CASE ILLUSTRATION WITH REVIEW

Intracranial metastasis from primary spinal primitive neuroectodermal tumor

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ABSTRACT

Primary spinal primitive neuroectodermal tumors (PNET) are rare tumors, with only 94 cases reported till date. Metastasis to brain from a spinal PNET is even rarer. In the present report, we evaluate the pathology and treatment of solitary intracranial metastasis from spinal PNET in a 22-year-old female who presented with headache and left hemiparesis and was diagnosed to have right parietal parasagittal tumor. She has been previously diagnosed to have cervicothoracic primary spinal PNET, and was treated by surgery, radiotherapy, and chemotherapy seven years back. The intracranial tumor has been removed and pathological examination confirmed as PNET. She received radiotherapy and chemotherapy with ifosfamide and etoposide, following surgery for the right parietal PNET. At 20 months follow-up, patient is stable and has no recurrence of the disease. Critical review of reported cases of primary spinal PNET metastsising to brain was done.

Key words: CD 99, metastasis, primitive neuroectodermal tumor, spinal tumor

Introduction

Primitive neuroectodermal tumors (PNETs) are a group of highly malignant tumors composed of small round cells of neuroectodermal origin. Cranial PNETs are commonly located infratentorially in the cerebellum and are rarely supratentorial. Most of the spinal PNETs are caused by drop metastasis, in which the malignant cells from the cranium drop into the spine along with the cerebrospinal fluid (CSF);[1] however, the reverse is quite unusual. Primary spinal PNETs account for a small percentage of the PNETs. Intracranial PNETs commonly occur in children, whereas intraspinal PNETs are more common in young adults.[2,3] Spinal PNETs can be central nervous system (CNS)/central PNET (cPNET) or peripheral PNET (pPNET). Primary spinal PNETs are rare tumors, with only 94 cases reported till date.[3-12] Brain metastasis from primary spinal PNET is still rarer with only 10 cases reported in literature published in English so far.[4,5,13-19] We report one more rare case of primary spinal PNET metastasizing to brain after a long interval.

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Case Report

Presentation

A 22-year-old female presented with a one month history of headache and left hemiparesis in March 2010. On examination, she had grade 4/5 power in left upper and lower limbs. Contrast enhanced computed tomography (CECT) of the brain revealed enhanced hyperdense solitary right parietal parasagittal tumor [Figure 1]. In April 2003, she was diagnosed to have primary spinal PNET at C6-D2 level with dumbell like extension into the thoracic cavity [Figures 2a and b]. She underwent right posterolateral thoracotomy and excision of the tumor at another institution. Pathological examination of the tumor confirmed the tumor was pPNET. Immunohistochemistry (IHC) for CD99 was positive. Surgery was followed by radiotherapy (with 57.6Gy) to the right neck, superior mediastinum and the right upper lung. Chemotherapy with ifosfamide, adriamycin, and etoptoside was administered for seven cycles. Positron emission tomography (PET) scan done 5 years after the treatment for spinal PNET, in December 2008 revealed no residual lesion or metastasis [Figure 3].

Surgery

Right frontoparietal parasagittal craniotomy was done for the solitary parietal parasagittal tumor detected by CECT. It was found to be highly vascular and was present adjacent to the

motor cortex, infiltrating into the dura. Near-total excision of the tumor was done leaving a thin rim of tumor along the superior sagittal sinus. The infiltrated dura was resected and duraplasty done.

Pathology

Histopathological examination revealed a densely cellular infiltrate of loosely cohesive, mitotically active cells arranged in sheets and lobules with minimal intervening stroma [Figure 4a]. The tumor also shows perivascular necrosis, with pseudorosette formation and organized hemorrhage. The individual cells had scanty cytoplasm, with round to oval nuclei, coarse chromatin and conspicuous nucleoli in some cells. Tumor cells showed focal Periodic Acid Schiff (PAS) positivity. IHC stains for tumor cells showed membranous positivity for CD99 [Figure 4b]. Fluorescent insitu hybridization analysis (FISH) for translocation (11; 22) (q24; q12) was not done in this case, as it was not available locally. These findings were consistent with pPNET/Ewing's sarcoma (ES).

