

Synthetic treatment of intracranial peripheral primitive neuroectodermal tumor with multiple metastasis: a case report

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Abstract: Ewing sarcomas (ES) and peripheral primitive neuroectodermal tumors (pPNET) are now thought to belong to the same tumor family. Ewing sarcoma family tumor (ESFT) members commonly originate in bones and soft tissues. However, a few published articles describe ESFT arising from cranial cavities. Pathologically, ES/pPNET are composed of small round cells. Unambiguous distinction between pPNET and other small round cell tumors, in particular central PNET, is of clinical significance. Definitive diagnoses of pPNET can be obtained through CD99 (MIC2 gene product) membrane positivities and molecular identifications of chromosomal rearrangements between EWS and ETS family genes. Multimodal approaches comprising surgical resections, radiotherapies, and chemotherapies are required for the treatment of ESFT. Decompressive medical measures are preferentially performed when epidural masses are compressing spinal cords. In cases of ES-induced brain herniations, emergent radiotherapies may serve as effective tools. We report a case of multiple disseminated intracranial ES/pPNET for which synthetic treatments were used.

Keywords: primitive neuroectodermal tumors, brain neoplasms, spinal tumors, neoplasm metastases

Introduction

Ewing sarcomas (ES) and peripheral primitive neuroectodermal tumors (pPNET) are currently classified as a tumor family because they share unifying histopathological, immunohistochemical, and molecular features.^{1,2} Typical sites of occurrence for ESFT are in bones and soft tissues. However, rare cases have reported pPNET originating from cranial cavities. Here, we report a case of intracranial pPNET with multiple metastases.

Case

Informed consent was obtained from the patient and her family. The study was approved by the Institutional Review Board of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University. A 28-year-old female presented with progressive back pains occurring over 2 months' duration with pain radiating to the ipsilateral shoulder. She also had a 1-month history of upper-extremity weaknesses and a recent onset of slight headaches. No antecedent trauma had occurred in these areas. She denied having a history of nausea, vomiting, seizures, or losses of consciousness. Physical examination upon hospital admission revealed grade 4/5 power (Medical Research Council Scale) in the left upper limb and two palpable masses in the bilateral frontal regions (5 cm above the eyebrows). Further neurological examinations revealed no positive signs.

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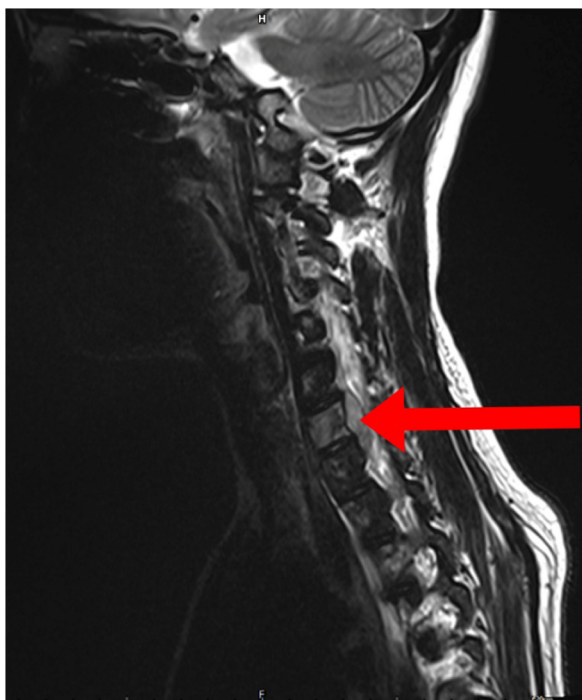


Figure 1 Magnetic resonance imaging of the spine demonstrating a mass located in the C7 epidural space (arrow).

Lactate dehydrogenase and alkaline phosphatase levels were both increased (353 and 478 U/L, respectively).

Magnetic resonance imaging (MRI; Figure 1) confirmed the presence of an extradural lesion at the spinal C7 level. The mass compressed the spinal cord, and a distinct heterogeneous enhancement was observed in the tumor. The MRI also revealed patch-like lesions with high signal intensity

(in T2 images) on the C2–5, C7, T2–5 level vertebra. Further brain MRI evaluations (Figure 2) showed two extramedullary meningeoma-like masses with bone involvements and frontal brain parenchymal compressions. A metastatic workup with a positron emission tomography and computed tomography scan was subsequently performed, and no other abnormalities were observed.

