

Extracranial Primary Intracranial Ewing Sarcoma/peripheral Primitive Neuroectodermal Tumor: Series of Seven Cases and Review of Literature

Abstract

Background: The Ewing sarcoma peripheral PNET (ES-pPNET) is very rare small round cell tumour that involves the CNS as either a primary dural neoplasm or by direct extension from contiguous bone or soft tissue. **Materials and Methods:** Biopsy proven cases of intracranial ES/pPNET with orbital involvement operated during Jan 2010-Jan 2014 were retrospectively included and their clinical data, operative and histological findings were reviewed from institutional oncology register. **Results:** seven patients (4 males; 3 female) were studied with mean age at presentation of 13 years. Six patients had orbital involvement in one or other form. Surgical excision was gross total in five, near total in one, and subtotal in one patient. All patients received adjuvant therapy, only chemotherapy in 2, only Radiotherapy in four, both in one. MRI characteristics were studied in six patients. Four patients died with average survival of 33.2 months and three patients are having Progression free survival of average 23.3 months. **Conclusions:** The EWS-pPNET is very rare tumour and very poorly described in literature. These tumours are showing special predilection for the frontotemporal dura and erode through the flat bone of cranium like orbital roof and lateral wall of the orbit. These tumours are aggressive, multi compartmental, vascular and very rapidly growing, so missing or overlooking the primary symptoms of dural stretching/bony involvement leads to delay in management and poor outcome.

Keywords: Chemotherapy, Ewing's sarcoma, peripheral primitive neuroectodermal tumor, radiotherapy, supratentorial, survival

Introduction

The extracranial intracranial Ewing sarcoma-peripheral primitive neuroectodermal tumor (EWS-pPNET) is a very rare small, round cell tumor described as a mesenchymal, nonmeningothelial tumors in the World Health Organization classification (International Classification of Diseases-9364/3).^[1] It usually involves the central nervous system (CNS) as either a primary dural neoplasm or by direct extension from contiguous bone or soft tissue (e.g., skull, vertebra, and paraspinal soft tissue) with only a few case reports described in literature.^[2-4] The EWS-pPNET found to have a wide age range with peak incidence in the second decade. Radiologically they mimic meningioma, but their management and outcome is not very well understood because of their rarity. Hereby, we are reporting seven cases of EWS-pPNET operated at our institute with review of literature.

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Materials and Methods

A total of seven patients of intracranial EWS-pPNET were included in this retrospective study. They extracted from our departmental data records of the past 5 years' duration from the Department of Neurosurgery and Neuropathology of our Tertiary Care Centre. All the patients included were biopsy proven round cell tumor with batteries of immunohistochemistry (IHC) analysis to exclude the other similar pathology considering the operative and radiology finding Ethical Committee Board of our institute evaluate and provide clearance for this study under project "clinical, radiological and prognostic indicators of nongliomatous nonmeningiomas supratentorial lesions of the brain cases" (IEC: 2015-94-IMP-86).

Results

The age ranged from 7 years to 21 years with mean age of 13 years. There were

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4 male and 3 female patients. The most common presenting complaints were unilateral painless progressive proptosis with decreased vision noted in six patients (85.7%), and one patient (14.3%) presented with features of raised intracranial pressure (ICP). The entire patient had relevant preceding complaints; out of them, six patients (85.7%) were having headache and one patient (14.3%) was of seizure.

The most common location had been frontal dura adjacent to orbital roof (4 patients; 57.1%); however, six patients (85.7%) had orbital involvement in one or other form. The primary intracranial location was noted in one patient (14.3%). All the patients had extra-axial intracranial component. The average intracranial volume was 157.3 cm³ and average extra-cranial size was 31.5 cm³. The ratio between intracranial and extracranial was 5:1. The T1-weighted characteristics were heterointense (2 patients; 33.3%), hypointense (1 patient; 16.7%), isointense (3 patient; 50%), and hyperintense (1 patient; 16.7%). The T2-weighted characteristics were heterointense (2 patients; 33.3%), hypointense (3 patients; 50%), and isointense (1 patient; 16.7%); on gadolinium-enhanced magnetic resonance imaging (MRI), enhancement was intense in 5 patients (83.3%) to moderate (1 patient; 16.7%). Calcification and necrosis were seen in five patients (83.3%); multiple flow voids and hypervascularity were noted in three patients (50%) [Table 1].

