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Case Report

Peripheral Primitive Neuroectodermal Tumor (pPNET) of the Penis: A Case Report and Literature Review

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Primitive neuroectodermal tumors are derived from primitive neuroectodermal cells and belong to a highly malignant subgroup of round-cell tumors. Peripheral primitive neuroectodermal tumors of the penis are an extremely rare malignant form among penile neoplasms. These tumors are often difficult to diagnose due to atypical symptoms. Here, we report a case of a 24-year-old patient in China with a neoplasm localized at the base of his penis. The initial symptom was dysuria without any inducement. The results of blood and urine examinations indicated no abnormalities. The imaging examination results indicated a firm mass near the base of the penis. The hematoxylin and eosin (H&E) staining revealed round, small tumor cells with heterotypical darkened nuclei. In addition, immunohistochemistry (IHC) revealed strong and diffuse positive staining for CD99 (mic-2), VIM (vimentin), and NCAM1/CD56 (neural cell adhesion molecule 1). In addition, 60% of cells were positive for the cell proliferation marker Ki-67. Based on the above results, the case was diagnosed with peripheral primitive neuroectodermal tumor (pPENT). We reviewed the literature from 1999 to 2013 and identified reports of pPENT with a low incidence and atypical symptoms. Accurate diagnosis with multiple detection technologies, including laboratory diagnostic tests, imaging, morphologic and immunologic examinations, is very important to reduce the misdiagnosis rate.

Key words: Primitive neuroectodermal tumor – Peripheral primitive neuroectodermal tumor – Penile neoplasms – Round cell tumors – CD99

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Primitive neuroectodermal tumors (PNET) are derived from primitive neuroectodermal cells and belong to a highly malignant subgroup of round cell tumors that exhibit clinical, immunohistochemical, and cytogenetic features reminiscent of primary Ewing's sarcoma (PES). Hence, these tumors are collectively defined as PNET/PES.[1] Depending on the tumor origin, PNET is classified as peripheral PNET (pPNET) and central PNET (cPNET). PNET/PES typically occurs in the chest wall, limbs, and soft tissues on both sides of the spine and occurs less frequently in genitourinary organs.[2] The incidence of penile cancer is lower than that of other malignant tumors. The mean age-adjusted incidence of penile cancer is 2.1/100,000 in Sweden.[3] Lowentritt[4] reported that the incidence of malignant penile tumors is approximately 0.5 to 5/100,000. Moreover, PNET/PES of the penis is very rare and is noted in less than 5% of these patients.[4] The youngest age of onset of pPNET of the penis is 5 years, and the eldest age is 70 years.[5–13] Here, we report another rare case of a 24-year-old male with pPNET of the penis admitted to our hospital in China.

Case Presentation

A 24-year-old male went to our hospital for dysuria without any inducement for 3 days. The patient had a previous history of acute lymphoblastic leukemia (ALL) at 5 years of age, and he recovered through conventional treatment as certified by a reexamination in our hospital.

After obtaining informed consent from the patient, he was subject to a series of medical examinations to determine the cause of dysuria. Palpation results revealed a firm mass approximately 6 × 8 cm near the base of the penis with poorly defined margins and mild tenderness. The physical examination revealed no gross hematuresis and no additional common urinary system anomalies. To relieve the dysuria, we performed an emergent urethral catheterization. We experienced difficulties in smoothly completing the catheterization. The blood and urine examination results indicated no abnormalities. The color Doppler ultrasound (CDUS) results revealed an irregularly shaped solid occupancy lesion that measured approximately 8.6 × 11.4 cm in size at the root of his penis. The dual-source computed tomography (DSCT) results indicated that the mass was localized in the soft tissue of his penis and approximately 6.8 × 8.7 cm in size. Magnetic resonance imaging (MRI) revealed a 9.8 × 7.0 × 11.2 cm lesion with hypointensity on T1WI and hyperintensity T2WI. The mass presented a uniform signal, occupied the corpus cavernosum and involved the urethra (Fig. 1A, 1B, 1C, 1D, 1E). To determine the cellular composition of the large mass, we recommended a biopsy. After obtaining informed consent from the patient, we obtained tissue from the mass at the base of penis near the scrotum for histopathologic examination.