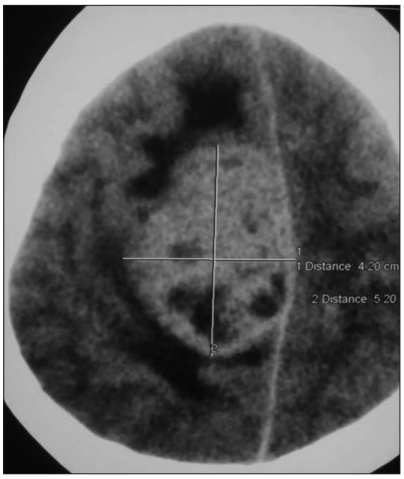

Figure 1: CECT of brain showing right parietal parasagittal metastatic tumor

Postoperative course

The patient had mild worsening of motor power on the left side to 3/5 after surgery, which gradually recovered in two months. She received postoperative radiotherapy of 40 Gy/250 cgy/16 Frs to brain and five cycles of chemotherapy with ifosfamide and etoposide. CECT scan of brain was done nine months after surgery; it showed no residual or recurrent disease [Figure 5]. Follow-up visit at 20 months after the surgery showed that she was normal with no recurrence of disease.

Discussion

The term "PNET" was coined by Hart and Earle in 1973 to describe predominantly undifferentiated tumors of the cerebrum, which contained 90-95% of undifferentiated cells and did not fulfill diagnostic criteria for other tumor entities.[20] PNETs are commonly located in the cranium. Primary spinal PNETs are rare, and to the best of our knowledge, only 94 cases have been published in the literature. Primary spinal PNETs commonly occur in pediatric and young-adult age group (median age-24 years) and male sex predominance of nearly 2:1.[3,21]

Approximately 30-50% of patients with intracranial PNETs develop spinal metastases; in contrast, metastasis from primary spinal PNET to brain is much less common. The pPNETs and ES represent different manifestations of the same tumor and have similar genetic alterations. Based on molecular cytogenetic analysis, both ES and pPNETs are known to share the same reciprocal translocations, mostly between chromosomes 11 and 22.[22-24] ES/pPNETs are characterized by translocations that occur in 95% of tumors. This translocation joins the Ewings sarcoma gene (EWS) located on chromosome 22 to an *ets* family gene; either friend leukemia insertion (*FLI*) 1 located on chromosome 11, t (11; 22) in 85% of cases, or *ets*-related gene (*ERG)* located on chromosome 21, t (21; 22) in 10% of cases.[22,25] Up-regulation

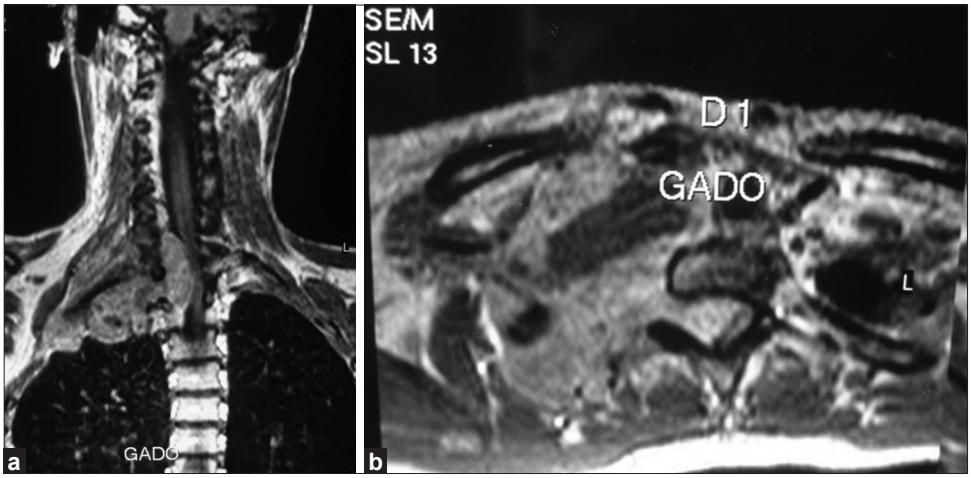

Figure 2: (a) MRI of cervico-dorsal spine demonstrating C6-D2 spinal tumor with dumbbell like extension into upper thorax; (b) MRI axial images demonstrating spinal tumor at D-1 extending outside

