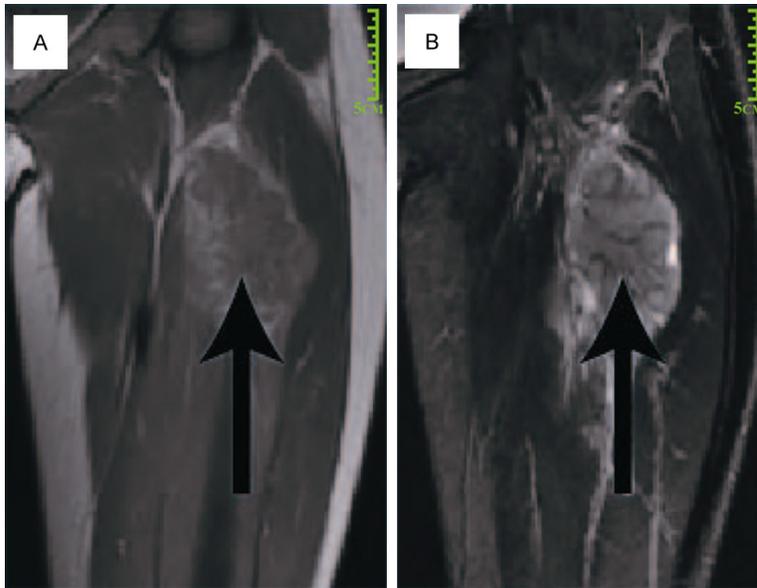


Figure 2. MRI images of pPNET of the right thigh. The tumor mass (Arrow) showed vague boundaries and are lobulated. A: Isointense signals on T1WI; B: Mildly hyper-intense signals on T2WI.

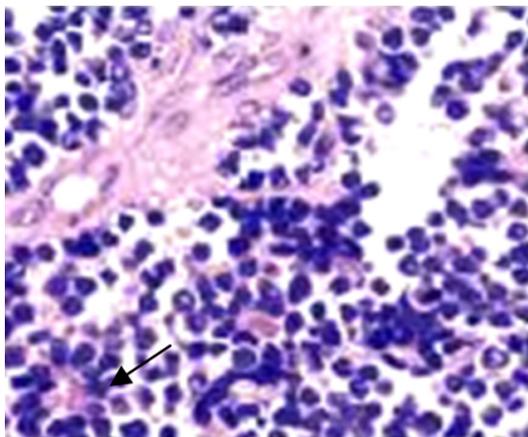


Figure 3. HE staining of pPNET (200×). The arrow indicates Homer-Wright type rosette forming.

with typical Homer-Wright rosette forming (Figure 3). The results of immunohistochemical staining indicated that the positive rates were 100% (12/12) for CD99, 50% (6/12) for NSE, 33.3% (4/12) for Vimentin, 58.3% (7/12) for Syn protein, and 16.7% (2/12) for S-100 protein (Table 2, and Figure 4).

Follow-up results

At 1-year follow-up, 4 patients had local recurrent lesions, with a recurrence rate of 33.3%, with 3 patients (including 1 case of postoperative bone metastasis and 1 case of postopera-

tive double-lung metastasis at 6 months, and 1 case of brain metastasis at 12 mon), with a metastasis rate of 25%.

Discussion

pPNETs are small round-cell malignant tumors which are of neural crest origin. They are rare and extremely harmful malignancies in clinical settings [12]. They occur most commonly in adolescents and children (more often in female than in male). The tumors are present mostly in the extremities, chest wall, and paravertebral areas where sympathetic nerves and peripheral nerves are intensively distributed [13]. The 12 patients enrolled in the current study varied in age from 8 to 50

years old. Most of them were adolescents, with more males than females. This might be attributable to the small sample size of the current study. Our results indicated that the lesions were located in lower extremities (2 cases), the pelvic cavity (5 cases), abdominal cavity (1 case), lung (2 cases), and chest wall (2 cases), consistent with the affected sites reported in the previous literature [14]. The vast majority of the soft tissue masses in the present study were larger than 5 cm in diameter, which might be related to the facts that the tumor masses are occult and grow in a big space as they are present in the abdominal cavity, pelvic cavity or the thoracic cavity, which was basically consistent with the result reported by Park et al. [15]. pPNETs grow rapidly due to their high degree of malignancy, and the tumors at an early stage may be associated with the symptoms of pain arising from soft tissue compression or destruction of bone tissue. Of the 12 patients in the current study, one had abdominal distention and pain, two had pelvic swellings, four had superficial soft-tissue masses, two had chest tightness and pain, and three had progressive local pain and symptoms of tumor compression without obvious incentives.

