

Primary Intracranial Ewing Sarcoma: Case series and review of literature

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ABSTRACT

Ewing sarcoma, along with peripheral primitive neuroectodermal tumour, belongs to a tumour family that shares clinicopathologic and molecular genetic features, including the characteristic chromosomal translocation that results in the fusion of EWS gene on 22q12 to either FLI1 gene on 11q24. In contrast, such translocations are not found in central primitive neuroectodermal tumours (cPNETs). Ewing sarcoma has only rarely been noted to primarily involve the central nervous system- extraosseous Ewing sarcoma (CNS-ESS). We report a case series of three patients with intracranial extension.

Keywords: Ewings sarcoma, neuroectodermal tumour.

INTRODUCTION

Ewing sarcoma/peripheral primitive neuroectodermal tumour (ES/pPNET) is a malignant small, round cell tumour seen in children and young adults arising from bone and soft tissue in children and young adults [1]. Its usual locations are diaphysis of long bones, pelvis, ribs, vertebrae, and rarely skull. Primary ES/ pPNET affecting CNS is rare, usually intraparenchymal or in the spinal cord [2] accounts for only 1-4% of extraosseous Ewing sarcoma. Ewing sarcoma differs from CNS embryonal tumours, formerly called central (supratentorial) primitive neuroectodermal tumours (cPNET) with respect to underlying genetics, treatment and prognosis [3]. An early and accurate diagnosis of ES/ pPNET is required so that multimodality treatment approach can be adopted as early as possible to prevent distant metastasis. As the tumour presents in young age, long term survival remains a challenge in the management of ES/pPNET.

Case Report 1:

A 16 year old male presented with recurrent episodes of headache and vomiting for 3 months without any neurological deficit. MRI Brain showed 62x60x78mm extra-axial mass lesion along posterior inter-hemispheric fissure & occipital lobe with marked dural thickening, mass effect & underlying bony erosions. Provisional diagnosis of atypical meningioma was made.

Preoperative MRI(1) coronal section (2) sagittal section of the brain showed a left occipital lesion, hypointense on T1, heterointense on T2, with heterogenous enhancement.

Patient was taken up for sub-occipital craniotomy with SOL excision with cranioplasty. Post op CT Scan showed ill defined hypodense area in left parietal region with mass effect. Patient was then taken up for re-exploration for excision of remnant of supratentorial extension of tumour.

HPER(18-2988/3288) showed malignant small round cell tumour ? Ewing's sarcoma/primitive neuroectodermal tumour.

Photomicrograph showing a richly vascular small round cell tumor adjacent the dura (H and E, ×100).

Immunoreactivity to the surface antigen CD99 / MIC2, which is expressed in up to 97% of the cases.

Immunopositivity for CD99, negative for synaptophysin, chromogranin & FISH positive for EWSR1 translocation confirmed the diagnosis..

PET-SCAN done to see multicentric origin showed post-op changes with no distant metastasis.

Patient was asymptomatic but considering the high risk of metastasis, patient was given six cycles of chemotherapy with vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide. Radiation with a dose of 45 Gy was prescribed at the local site. The treatment was completed with another 6 cycles of same combination of chemotherapeutic drugs.

A 3 month follow up MRI demonstrated post-op changes with gliosis in bilateral occipital lobe.

The patient is doing well and is under post treatment surveillance.

Case Report 2:

A 28 year old boy with no significant past medical or surgical history, presented to the emergency department of our institution with a one week history of noticeable weakness on the left side, particularly of the left upper extremity. Physical examination revealed a preference for movement of the right side and no voluntary movement of the left upper extremity, particularly hand grip. The remaining findings of the neurologic examination were intact and no papillary edema was noted.

MRI of the brain with and without contrast enhancement demonstrated a 6.8 x 6.5 x 6.5 cm circumscribed mixed solid and cystic intra-axial right frontal parietal lesion. FLAIR imaging revealed peritumoral white matter vasogenic edema.

HPER/(18-4699/4565) was suggestive of "neuroepithelial tumor possibly ependymoma".

Immunohistochemistry for GFAP demonstrated scant positive tumor cells.

Positive immunoreactivity for CD99, synaptophysin and epithelial membrane antigen (EMA). Immunohistochemistry also demonstrated strong nuclear immunoreactivity for BAF47.

FISH demonstrated a classic rearrangement of the 3' EWSR1 gene using a breakapart probe.

The patient remains well and tumor free 21 months after the initial diagnosis, and has completed chemotherapy and radiation therapy at the time of writing. He was given eight cycles of chemotherapy with vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide. Radiation with a dose of 45 Gy was prescribed to the post op site. The treatment was completed with another four cycles of same combination of chemotherapeutic drugs.

Since the completion of therapy, he has been admitted once for new onset of seizures and has had a gastric tube placed due to poor oral intake and failure to thrive, but continues to develop and maintain his near-normal neurologic baseline.

Case Report 3:

A 23 year old male presented with complaint of headache, vomiting, sudden episode of loss of consciousness for four days.

MRI Brain showed 7.2x7.5x5.0 cm well defined extra axial lesion in basifrontal region in the midline, arising from the floor of anterior cranial fossa, suggestive of large olfactory groove meningioma with intra tumoral vascularity and areas of hemorrhage.

Patient underwent craniotomy, decompression and excision of the tumour.