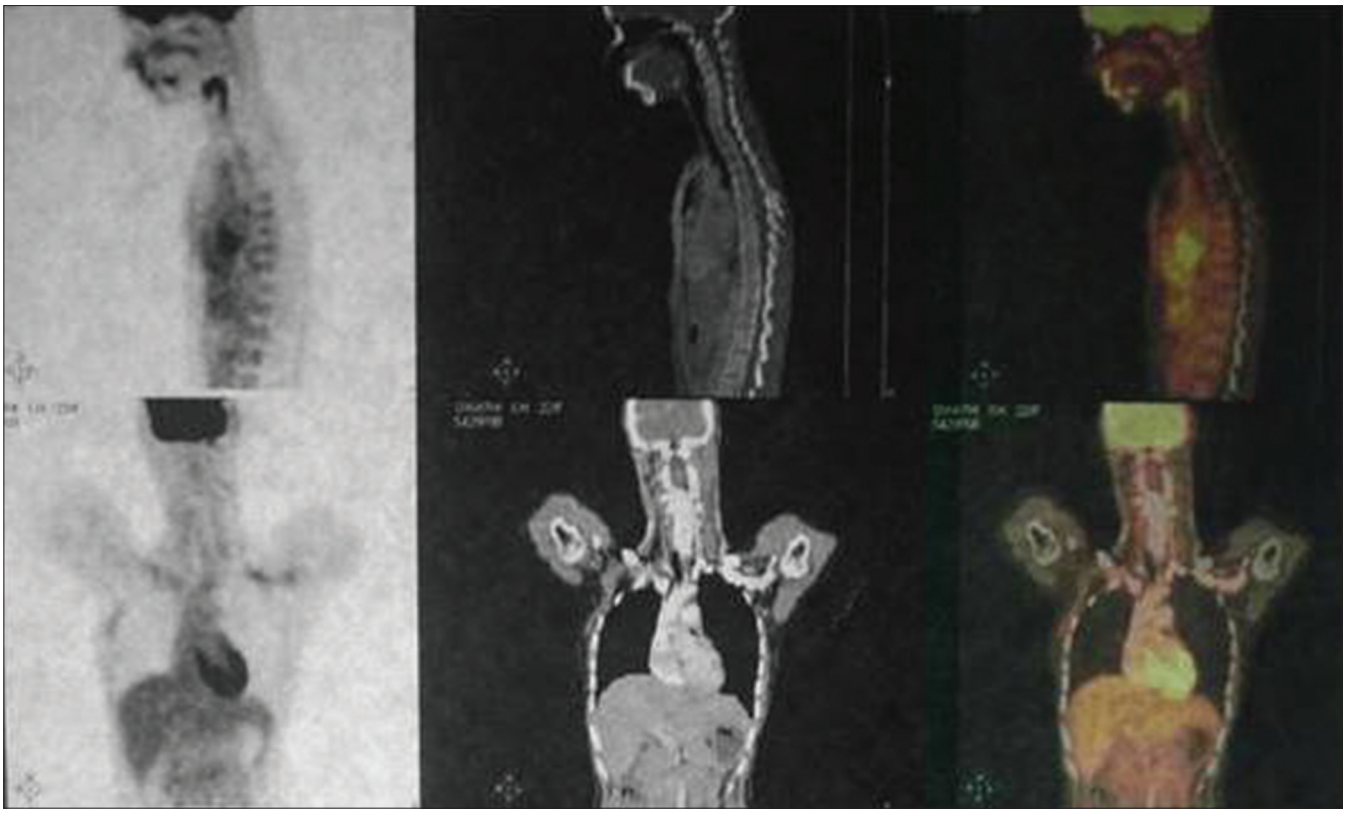

Figure 3: PET scan five years after surgery for spinal PNET showing no evidence of recurrence/metastasis

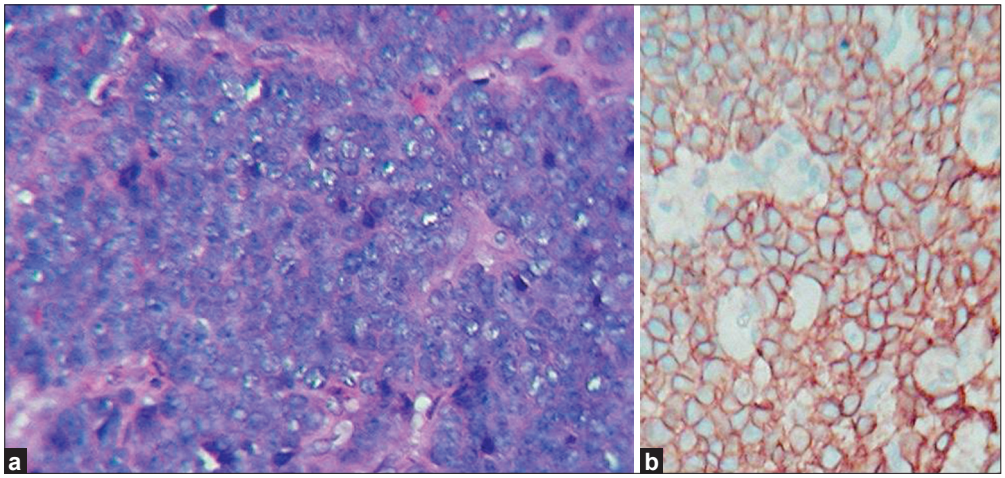

Figure 4: (a) Histopathology showing densely cellular tumor arranged in sheets and lobules with minimal intervening stroma; (b) Immunohistochemistry showing membranous positivity for CD99