The hematoxylin and eosin (H&E) staining results revealed that the tumor cells were round and small and exhibited heterotypical darkened nuclei. Immunohistochemical (IHC) staining revealed strong and diffuse positivity for CD99 (mic-2), VIM (vimentin), and NCAM1/CD56 (neural cell adhesion molecule 1). In addition, 60% of cells were positive for the cell proliferation marker Ki-67. No immunoreaction was observed for LCA (leukocyte common antigen), EMA (epithelial membrane antigen), SMA (spinal muscular atrophy), SYN (synapsin), CgA (chromogranin A), PKC (proline-rich transmembrane protein 2), or CD68 (Fig. 2A-L). To determine tumor cell origin, we recommended full-body CT screening, and the results indicated no additional suspicious lesions.

Taken together, we confirmed that the tumor cells were small round blue cells and diagnosed the patient with pPNET of the penis. Given the danger and possibility of pPNET recurrence and metastasis, we advised the patient to undergo a complete penectomy and perineal urethrostomy. He refused the radical surgical treatment because the surgery could damage his sexual function. After careful consideration, he received ifosfamide (IFO) and etoposide (VP16) combination chemotherapy.

The patient undergoes regular CT and ultrasonography reexaminations, and the 1-year follow-up results indicate that the lesion in the penis markedly diminished. The size of the mass was reduced to 4.5 × 3.0 × 5.8 cm. The patient continues to receive chemotherapy and has been closely followed for 1 year with no evidence of tumor progression.

Discussion

Stout and his colleagues first described this type of penile cancer in 1918. The tumor was characterized by undifferentiated small round cells with rosettes