Totally nine surgeries were performed in our series. In one case, staged surgeries (intracranial lesion in the first stage followed by intramaxillary sinus component removal in the second stage) and resurgery (for the recurrence after 1 year) was performed. Subciliary orbital approach was taken in one patient (14.3%); frontal craniotomy was done in two patients (28.6%); frontotemporal (FT) craniotomy was done in two patients (28.6%); FT-zygotomy craniotomy was done in two patients (28.6%); FT-orbito-zygotomy was done in one patient (14.3%). In one patient, two-staged surgery was done, in the first stage, intracranial lesion was removed by craniotomy followed by intramaxillary sinus component removal in the second stage by facial degloving and resurgery for the recurrence in the infratemporal compartment was performed by preauricular subtemporal craniotomy and zygomatic osteotomy [Figure 1]. The squash was sent in five cases (71.4%) and in four cases (57.1%), the report was consistent with round cell tumor. The maximum blood loss was 2500 ml, and average blood loss was 1350 ml. The histopathological evaluation of all tumors categorized as gross features, morphology, and IHC is described in Table 2. Only chemotherapy (CT) as an adjuvant treatment was given in two patients (28.57%); only radiotherapy (RT) was given in four patients (57.14%). One patient that had recurrence was initially given RT, but after recurrence, concomitant RT and CT were given.

Discussion

EWS-pPNET is an uncommon small blue cell tumor, primarily of bone mainly affecting pelvis (26%), femur (20%), and chest wall (16%) found most typically in the second decade of life with slight male preponderance.^[5,6] pPNET is a rare tumor that has the same translocation, between genes EWS and FLI1 on chromosomes 22 and 11, and is now considered to be identical to Ewing's.^[7] The Ewing's family of tumors includes EWS of bone, extrasosseous Ewing's, and peripheral PNET.

Demographic and clinical profile

In our series of seven cases, the mean age was 13 years and M:F ratio of 4:3 similar to clubbed case reports and literature to date.^[8,9] As per literature, the intracranial primary EWS-pPNET nearly always a dural-based tumor. Only two cases of primary EWS-pPNET of the CNS have been reported to be nondural-based or involving the neuraxis.^[10,11] In our series, all the cases seem to be arising from the dura and growing intradurally as well as extradurally in four cases; there is radiological evidence of destruction of the orbital roof or SOF and extension of the tumor in the orbit leading to painless ipsilateral proptosis with visual deterioration. One case presented with infratemporal extension as well. Noticing the trend, it was found that the basifrontal and temporal dura are more preferred site and because of aggressiveness of the lesion, it is eroding the thin, flat bone of orbital roof and/or lateral wall of the orbit. The involvement of these bones can be because of direct erosion by the dural-based EWS-pPNET or they are some variant of primary osseous EWS of flat bone of cranium, this requires further studies.

Six cases presented with obvious cosmetic disfigurement (proptosis) and visual deterioration. However, feature of local dural involvement and stretching in the form of headache was presented a few months earlier to the presenting complaints in these cases. The reason for such delay was because of ignorance by the family in the background of poor socioeconomic status, and in a few cases considering their age, the patient was evaluated for the refractory error and frontal sinusitis; thus, the presentation was delayed. One case of long-standing seizure was ignored and presented late with features of raised ICP. Lack of awareness and suspicion for these entities remains the major cause for delayed presentation from the onset of symptom in our series.