of MIC2 gene in pPNET/ES results in a high degree of expression of the transmembrane glycoprotein CD99.[24,26,27] CD99 immunopositivity is seen in ES/pPNETs but not in CNS PNETs. Though CD99 immunopositivity can be useful in differentiating ES/pPNET and CNS PNETs, the presence of (11; 22) (q24; q12) translocation is necessary for definitive diagnosis. The differentiation between cPNET from pPNET can be helpful in clinical progression and their treatments. CNS-PNETs have to be clearly distinguished from ES/pPNETs because of differences in biology of tumor growth (pPNETs of the spine arise generally from the extradural space and often extend into the paravertebral soft tissue) and their dissemination (cPNETs very rarely metastasize to outside CNS, but can spread along the CSF in 10-30% of cases; whereas, pPNETs metastasize into bone, lung, lymph nodes, and liver).[28] Till date, there are no specific protocols to treat spinal PNETs. Most centers use surgery, radiotherapy, and chemotherapy for their treatments.[3,21] Distinction between the central and peripheral PNETs needs to be made before the initiation of treatment, as peripheral PNETs should be treated on protocols

Table 1: Intracranial metastasis from primary spinal primitive neuroectodermal tumors

Author and year	Number of patients	Age (in years)	Primary spinal pnet location	Cpnet/ ppnet	Metastatic cranial pnet location	Radiotherapy and chemotherapy for metastatic cranial pnet	Surgery for metastatic cranial pnet	Survival (from diagnosis of spinal pnet)
Kosnik *et al.*, 1978	1	NA	Thoraco-lumbar, intramedullary	cPNET	Subarachnoid space and ventricles	-	-	<12 months
Jaksche *et al.*, 1988	1	26/male	T8-L2, intramedullary and extra medulalry	cPNET	Between both frontal horns of lateral ventricles and roof of 4th ventricle	Radiotherapy (30 Gy)(craniospinal)	-	36 months
Ogasawara *et al.*, 1992	1	16/female	L-2 , intramedullary	cPNET	Cisternae, around ventricles, corpus callosum and brainstem, ant horn left lat ventricle, cerebral hemispheres	45.4 Gy whole brain radiation followed by 20 Gy local irradiation to brain metastasis and chemotherapy (Ranimustine (MCNU), cisplatin and etoposide)	-	29 months
Kwon *et al.*, 1996	1	0.25/ female	T7-L5, intramedullary	cPNET	Cisternal spaces and fourth ventricle	One cycle of chemotherapy (vincristine, cisplatin, procarbazine, hydroxyurea, lomustine, cytosine, arabinoside, cyclophoshamide)	-	21 days
Meltzer *et al.*, 1998	1	30/male	Cervico-thoracic, intramedullary	cPNET	Corpus callosum, midbrain, medulla , hippocampus and intraventricular location	Radiotherapy to brain stem	-	5 years
Dorfmuller *et al.*, 1999	1	32/male	Right sacral nerve root intradural with extradural extension	pPNET	Multiple small lesions bilaterally	Four agent combination chemotherapy (vincristin, actinomycin D, ifosfamide and adriamycin) and Radiotherapy	-	29 months
Akyuz *et al.* 2004	1	31/female	Cauda equina, intradural extramedullary	pPNET	Left fronto-parietal	-	Yes (gross total resection)	6 months
Benesch *et al.*, 2010	2	10 months/ female 23 months/ male	T 10-L 2, intrameduulary and cauda equine T7-T10, intramedullary	cPNET cPNET	Multiple intracranial metastasis Basal meninges, multiple intracranial metastasis	- Chemotherapy (cisplatin, vincristine, cyclophosphamide, etoposide , high dose methotrexate and intraventricular methotrexate with autologous stem cell support followed by Radiotherapy	- -	6 months 40 months
Gollard *et al.*, 2011	1	21/female	Thoracic, intramedullalry	cPNET	Cerebellum adjacent to fourth ventricle	Chemotherapy (cisplatin, cytoxan, and Etoposide) followed by high-dose chemotherapy with autologous stem cell support	Biopsy	11 years
Present case	1	15/female	C6-D2, extradural	pPNET	Right parietal parasagittal	Radiotherapy of 40 Gy to brain and 5 cycles of chemotherapy (ifosfamide and etoposide)	Yes (near total resection)	8 years

cPNET – Central primitive neuroectodermal tumors; pPNET – Peripheral primitive neuroectodermal tumors