In view of the severe spinal cord compression of the C7 level extradural lesion, the patient was subjected to laminectomy and mass removal. At laminectomy, a dark red mass was found in the epidural space. The mass had adhered slightly to the dura mater, compressing the adjacent dural sac and spinal cord. The tumor was easily separated from the adjoining dura mater, allowing a gross total resection to be performed. Postoperatively, symptoms of back pain and upper-extremity weakness were dramatically resolved. After the surgery, therapeutic agents were administered, including dehydrants, steroids, lansoprazole, and neuro nutrition. Gross visualizations by histopathological analyses showed that the epidural tumor was composed of dark-red soft tissue, which measured ~1.2 cm at its largest diameter. Upon microscopic analyses of hematoxylin and eosin stained sections, the neoplasm displayed monotonous, closely packed small round blue cells with high nuclear-to-cytoplasmic ratios (Figure 3A). Typical Homer Wright rosettes were not observed. Using immunohistochemical analyses, the cells strongly expressed CD99 (Figure 3B), vimentin, and Bcl-2. Stains for neuron specific enolase (NSE), synaptophysin (Syn), and epithelial membrane antigen (EMA) were negative. For this case, further

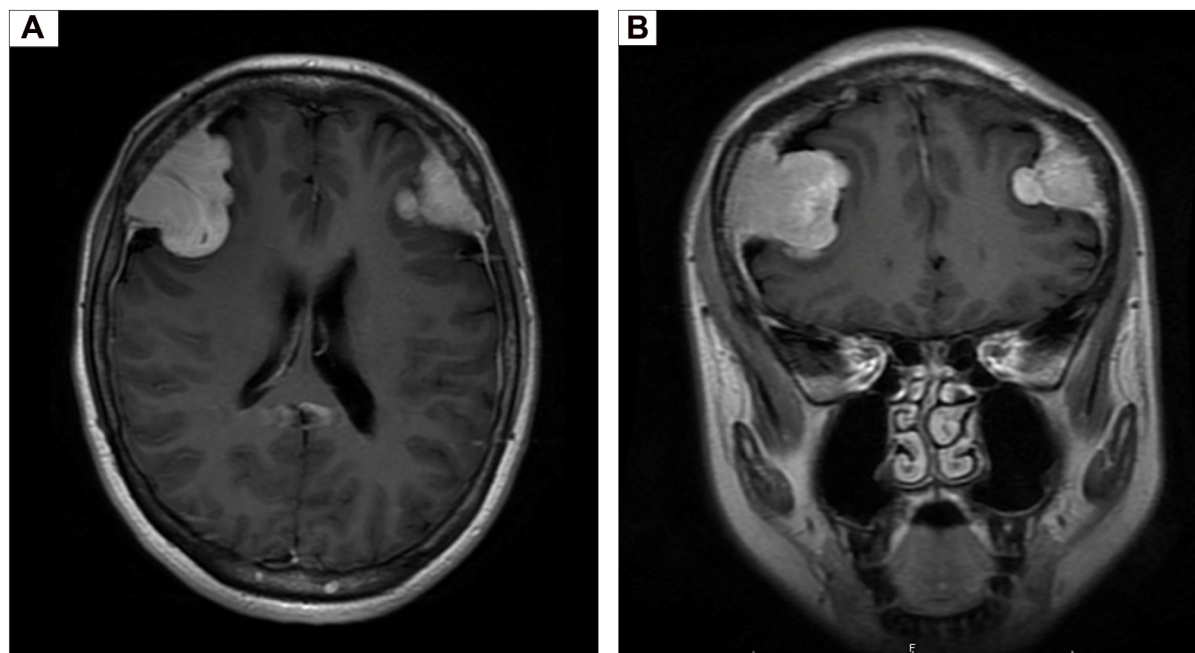


Figure 2 Axial (A) and sagittal (B) magnetic resonance imaging of the brain showing two extra-axial intracranial masses in the bilateral frontal regions.