Radiological profile

In our series contrast, MRI was done in six cases, and contrast CT was done in one case. All the cases in our series revealed a large, single supratentorial intracranial lesion with extension to the surrounding structure except one case which was purely intra-axial lesion. None of our patients had any pulmonary metastasis. Out of seven cases, six cases had the finding of large lobulated,

Table 1: Clinico-radiological profile and management of patients in our study

Age/sex (years)	Clinical features	Location	Size (cm ³)	Radiological features	Treatment	Adjuvant therapy	Follow-up
7/female	Painless proptosis in left eye and headache (9 months)	Left orbit with greater wing of sphenoid and anterior skull base extension	4×4×6	T1-weighted: Heterointense T2-weighted: Heterointense Contrast: Heterogeneous enhancement with area of necrosis DWI: Nonrestricted	Subciliary orbital approach with total exenteration of left eye EOR: STE BL: 150 ml	Right: Not received CT: Actinomycin; vincristine; cyclophosphamide alternated by ifosfamide, etoposide, on week 0, 3, 6	35 months, expired
13/female	Painless proptosis in left eye and headache (6 months)	Left orbit with extension into anterior skull base (bifrontal extra-axial extension) via superior orbital fissure	6.5×3.5×4.5 (frontal) 3.5×3×3 (orbital)	T1-weighted: Hypointense T2-weighted: Hypointense Contrast: Moderate enhancement with areas of calcification DWI: Not restricted	Bicoronal flap with left frontal craniotomy EOR: GTE BL: 2000ml	Right: 8 Gy in 1 fraction (6/9/13) in pelvis for metastasis (palliative) 50.4 Gy in 28 fractions (1/9/10) CT: Not received	48 months, expired
11/male	Proptosis right eye and headache (2 months)	Right temporal extra-axial mass, attached to tentorial dura and extending to infratemporal fossa and involving the superior orbital fissure	7.5×6.8×7.0 intracranial 4.5×4×3 infratemporal	T1-weighted: Isointense T2-weighted: Hypointense Contrast: Well enhanced with peripheral cyst and calcification DWI: Restricted	First stage: Right frontotemporal craniotomy with zygomatic osteotomy Second stage: Facial degloving approach - transmaxillary approach Third surgery for recurrence after 1 years: Reexploration with preauricular subtemporal craniotomy with zygomatic osteotomy EOR: GTE BL: 1500 ml, 1000 ml and 2500 ml in each stage, respectively	Right: 55.8 Gy in 31 fractions (11/1/13) 45 Gy in 25 fractions (5/3/15) CT: Actinomycin; vincristine; cyclophosphamide alternated by Ifosfamide, Etoposide, on week 0, 3, 6	31 months, expired
9/male	Right eye proptosis and headache (7 months)	Right orbital roof with bone destruction and extra-dural frontal extension	4×3.6×2	T1-weighted: Heterointense T2-weighted: Hypointense Contrast: Intense contrast enhancement with dural enhancement with necrotic and calcification area DWI: Unavailable	Right frontotemporal craniotomy with orbito-zygotomy EOR: NTE	Right: 50 Gy in 28 fraction CT: Not received	19 months, expired

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Table 1: Contd...

Age/sex (years)	Clinical features	Location	Size (cm ³)	Radiological features	Treatment	Adjuvant therapy	Follow-up
21/male	Diplopia and right proptosis with headache (6 months)	Right orbital roof and lateral wall involvement with extra-axial frontotemporal extension	4.5×4.5×3.8	T1-weighted: Isointense with peripheral hyperintense areas T2-weighted: Heterogeneous Contrast: Intense contrast enhancement with necrotic and calcification area DWI: Nonrestricted	Right frontotemporal craniotomy with Zygomatic osteotomy EOR: GTE of intradural and orbital portion BL: 1200 ml	Right: 55 Gy in 30 fractions CT: Not received	24 months, expired
18/male	Raised ICP with seizure (12 months)	Left frontoparietal convexity	7×7×6	T1-weighted: Hypointense T2-weighted: Hyperintense Contrast: Intense contrast enhancement DWI: Restricted	Left frontal parasagittal craniotomy EOR: GTE BL: 1500 ml	Right: 55 Gy in 30 fractions CT: Not received	12 months, expired
12/female	Right eye proptosis with headache (9 months)	Right lesser wing of sphenoid involvement with extra-conal orbital extension via superior orbital fissure	5×4.5×6.5	CECT: Hyperdense with extensive vascularity in the tumor with intense contrast enhancement	Right frontotemporal craniotomy with orbito-zygotomy EOR: NTE BL: 1800 ml	Right: 50 Gy in 28 fraction CT: Not received	19 months, expired