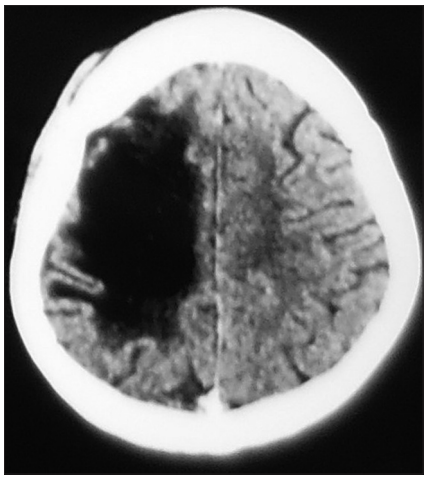

Figure 5: Post-operative CECT brain at nine months after surgery showing no evidence of tumor

designed for Ewing sarcoma.[4] For pPNET cases, radiotherapy is used only for local disease control; while for cPNET cases, radiotherapy is given for entire neuraxis.[28] The chemotherapy regimen for cPNET is different from pPNET which belongs to ES Family.[21,28] The distinction between cPNET and pPNET is also useful in planning the order of treatment sub-modalities and specific chemotherapy regimens.[28] Both cPNET and pPNET are aggressive tumors and survival rates are quite similar provided that appropriate protocols are used. Prognosis for spinal PNETs is poor with median survival of 1 to 2 years.[3] Spinal PNETs can metastasize to brain and extraneural tissues like bone, liver, cervical lymph nodes.[3,21,28] Investigations like Magnetic Resonance Imaging (MRI) and PET scans during the follow-up are helpful in the early diagnosis of metastasis.[17] Intracranial metastasis from primary spinal PNET is rare, and only 11 cases have been identified so far, including our case [Table 1]. This accounts to 11.7% (11/94) of spinal PNET cases metastasizing to brain. The average age at presentation was 17.4 years with female preponderance. The primary location of the spinal PNETs in these cases is varied, with slight predilection for thoracic spine. There was no data available regarding CD99 or presence of (11; 22) (q24; q12) translocation in the initial five cases, though cases 1-4 have been categorized as cPNET by Kampman *et al*.[28] The remaining six cases had equal distribution of cPNET and pPNET cases. The present case is only the third instance where a pPNET of spine had metastasis to the brain. In eight cases, multiple metastases were present, and in three cases, single metastasis was present. Of these three cases with solitary metastasis, gross total resection (GTR) was done for the solitary lesion in the first case. The second case required biopsy, whereas a near-total excision was done in our case [Table 1]. In two cases, metastasis was detected postmortem.[13,17] Metastasis occurring 10 years after initial diagnosis of spinal PNET has been reported by Gollard *et al*.[4] Most of the patients received chemotherapy. In our case, metastasis to brain occurred seven years after the diagnosis of spinal PNET. Surgery was followed by radiotherapy to brain and then five cycles of chemotherapy and the disease was under control at 20 months of follow-up. There are no specific protocols for treatment of intracranial metastasis from spinal PNET, as most of the published cases are single case reports. For multiple intracranial metastasis, chemotherapy and radiotherapy are routinely given.[15,18] Recently, high dose chemotherapy with autologous stem cell support is being used for better results.[4,5,29] Surgery is restricted to solitary intracranial metastasis, ranging from biopsy to GTR.[4,19] Prognosis for patients with intracranial metastasis from spinal PNETs appears to be poor with median survival of one year (range: Few days-40 months).

Conclusion

Nearly 12% of spinal PNET tumors had intracranial metastasis. In spite of aggressive management, the median survival of these patients is one year. No standard treatment guidelines are there for the management of these tumors. Understanding the nature of these tumors and their subtypes (cPNET/pPNET) can help in better management of these tumors. Early diagnosis of metastasis and use of appropriate chemotherapy and radiotherapy, along with surgery in cases of solitary metastasis, can improve the prognosis of these patients.

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