Histologically, pPNETs are extremely similar to other types of small round malignancies which include Ewing's sarcoma, but they are still different in nature [16]. Currently, the differential

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Table 2. Results of immunohistochemical staining in 12 patients

Case	CD99	NSE	Vimentin	Syn	S-100
1	+	-	+	+	-
2	+	-	-	+	+
3	+	+	-	-	-
4	+	-	+	+	-
5	+	+	-	+	-
6	+	-	+	-	-
7	+	-	-	+	-
8	+	+	-	-	+
9	+	+	-	-	-
10	+	+	-	+	-
11	+	-	+	-	-
12	+	+	-	+	-

Note: NSE, denotes neuron-specific enolase; Syn, synaptophysin.

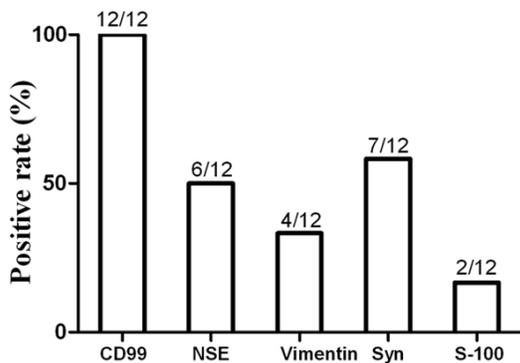


Figure 4. Determination of the positive rates of CD99, NSE, Vimentin, Syn, and S-100 proteins by immunohistochemical staining.

diagnosis of pPNETs depends on pathological examination. Additionally, under a light microscope, the cells of pPNET were small and uniform in size, with less cytoplasm, hyperchromatic nuclei, and apparent nuclear division with typical rosette forming. The immunohistochemical staining showed the expression of at least two differentiated neural antigens. The results of immunohistochemical staining in the current study revealed that CD99 was positive in 100% of the pPNET cases (12/12); NSE positive was in 50% (6/12); Vimentin was positive in 33.3% (4/12); Syn protein was positive in 58.3% (7/12); S-100 protein was positive in 16.7% (2/12); and at least two differentiated neural antigens were expressed in each tumor, suggesting that the patients enrolled in

the present study met diagnostic criteria for pPNETs.

The current study also demonstrated that on CT images, pPNET lesions in soft tissue were characterized uneven density nodules with necrosis and cystic changes, but no calcification. The tumor foci were evidently heterogeneous after enhancement scan. They were moderate or significantly heterogeneous enhancement in the arterial phase, and maintained incrementally homogeneous enhancement in the parenchymal phase. MRI scans revealed isointense or mildly hypo-intense opacities on T1W images, and isointense or hyper-intense opacities on T2W images. The regions with tumor cystic degeneration or necrosis showed hypo-intense on T1W images and hyper-intense on T2W images. Contrast-enhanced MRI scans showed moderate or significant enhancement in the arterial phase and sustained homogeneous or heterogeneous enhancement in the parenchymal phase. CT scanning in the current study revealed intra-tumor cystic degeneration and necrosis which might be related to necrosis in blood-supply areas arising from infiltration of tumors into the mass or the peripheral blood vessels. This is basically in line with the findings reported in previous studies [17, 18].

Surgical resection is the primary modality for treating pPNETs. It has been reported that surgical resection in combination with adjuvant radiotherapy and chemotherapy benefit the patients with appropriately prolonged survival [19]. pPNETs are highly malignant tumors. Although postoperative adjuvant radio-chemotherapy can properly prolong the patients' survival, the rates of local recurrence and metastasis remain high after surgery [20]. In the current study, we paid follow-up visits to the patients with surgically resected pPNETs for 1 year and found that the recurrence rate was 33.3% and the metastasis rate was 25%.

In conclusion, as pPNETs do not have specific manifestations on CT and MRI images, the definitive diagnosis is still dependent on pathological examinations. CT and MRI imaging clearly show the tumor density and signal characteristics, and define the scope and metastasis of tumors, which can provide reliable evidence for further development of surgical protocols and assessment of the therapeutic effects.

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Disclosure of conflict of interest

None.

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