GTE – Gross total excision; NTE – Near total excision; STE – Subtotal excision; CECT – Contrast enhance computerized tomography; EOR – Extent of resection; BL – Blood loss; ICP – Intracranial pressure; DWI – Diffusion-weighted image

well-circumscribed, diffuse intense enhancement with broad dural attachment, which was consistent with major radiological study by Pekala *et al.*^[12] The detail radiological description of eight cases from different studies summarized by Pekala *et al.* concluded that variability is the rule with both T1 and T2 signal intensity in CNS-EES cases and that variability noticed in our series with the common T1 characteristics was heterointense or isointense (83.3%) and common T2 characteristics was heterointense or hypointense (83.3%) [Figure 2]. The factors proposed by Pekala *et al.* for this variability were cyst and hemorrhages in the tumor; however, in our series, we have noticed significant incidence of necrosis and calcification within the tumor (50%) and (66.7%), respectively, which was confirmed on biopsy. The incidence of the cyst was less and was encountered in two cases (28.6%) and mainly in peripheral part of the intracranial tumor. The diffusion-weighted image was done in four cases, and no specific pattern was observed in contrast to the early observation made by Pekala *et al.*^[12] We have also encountered a hyperdense tumor on CT with intense contrast enhancement similar to the finding reported in the above study. The radiological pattern in our cases was

consistent to hypercellular, vascular tumor, and common radiological differential diagnosis had been aggressive meningioma, hemangiopericytoma, or rhabdomyosarcoma considering the locations. The MRS report was not available; however, it can contribute similarly to the other PNET in the form of decreased *N*-acetylaspartate and creatinine, increased choline, and presence of lactate peak overlapping with alanine peak. Doubtful taurine peak at 3.4 ppm had been also appreciated in a few cases.^[13]

Surgical treatment

The maximum safe resection followed by chemo-RT or both is the main management policy of these tumors. The craniotomy was performed in six cases based on their location. One case operated by the neuro-ophthalmology team, the subciliary orbital approach was taken, and subtotal excision (STE) was performed. Rest of the patient was operated by the neurosurgical team, and gross total excision (GTE) or near total excision (NTE) was achieved. The average blood loss was 1350 ml. In case no. 3, staged surgery after the first craniotomy in the form of facial degloving was done to remove tumor from the maxillary sinus, and resurgery for the recurrence in the infratemporal