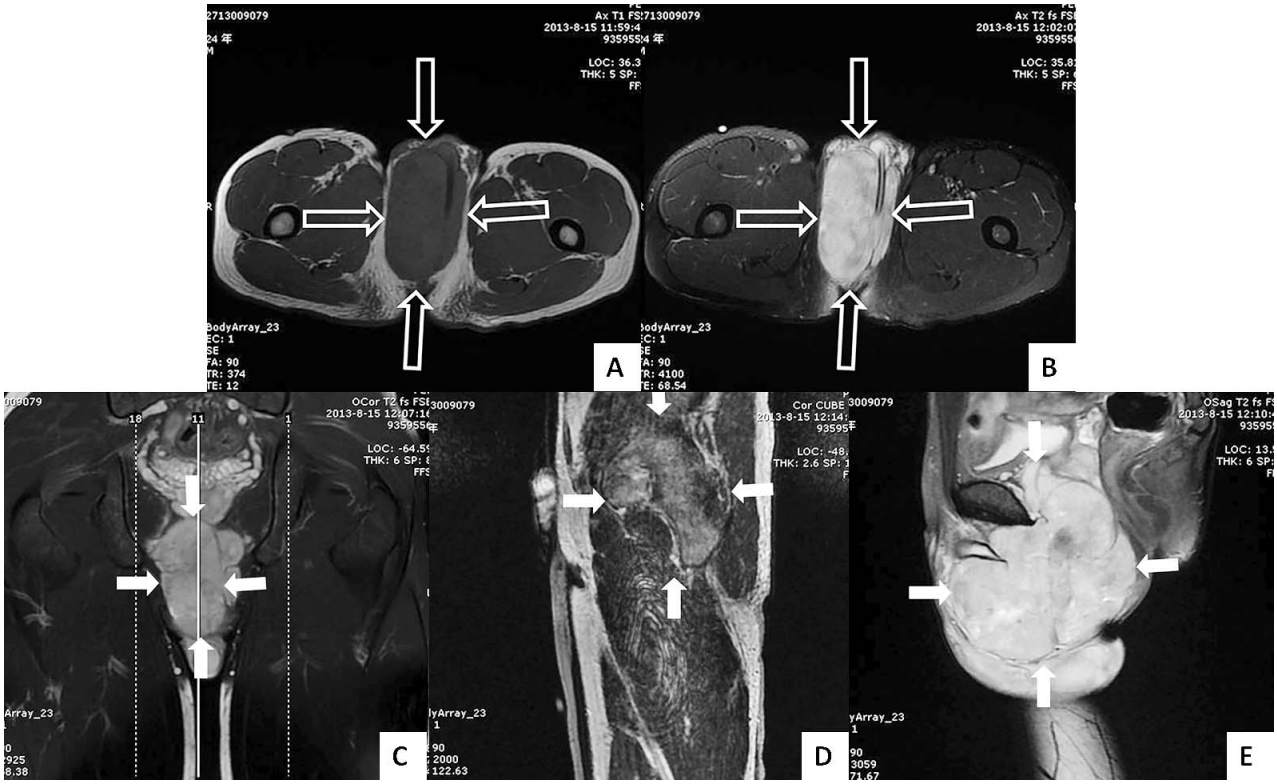

Fig. 1 MRI results revealed high signals on T1WI (A) and T2WI (B, C, D, E) from a large $9.8 \times 7.0 \times 11.2$ cm mass occupying the corpus cavernosum and involving the urethra. MRI images indicated a uniform density of the mass (the transverse, sagittal, and coronal sections are presented).

in the ulnar nerve and subsequently referred to as PNET.[14] James Ewing reported a radiosensitive tumor in long bones that was also composed of undifferentiated cells (Ewing's sarcoma).[15] In 1973, Hart and Earle proposed that PNET is a type of primitive small round cell tumor derived from the neural crest that primarily consists of primitive neuroectodermal cells.[16] No difference in the morbidity of PNET/ES is noted between men and women; however, we found that most cases occur in children and adolescents.[5–13] These "small round blue cell" tumors can arise in all parts of the body, especially in the chest wall and soft tissues on both sides of the spine and limbs.[5] Primary PNET/PES is rarely noted in the genitourinary system, especially in the penis.

The first case of PNET/PES of the penis was reported in 1999 by Toh *et al*.[6] Currently, we found only 9 relevant reports in the medical network database. The various characteristics of those cases are compared and summarized in Table 1.[5–13] From the limited clinical data of 9 patients with pPNET of the penis, we discovered that younger patients may be at high risk for the disease, as the age of onset in 7 cases ranged from 16 to 29 years of age with the exception of 1 case at 5 years of age and 1 case at 70 years of age. The age of onset of the present case was 24 years, which was also classified as occurring during youth. The initial symptoms varied in all cases. Four patients experienced a painful-penile mass or enlargement, whereas the remaining 5 patients had a palpable painless mass or nodule in their penis. A pPNET mass in the penis is always a single firm, hard-to-move nodule that can be easily identified by palpation.[12] pPNET can involve any part of the penis, such as the glans, shaft or base,[9,11] In our case, the patient's initial symptom was dysuria without any obvious exogenous swelling. Palpation of a mass or nodule is necessary and helpful for diagnosing pPNET in the penis as early as possible; nevertheless, one should also pay close