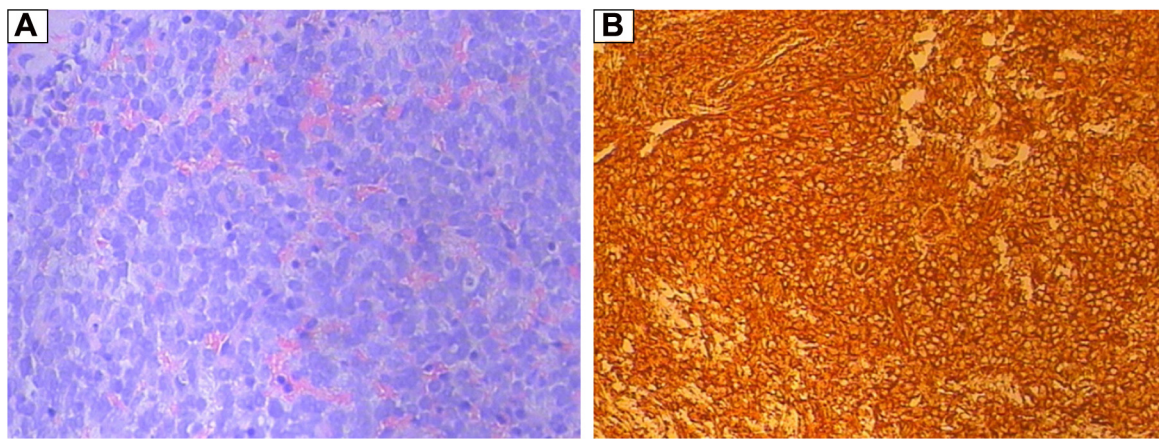


Figure 3 Hematoxylin and eosin staining (A) showing small round blue cells with a high nuclear-to-cytoplasmic ratios, and immunostaining (B) demonstrating positivity for CD99. Magnification $\times 100$.

chromosomal translocation studies were not performed. Based on the collective histopathological and immunochemical findings, a diagnosis of ES/pPNET was made.

On day 10 after the surgery, the patient's consciousness level deteriorated gradually and headache intensity increased. Upon examination, her right pupil was dilated to 5 mm, and bilateral papilledema was detected. A subsequent head computed tomography scan indicated cerebral hernia with ventricle compression. The patient was immediately transferred to our treatment center.

When arriving at our unit, the patient was in a state of stupor. Given the special symptoms she presented and the radiosensitivity of ES, the oncology team performed emergent radiotherapy. One hour later, the first four Gy were given to the whole brain. Concomitant infusion treatment strategies were also given, and included dehydrants, hormones, and parenteral and neuro nutritions. After the delivery of eight Gy/two fractions to the whole brain, her consciousness level gradually improved. Therefore, subsequent boosts of 21 Gy/seven fractions were carried out on the cerebral epidural masses. After implementation of radiation therapies, the patient underwent eight total cycles of multiagent chemotherapy treatments (ie, vincristine, cyclophosphamide, and doxorubicin) every 21 days. The patient tolerated these treatments well with the exception for myelosuppression. A complete response was observed after four cycles of chemotherapy. Subsequently, the patient has been on regular follow-up and, 13 months after diagnosis, has remained disease-free.

Discussion

ES and pPNET are now commonly considered to be one tumor family because they share histopathological features and molecular properties and have been renamed Ewing

sarcoma family tumor (ESFT).^{1,2} ESFT preferentially afflicts children and adolescents, exhibiting a slight predilection for females. Typically, ESFT occur in bones or soft tissues; origination from cranial cavities is rare. To our knowledge, only 29 cases have been reported in the body of English ESFT literature (Table 1). Despite the present case acts as multifocal disease, it was still reasonable to regard the intracranial lesions as the primary sites, because 1) size discrepancy surely exists between the intracranial masses and the spinal epidural lesion, 2) most spinal PNETs are caused by “drop” metastasis from an intracranial tumor through cerebrospinal fluid circulation,³ 3) 2 years prior to symptom of spinal tumor development, frontal masses had been palpated, and 4) at laminectomy, the spinal epidural mass was only slightly adhered to the surrounding tissue and could be easily separated. Conversely, the cerebral lesions were significantly invasive, as indicated by MRI.