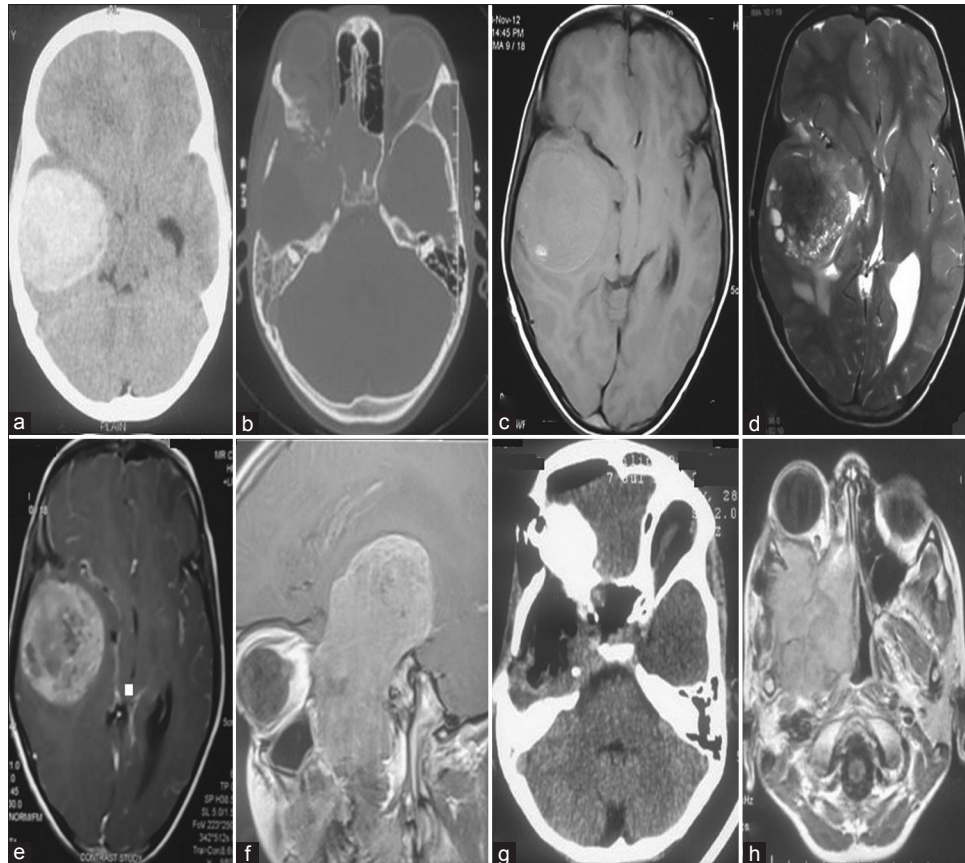


Figure 1: (a and b) Noncontrast computed tomography showing dural-based hyperdense lesion in infratemporal fossa and extra-axial temporal region with bony destruction, (c) T1-weighted magnetic resonance imaging-isointense, (d) T2-weighted magnetic resonance imaging-hypointense lesion, (e and f) heterogeneous contrast enhancement, (g) complete removal after surgery in postoperative contrast-enhanced computed tomography, (h) recurrence of lesion after 1 year in infratemporal fossa and paranasal sinus seen in contrast magnetic resonance imaging

compartment was performed by preauricular subtemporal craniotomy and zygomatic osteotomy with the help of neuro-otologist. The squash was sent in five cases (71.4%) and in four cases (80%), the report was consistent with round cell tumor.

Histopathological evaluation

In 1921, James Ewing first described “round cell sarcoma” occurring in long bones.^[14] These tumors are composed of broadsheets of small, round cells showing sparse cytoplasm, smooth, round nuclei with fine chromatin pattern with low mitotic rate with few organelles and sparse glycogen content.^[15] pPNET, however, shows more variation than conventional EWS with occasional rosette formation and sometimes pinkish appearance with more cytoplasm. These cells typically show high mitosis in contrast with classical EWS.^[15] In our series, we found sheets of round to oval tumor cells, having mildly anisomorphic round nuclei, dispersed chromatin, inconspicuous nucleoli, and scant amount of cytoplasm [Figure 3].