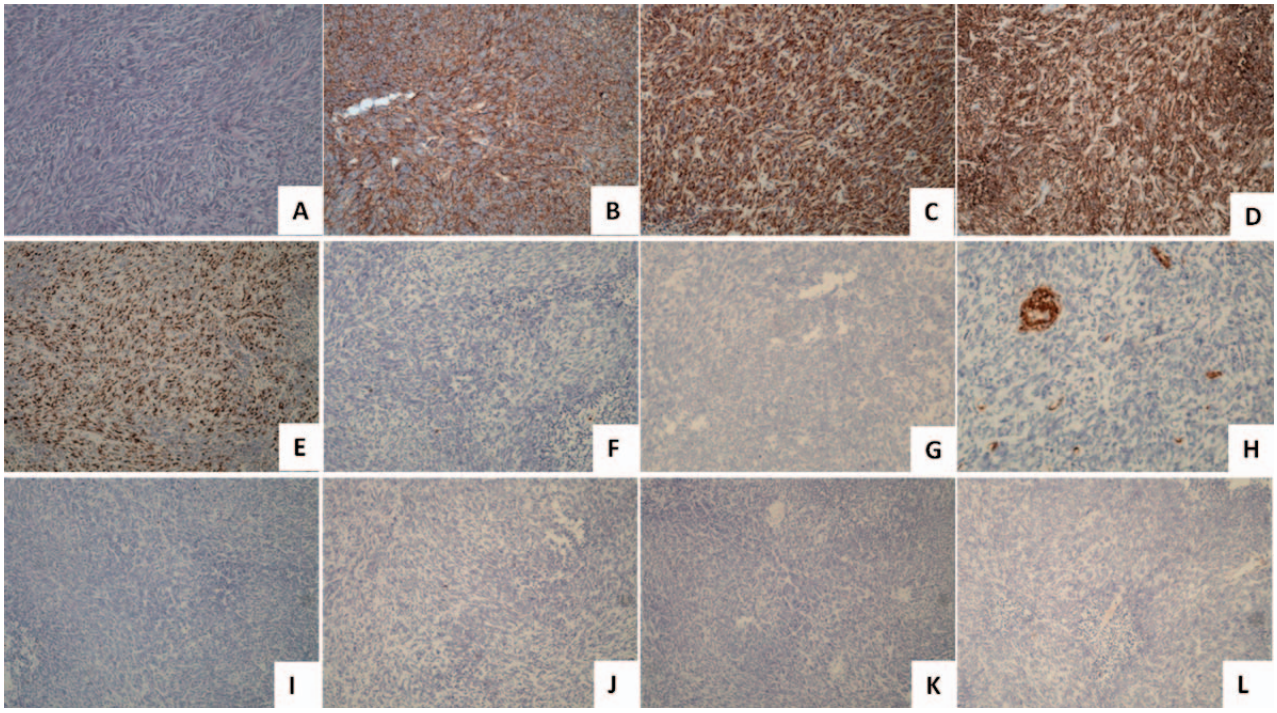

Fig. 2 H&E staining revealed that the tumor cells were uniform small round blue cells with darkened nuclei (A). The immunohistochemical staining results indicated that the tumor cells were positive for CD99 (B), VIM (C), CD56(D), and Ki-67(E) in a membranous pattern, whereas the tumor cells were negative for LCA (F), EMA (G), SMA (H), CD68 (I), SYN (J), CgA (K), and PKC (L) (100×).

attention to other abnormal urinary symptoms, such as dysuria.

In the present case, we used both CT and MRI to better characterize the tumor, and detailed whole-body CT screening revealed no explicit enlarged lymph nodes or metastasis. Medical imaging can provide valuable information for clinical treatment; furthermore, pathologic and immunohistochemical analyses will lead to an exact diagnosis of the tumor's malignancy grade. Morphologically, PNET tumor cells are undifferentiated small round blue cells with rosettes. In the ICH analysis of PNET, diffuse membranous mic-2 immune positivity is the most specific indicator, although mic-2 positivity is also noted in some other tumors, including lymphomas, synovial sarcoma, and rhabdomyosarcoma.[17] Other proteins, including CK, SYN, CGA, NSE, CD57, and S-100, are expressed in PNET, but these proteins are not specific diagnostic markers of PNET.[9]

Based on the analysis of the limited number of available reports, pPNET of the penis appears to be an aggressive tumor with a poor prognosis and high recurrence even after combined treatments involving surgical resection, chemotherapy (CAV), and radiotherapy (brachytherapy with 20–30 Gy). Five of the 9 patients were subject to surgical resection, and almost all of them received chemotherapy and (or) radiotherapy. Even though 5 patients underwent penectomy (4 of them also received chemotherapy or radiotherapy), 2 patients still experienced distant metastases (1 of the 2 died at the 14th month of follow-up). Nonetheless, 4 patients who underwent standardized treatment had no evidence of disease progression. Therefore, multimodal therapy, including aggressive surgery, intensive chemotherapy and adjuvant radiotherapy, is necessary for local tumor control and to the prevention of metastasis. Surgical intervention should be considered as the first choice in comprehensive therapy because it can directly eliminate tumor cells localized in the