Unambiguous distinction between pPNET and other small round cell tumors, in particularly central PNET, is of clinical significance. CD99-positive membrane staining is detected in nearly all cases of pPNET, which is a highly reliable biomarker, but on no account pathognomonic; CD99 also identifies other small round cell tumors, albeit with staining patterns that diverge from those observed in pPNET.⁴ Advanced molecular detection of EWS–ETS gene fusions are confirmatory for final pPNET diagnoses.⁵

Multimodal strategies, including surgery, radiation therapy, and chemotherapy, are required for the treatment of intracranial ESFT with epidural space metastases.⁶ Priority must be given to laminectomies and tumor removals when epidural masses present with spinal cord compressions. These techniques aim to obtain specimens for pathologic diagnoses and avoid permanent neurological dysfunctions.^{7,8} In these cases, close attention should be made to intracranial

Table 1 Published articles of intracranial peripheral primitive neuroectodermal tumors

Author	Case	Age/sex	Symptoms	Location(s)	Meta	Treatment(s)	Follow-up
Moblely et al ¹⁷	1	21/M	Headache, double vision, hemianopia	Right occipital parafalcine region	No	PR+CT+RT	18 months after surgery: recurrence and metastasis
Mazur et al ¹⁸	2	8/F	Headache, nausea, vomiting	Tentorium	No	PR+CT+RT	2 years after diagnosis: NED
	3	7/F	Headache, vomiting	Right frontal lobe	Lung	Surgery removal+CT+RT	N/A
Pekala et al ¹⁹	4	8/F	Headache, nausea, vomiting	Tentorium cerebelli	No	N/A	N/A
	5	7/F	Headache, vomiting, nausea	Medial right frontal lobe	Lung	N/A	N/A
Kazmi et al ²⁰	6	7/F	Headache, sluggish pupillary responses	Bifrontal tumor Extending on both sides of falx cerebri	Sphenoid sinus	GTR+RT+CT	N/A
Jay et al ²¹	7	4/M	Headache, vomiting, ataxia	Cerebellum	Conus and cauda equina	GTR+RT+CT	N/A
Papotti et al ²²	8	30/F	Headache, vertigo	Right frontal meninges	Multiple bones	GTR+CT+RT	7 years after diagnosis: NED 10 years after diagnosis: succumb to the disease
Antunes et al ²³	9	6/M	Lethargy, vomit	Right frontal dura mater	No	GTR+CT+RT	N/A
Dedeunwaerdere et al ²⁴	10	17/M	Headache	Right frontal dura mater, contralateral CP angle	No	GTR+RT	8 years: recurrence
D'Antonio et al ²⁵	11	12/M	Severe headache, left neck, arm, chest paresthesia	Right frontal dura mater	No	GTR+CT+RT	12 months after retreatment of recurrence: NED
	12	50/F	Headache, vomiting, drowsiness	Right parietotemporal dura mater	No	GTR	27 months: NED 12 months after surgery: NED
Attabib et al ²⁶	13	48/F	Headache	Cavernous sinus	No	Debulking+RT+CT	14 months after surgery: stable
Navarro et al ²⁷	14	3/M	Headache, vomiting	Right tentorium extending into both supratentorial and infratentorial compartments	No	Subtotal removal+RT+CT	14 months after surgery: NED
Mellai et al ²⁸	15	56/F	Headache, confusion, hemiparesis	Right temporal region	No	GTR	14 months after surgery: NED
Choudhury et al ²⁹	16	11/F	Headache, vomiting, left temporal scalp swelling	Left temporoparietal region	No	Surgery removal+RT+CT	N/A
Bunyaratavej et al ³⁰	17	17/F	Dizziness, left numbness weakness, headache, emesis	Right frontoparietal junction	No	GTR+RT	24 months: NED
	18	17/M	Emesis, headache	Left temporal lobe	No	GTR+RT+CT	12 months after surgery: NED
Katayama et al ³¹	19	5/M	Vomiting, left abducens nerve palsy	Tentorium	No	GTR+RT+CT	7 years after surgery: NED
Niwa et al ³²	20	5/M	Exophthalmos, bloody nasal discharge	Bilateral frontal region	No	GTR	20 days after surgery: died of renal failure
Simmons et al ³³	21	67/F	Facial pain, deterioration of hearing, headache	Cerebellopontine angle	No	Palliative RT	13 months after surgery: succumb to the disease
VandenHeuvel et al ³⁴	22	3/F	Tongue smacking, left facial twitching, impaired coordination	Right frontal lobe	No	GTR+RT+CT	6 years after diagnosis: NED
	23	2/M	Increasing number of falls	Frontal parietal lobe	No	Surgery+CT	21 months after diagnosis: NED
	24	61/M	Depressed mood, poor concentration, decreased appetite, slumping of speech, word-finding difficulty, left-sided facial droop, and left-sided weakness	Right temporal lobe	No	Surgery	Lost to follow-up