On IHC, these tumors are not only characterized by the expression of CD 99 (cell surface glycoprotein p30/30MIC2), the so-called “EWS antigen,” but CD99 can also be expressed by CNS PNET, medulloblastoma,

and hemangiopericytoma. Most of these tumors are immunoreactive for vimentin, may also express neuron-specific enolase (NSE), or positivity for S-100 protein, leu-7. In our series, we found all tumors to be positive for CD99 (one showed focal positivity), four showed positivity for vimentin and NSE positivity in three. These tumors also show reactivity for cytokeratin in up to 20% of cases.^[16]

As these tumors show similarity with other small round cell tumors, detailed IHC studies should be done in these patients. Neuroblastoma also shows immunoreactivity to NSE, S-100, and Leu-7 but is negative for vimentin and neurofilament protein which are positive in pPNET variant of EWS. Similarly, lymphoblastic lymphoma shows immunoreactivity for CD99 similar to EWS, but these lesions can be differentiated by formers immunoreactivity for leukocyte common antigen (CD 45), other lymphoid markers, and the periventricular location of tumors compared to peripherally place dural-based lesions of EWS-pPNET.

Molecular genetics studies such as reverse transcriptase (RT) polymerase chain reaction, fluorescence *in situ* hybridization serve as an indistinct tool for the

Table 2: Histopathological characteristics

Age/sex (year)	Gross	Morphological characteristics	Immuno-histochemistry (positive)	Immuno-histochemistry (negative)	CD99	Vimentin	Intraoperative squash smear
7/female	Multiple grayish white tissue pieces	Section shows infiltration of fibro-fatty tissue by sheets and cords of small round atypical cells. Rosettes are also seen at places. Large areas of necrosis hemorrhage and congested blood vessels are also seen	Diffuse positivity for CD99, NSE and focal positivity for chromogranin, synaptophysin, and neurofilament	Negative for desmin, myogenin, vimentin, s100 and cytokeratin	+	-	
13/female	Irregular grayish white tissue piece	Highly cellular tumor arranged in sheets with formation of nodules in places. Foci of hemorrhage and coagulative tumor necrosis. Increased mitotic activity	Positive for CD99, NSE	Negative for LCA and synaptophysin, vimentin	Focal +	-	Small round cell tumor
11/male	Grey brown globular tissue	Sheets of tumor cells separated by fibrous septa. PAS stain reveals granular cytoplasmic positivity suggestive of glycogen. Mitosis is frequent. Large areas reveal tumor diathesis, infarct type necrosis, and hemorrhage	Strong positivity for CD99 and vimentin and are (Ki-67 index is 30%)	Negative for EMA, desmin, myogenin, synaptophysin and CD117	++ strongly	+	
12/female	Grayish white tissue pieces	Cellular tumor disposed in sheets separated by thick fibrocollagenous tissue. Frequent mitotic activity and large areas of necrosis are seen	Positive for neuron-specific enolase and CD99	LCA, vimentin, and desmin are negative	Strongly +	-	Small round cell tumor
9/male	Multiple gray-white tissue pieces	Infiltrating tumor disposed in solid sheets separated by thin fibrovascular septa. Brisk mitosis, areas of necrosis is seen	Positive for CD99 and vimentin	EMA and NSE are negative	Focally +	Focally +	Round cell tumor
21/male	Gray-brown tissue piece	Infiltrative tumor with areas of hemorrhage and large areas of necrosis. The tumor cells are disposed in sheets with few interspersed thin-walled blood vessels showing a hemangiopericytomatous pattern at places. Mitosis is frequent. The right temporal bone flap and the dura show infiltration by a similar tumor	Diffusely positive for CD99 and vimentin and focally positive for NSE	Negative for myogenin, LCA, and synaptophysin	+	+	Findings suggest mesenchymal malignancy

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Table 2: Contd...

Age/sex (year)	Gross	Morphological characteristics	Immuno-histochemistry (positive)	Immuno-histochemistry (negative)	CD99	Vimentin	Intraoperative squash smear
18/male	Gray-brown tissue	Highly cellular tumor disposed in sheets and nests dissected by multiple variable sized congested vascular channels. Nuclear molding at places. Numerous mitotic figures and apoptotic bodies are seen. Foci of necrosis and hemorrhage are also noted	Positive for CD99 and vimentin, focally positive for GFAP (Ki67 index is ~80%)	Negative for LCA	+	+	Round cell tumor