HPER(3085/18)- Histological features were suggestive of small round blue cell tumour possibly Ewing Sarcoma/ Primitive Neuroectodermal Tumour.

On IHC, tumour cells were strongly positive for CD99(A), Vimentin(B), S100 and CD34.

FISH demonstrated EWSR1 Gene translocation.

Post op Scan was suggestive of residual disease.

In WHOLE BODY PET-CT, no other abnormal FDG AVID lesion was seen in rest of the region surveyed

Patient underwent VP shunting with tumour removal, followed by six cycles of chemotherapy with vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide. Radiation with a dose of 45 Gy was prescribed to the post op site. Six more cycles of adjuvant chemotherapy were given. The patient remained asymptomatic but lost to follow up 8 months after the completion of the treatment.

Case Report 4:

A 18 year old male presented in emergency with an episode of left facial twitching, impaired co-ordination and simple partial seizures. Fundus examination revealed no abnormalities. Computerized tomography (CT) without contrast enhancement demonstrated a circumscribed right frontal lobe hyperdense mass with central cavitation and surrounding vasogenic edema.

CT image of Case 4 demonstrates a round lesion with peritumoral vasogenic edema (A). Remodeling of the bone overlying the tumor is also noted (B)

Patient underwent craniotomy and decompression of tumour. HPER showed small round blue cell tumour? Ewings sarcoma. Positive immunoreactivity for CD99, synaptophysin and FISH positive for EWSR1 gene confirmed the histopathology. After gross total resection, the patient was subsequently treated with radiation therapy and chemotherapy with vincristine, cyclophosphamide, and doxorubicin alternating with Ifosfamide, Etoposide. As a complication of therapy, she developed heart failure and died.

CASE	AGE	SITE	PRESENTATION	STAGING	SURGERY-RT	REGIMEN	RECURRENCE	FOLLOW UP
1	16	Left parietal lobe	Headache, vomiting	Localised	Y	VAC+IE	-	9 months
2	28	Rtfrontoparietal lobe	Left upper limb weakness	Localised	Y	VAC+IE	-	22 months
3	23	Basifrontal region	Headache, vomiting, loss of consciousness	Localised	Y	VAC+IE	-	Lost follow up
4	18	Rt frontal lobe	Simple partial seizures	Localised	Y	VAC+IE	-	Death

Discussion

James Ewing first described Ewing Sarcoma[4], a lethal primary bone tumour that affects children and young adults and most frequently originates in the long bones(47%), pelvis(19%), ribs (12%).The skull is rarely involved in less than 4% cases.[5,6].

Extrasosseus Ewing sarcoma is a distinct disease entity that affects young adults in the second and third decade of life, with equal sex predilection.. They commonly involve paravertebral regions of the spine, rarely arise in the intracranial compartment, where they are commonly misdiagnosed as c-PNET, because of histological similarity[7].

Jay *et al* first described a patient with isolated posterior fossa mass that resembled medulloblastoma histologically, but demonstrated t(11;22) (q24;12) translocation, which confirmed CNS-EES[8].

Primary intracranial ES/ pPNET is a recently recognised entity of CNS PNET[9]. Paulus *et al* studied 2500 cases of brain tumours out of which only 9 were sarcomas. Of these, only one case was reported as Ewing sarcoma[10]. Krishnamani *et al* studied 332 cases of Ewing sarcoma over 11 years, out of which only 7 cases were Ewing sarcoma skull[11]. The term ES is used for tumours with absent or limited neuroectodermal differentiation whereas ‘‘PNET’’ is employed for tumours with definite neuroectodermal features. ‘‘ES/ pPNET’’ best describes this overlapping entity[7]. Both cPNET and pPNET

are aggressive tumours but they differ in their cell of origin. The cPNET arise from precursor cell of subependymal matrix of the CNS or external granular layer of the cerebellum, pinealocytes, subependymal cells of the ventricles while Ppnet are derived from the neural crest located outside the CNS[8].

These tumours are composed of small undifferentiated neuroectodermal cells with microscopic features of glial or neuronal differentiation[12]. CNS-EES demonstrates a strong membranous expression of the MIC-2 gene product, CD-99, which is specifically recognised by the monoclonal antibodies O13 and HBA71[12-15]. The chromosomal translocation t(11;22)(q24;12), detected by FISH, is found in 90% EES but not in cPNET.

Large collaborative studies have shown that interval compressed chemotherapy results in improved survival outcomes and is the standard of care[16]. A Brazilian collaborative study found that patients treated with radiation alone had worse outcomes as compare to chemoradiotherapy[17].

The approach now a days is multimodality treatment comprising of surgery, chemotherapy, and radiation. Chemotherapy forms the backbone of the treatment modality. Multiagent chemotherapy regimens include cyclophosphamide, ifosfamide, doxorubicin, dactinomycin, and etoposide[18,19]. The primary treatment for localized EES consists of neoadjuvant chemotherapy, with a combination of treatment is completed with similar chemotherapy combination for 36 to 49 weeks. Patients with EES that arises from structures within or around the CNS have more favourable outcome than patients with cPNET[21].

Conclusion

While cPNET and ES/pPNET are both treated with surgical resection, chemotherapy and radiation, the regimens used differ greatly, and response to the therapy is driven by different factors. It is for this reason that these must be carefully differentiated, and this can often be accomplished through use of special stains, IHC, testing for EWSR1 mutation. Long term disease free survival is possible with adherence to the appropriate therapeutic regimen.

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