Bano et al ³⁵	25	1 I/F	Midline frontal scalp swelling, headache, giddiness, epiphora, diplopia	Anterior falx	No	Subtotal resection	N/A
Amita et al ³⁶	26	3/N/A	Generalized tonic-clonic seizure, headache, vomiting	Dura and frontal lobe	No	Surgery+CT	N/A
Idrees et al ³⁷	27	46/M	Headache, nausea, vomiting, right ophthalmoplegia, ptosis	Right cavernous sinus	No	Tumor biopsy+CT+RT	N/A
Furuno et al ³⁸	28	15/M	Headache	Right frontotemporal region	No	GTR+RT+CT	6 months after diagnosis: NED
Velivela et al ³⁹	29	13/F	Occipital headache, blurred vision	Left temporoparietal and occipital regions attached to tentorium	No	GTR+RT	24 months: NED

Abbreviations: CP, cerebellopontine; CT, chemotherapy; GTR, gross total resection; Meta, metastasis; N/A, not available; NED, no evidence of disease; PR, partial resection; RT, radiotherapy; M, male; F, female.

tumor masses to prevent disease progression due to cure delays and surgical stressors. In the present case, symptoms and signs of intracranial neoplasms became suddenly severe with subsequent development of herniation. For such cases, typical care includes immediate surgical measures to relieve cerebral hernias. Under certain circumstances, feasibility and safety of such surgeries may be dramatically limited (eg, tumors are in high-risk locations or patient rejections of further traumatic treatments). Thus, in some cases, nonsurgical methods may be useful treatment modalities. In this case, radiotherapy was chosen, with some uncertainty, as the primary treatment modality given the highly radiosensitivity of ES. In addition to radiation, other therapies, in particular dehydrants and hormone treatments, were also clinically crucial. First, they directly reduced intracranial pressures. Moreover, cellular edema occurring in initial stages of radiotherapy was alleviated by these adjuvant therapies. Overall, this case provided a novel demonstration of emergent radiation as a feasible treatment for intracranial radiosensitive tumor-induced hernias. Given that this study presents a single case, there are limitations that warrant further investigations.

Prognostication of localized pPNET has been markedly improved by multidisciplinary collaboration in the development of therapeutic proposals. However, patients with primary disseminated multifocal ES still harbor very low survival rates. Previous reports revealed that sites of metastasis were overt, independent prognostic factors. Conversely, primary disseminated ES with single pulmonary metastases often have had much better outcomes compared with metastases to other sites.⁹⁻¹¹ Additionally, negative prognoses for primary disseminated multifocal ES have correlated with relatively older patient ages (>14 years old,¹⁰ >15 years old⁹), larger primary masses volumes (>200 mL), bone marrow involvements, the presence and number of bone lesions, additional lung metastases, and fevers at diagnosis.^{9,10} ES are routinely characterized by gene fusions between EWS and ETS family genes. Retrospective studies have demonstrated different types of chromosomal rearrangements predicting divergent outcomes.^{12,13} One recent prospective cohort study found no prognostic value for characterization of any gene fusions.¹⁴ van Doorninck et al¹⁵ attributed these discrepancies regarding the value of type 1 fusions in ES prognostication to current intensive treatment proposals. Additionally, new biomarkers and molecularly detectable minimal disseminated diseases are completely novel areas for prognostication.¹⁶ Although, these new directions have potential promise, their clinical utilities require further study.

Conclusion

Intracranial pPNET are rare, but serious, diseases. Classifications of pPNET and central PNET should be completely differentiated as they display unique treatment proposals and prognostications. Emergent medical measures ought to be performed when metastatic neoplasms present as spinal cord compressions. Radiotherapy may be an effective choice to alleviate brain herniations induced by radiosensitive intracranial pPNET.

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Disclosure

The authors report no conflicts of interest in this work.

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