NSE – Neuron-specific enolase; LCA – Leukocyte common antigen; PAS – Periodic acid-Schiff; EMA – Epithelial membrane antigen; GFAP – Glial fibrillary acidic protein

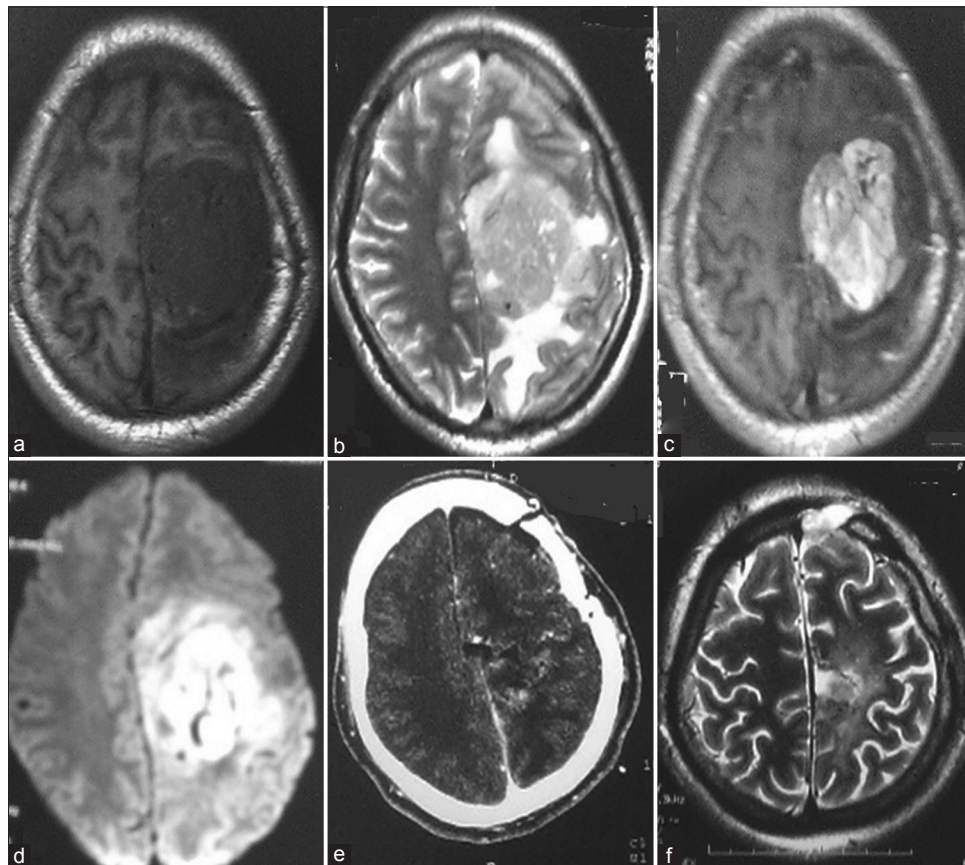


Figure 2: (a) T1-weighted magnetic resonance imaging showing hypointense lesion in frontoparietal convexity region, (b) T2-weighted magnetic resonance imaging: Hyperintense with multiple flow voids and adjacent edema, (c) well-enhanced on contrast, (d) diffusion-weighted image suggestive of restriction in lesion. (e and f) Postoperative chemotherapy (immediate postoperative) and magnetic resonance imaging (after 3 months) suggestive of complete excision after surgery

evaluation of undifferentiated small round cell tumors, especially when histological and IHC features are not confirmatory. Detection of specific translocations are helpful for definitive diagnosis of EWS-pPNET. A balanced translocation involving chromosomes 11 and 22, which fuse portions of the EWS gene on 22q12 with the FLI1

gene on 11q24, ($t[11;22] [q24; q12]$) considered to be pathognomic of the lesion is found in 85% of these tumors, and this lead to the formation of a new fusion gene with oncogenic properties.^[17] Various other translocations have been described, most of these resulting in fusion between EWS gene on chromosome 22 and other members of