Table 1 Literature review of 9 cases of primary penis PNET from 1999 to 2013

First author	Country	Publish year	Age	Initial symptom and sign	Size (cm)	Location	Metastasis at presentation
Akino[7]	Turkey	2013	16	Painful penile swelling	8.1 × 7.1	Glans penis	No
Ma[8]	USA	2013	28	Painless mass for 2 years	4.3 × 2.2 ×1.9	Left side of penis	No
Song[5]	China	2012	5	Progressive and painful penile enlargement	5.1 × 2.1 × 0.8	Base of penis	Multiple metastatic lesions in chest
Sharma[9]	India	2011	29	Painful mass and penile erection	9.1 × 7.1 × 6.2	Base of penis and shaft penis	No
Liu[10]	China	2008	70	Painful penile enlargement without any inducement	3.6 × 2.0	Shaft penis	No
Kilicaslan[11]	Turkey	2008	19	Painless mass	3.0 × 3.0	Dorsal side of penis	No
Paruliya[12]	India	2007	17	Painless penile swelling	Multiple, 1-cm hard nodules	Lateral surfaces of penile shaft	No
Huang[13]	China	2004	18	Painless nodule progressive and painful penile enlargement	2.0 × 2.0	Glans penis	Metastasis in inguinal lymph node
Toh[6]	Singapore	1999	21	Painless mass	Not know	Glans penis	Not know

IVAD3 (ifosfamide, 3 g/m^2 on days 1, 8, and 15; vincristine, 2 mg/m^2 on day 1; and epirubicin 20 mg/m^2 on days 1, 8 and 15); IVAD2 (ifosfamide, 3 g/m^2 on days 1 and 8; vincristine, 2 mg/m^2 on day 1; and epirubicin 20 mg/m^2 on days 1 and 8); IVA (ifosfamide 3 g/m^2 on days 1 and 8; vincristine, 2 mg/m^2 on day 1; and actinomycin D, 1.5 mg/m^2 on day 1); CAV, cyclophosphamide, adriamycin, and vincristine; IE, ifosphamide and etoposide; CAVE, cyclophosphamide, adriamycin, vincristine, and etoposide.

penis. The standard chemotherapy regimen involves CAV (cyclophosphamide, adriamycin, and vincristine) alternated with IE (IFO and VP16).[18] Brachytherapy may play serve as a palliative therapeutic option to prevent or delay tumor metastasis.

Conclusions

pPNET of the penis is an extremely rare type of penile cancer. Including this case, 9 of the 10 reported cases have occurred in Asia, and only 1 case was noted in the USA. More attention should be given to young patients with a penile mass. Given the rarity of this malignant tumor, further studies on its morphology and contributing factors may help to determine potential site-specific characteristic features. Emphasizing the clinical presentation of pPNET as well as better diagnostic techniques and therapeutic strategies may increase disease-free survival. Due to the limited literature, no standard treatment for pPNET of the penis is available. Surgery, chemotherapy, and radiotherapy have positive effects on cancer inhibition, but even these active treatments cannot fully protect all patients from the high metastasis incidence of pPNET. We should continue to seek more sensitive and specific medicines for optimized therapeutic options, which would be beneficial for improving patient prognosis and survival time.

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Ruibao Chen conceived of and designed the project. Wanqiu Huang, Tao Wang, and Zheng Liu acquired and interpreted the data. Wanqiu Huang drafted the article. Zheng Liu and Ruibao Chen critically revised the manuscript for important intellectual content. Ruibao Chen, Ruzhu Lan, and Jihong Liu approved the final published version. The authors report no conflict of interest.

Table 1 Extended

Surgical procedure	Chemotherapy*	Radiotherapy	Follow-up length (months)	Patient's status
Total penectomy and perineal urethrostomy	IVAD3 + IVAD2 + IVA	No	84	No evidence of recurrence
No known treatment received (patient left)	No	No	7	No evidence of disease progress
No	CAV + IE	Brachytherapy with 20 Gy	9	The metastatic lung lesions diminished and the penis decreased in length
No	VAC + IE	Brachytherapy with 30Gy	18	Increased size of lung metastasis and local recurrence of severe local pain
Total penectomy and perineal urethrostomy	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Total mass resection and bilateral inguinal lymphadenectomy	CAV + IE	Brachytherapy (20 Gy- 34 Gy)	24	Iliac lymph node and bilateral pulmonary and pleural metastasis
Total penectomy and perineal urethrostomy	CAV	Not mentioned	18	Asymptomatic
Segmental penectomy and bilateral inguinal lymphadenectomy	CAVE	Not mentioned	14	Multiple metastasis of osteogenesis. Death of extended metastasis.
Excisional biopsy	CAVE	No	8	No evidence of disease progress

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