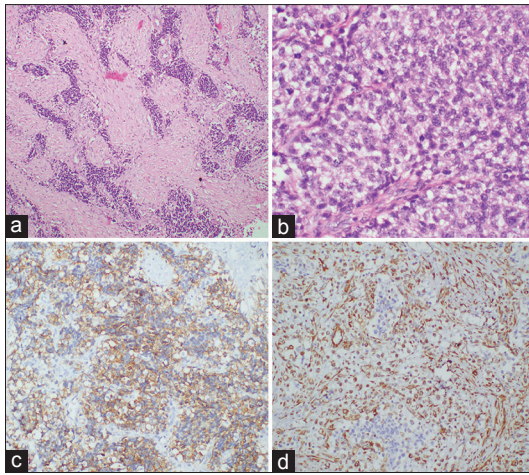


Figure 3: (a) Low power view showing tumor islands separated by desmoplastic stroma (×40), (b) pictomicrograph showing a cellular tumor composed of cells having round to irregular hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm with increased mitotic activity (H and E, ×400), (c) tumor cells showing cytoplasmic CD99 positivity (×400), (d) vimentin immunostain showing positivity in stromal cells, tumor cells are negative (×200)

transcription regulator family ETS, such as ERG on 21q22, E1AF on 17q12, ETV1 on 7p22, and FEV on 2q33. Moreover, rare cases of FUS-ERG fusion transcripts are described.^[18] These translocations help in differentiation ES-pNET from other round cell tumors.

Adjuvant chemo-radiotherapy

The treatment protocol of EWS-pNET is poorly described in literature because of the paucity of the large series and follow-up; however, in most of the scattered case reports, it is agreed upon that differentiation between central-PNET (c-PNET), and EWS-pNET is important as the treatment and prognosis is entirely different.^[19,20] The main-stay of treatment for these tumors is gross total excision of tumor followed by RT and CT. For adjuvant therapy, we consider the following facts if tumor bed is relatively small and there is no evidence of multicentricity of the lesion RT along with CT (modified St Jude protocol) is preferred.^[21-23] Whereas in cases of pediatric patient (age below 3 years), very large tumor or multicentric tumors only CT is preferred. However, in our series, patient/relatives were counseled, and adjuvant treatment was tailored as per their need and agreement. In our series, adjuvant CT in the form of VAC (vincristine; actinomycin-D; cyclophosphamide) regimen alternated with II regimen (ifosfamide; etoposide) was given alone in two cases.^[22] Adjuvant RT alone was given in four cases and both was given in only one case that is case no. 3 on different occasions.

Outcome and prognosis

In supratentorial c-PNET, the 5-year progression-free survival and overall survival reported by Reddy *et al.* are 37% and 53%, respectively, in contrast to p-PNET which are showing

better long-term disease-free survival.^[19,20,24] In our series, four patient died (57%) with minimum survival of 19 months and maximal survival of 48 months with an average survival of 33.25%. Out of remaining three patients, two are progression free for 24 months and one is for 22 months. The apparent poor prognosis in our series can be attributed to the large tumor size, late presentation, multicompartmental location, and aggressive tumoral behavior.

Limitation of study

In spite of involvement of very rare EWS-pNET case series with review of literature, some limitations include only small retrospective sample size and unavailability of molecular diagnosis in tumor evaluation.

Conclusion

The EWS-pNET is a rare tumor with poorly described in literature till date. These tumors are showing special predilection for the FT dura and erode through the flat bone of cranium such as orbital roof and lateral wall of the orbit. Whether they are arising from the flat bone of cranium such as osseous ES or these flat bones are stimulating the nearest dura to produce the tumor is matter of further large study. These tumors are aggressive, multicompartmental, vascular, and growing rapidly, so missing or overlooking the primary symptoms of dural stretching/bony involvement leads to delay in management and poor outcome.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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