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CLINICAL STUDY

Primary orbital Ewing sarcoma family of tumors: a study of 12 cases

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Abstract

Purpose **The purpose of this study is to discuss the clinical presentation, management, and outcomes of patients with primary orbital Ewing sarcoma family of tumors (ESFTs).**

Patients and methods **Retrospective study of 12 patients with biopsy-proven primary orbital ESFT.**

Results **The mean age at presentation of primary orbital ESFT was 12 years (median, 8 years; range, 5 months to 28 years). There were seven (58%) females and five (42%) males. The presenting complaints included proptosis ($n=10$; 83%) and swelling in the upper eyelid ($n=2$; 17%). The mean duration of symptoms was 9 weeks (median, 5 weeks; range, 2–24 weeks). Tumor epicenter was located in the superior orbit ($n=6$; 50%), lateral orbit ($n=3$; 25%), inferior orbit ($n=2$; 17%), and medial orbit ($n=1$; 8%). Computed tomography of the orbits revealed predominant bony lesion ($n=10$; 83%) or isolated soft tissue/extraosseous lesion ($n=2$, 17%). At presentation, extraorbital extension was noticed in 10 patients including intra cranial extension ($n=7$; 58%), extension into temporal fossa ($n=4$; 33%), nasal cavity ($n=2$; 17%), maxillary sinus ($n=2$; 17%), and ethmoid sinus ($n=1$, 8%). Systemic metastases at presentation was detected in five (42%) patients involving the bone marrow ($n=4$; 33%), kidney ($n=1$; 8%), and retroperitoneal lymphnode ($n=1$; 8%). Multimodal treatment including a combination of neoadjuvant chemotherapy, excision biopsy/debulking, and/or radiotherapy was given. Over a mean follow-up period of 21 months (median, 7 months; range, 1–152 months), disease-related death occurred in 11 (92%) cases.**

Conclusion **Primary orbital ESFT is aggressive at presentation and is associated with poor prognosis.**

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Introduction

Ewing sarcoma family of tumors (ESFTs) are malignant tumors of neuroectodermal origin, arising within the bone or soft tissue. ESFT encompasses Ewing sarcoma of the bone (ESB), extraosseous Ewing sarcoma (EES), peripheral primitive neuroectodermal tumor (pPNET) of the bone, and Askin's tumor of the chest wall.[1] Classical Ewing sarcoma (ESB and EES) displays minimal evidence of neural differentitation and pPNET is characterized by neural differentiation by standard microscopy, electron microscopy, or immunohistochemistry.[1] These tumors are characterized by similar morphological features of small round blue cell tumors, immunohistochemical features of expression of membrane CD99 protein, cytogenetic features of t(11;22) translocation or t(21;22) rearrangement, and molecular features of hybrid transcripts of the EWS gene with the FLI1 or ERG gene.[1,2]

In a study of 856 cases of ESFT, the tumor site included lower extremity (35%), chest (21%), pelvis (17%), spine (10%), upper extremity (9%), head and neck (6%), and abdomen (2%).[3] Primary orbital ESFT is extremely rare with isolated case reports and small case series reported in literature.[4–22] Herein we discuss the demographic profile, clinical features, radiological features, treatment modalities, and outcomes of primary orbital ESFTs.

Methods

Institutional review board approval was obtained for the study. A database search was conducted for the diagnosis of 'Ewing sarcoma orbit' managed at the Operation Eyesight Universal Institute for Eye Cancer, LV Prasad

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Table 1 Details of patients with primary orbital Ewing family of tumors

Case	*Age (years)*	*Gender*	*Tumor location in the orbit*	*Osseous or extraosseous lesion*	*Locoregional tumor extension*	*Final diagnosis*	*Metastasis at presentation*	*Final outcome*	*Follow-up duration (months)*
1	28	M	Superior	Osseous	Intracranial	pPNET	Yes (bone marrow)	Dead	3
2	28	F	Temporal	Osseous	Intracranial, temporal fossa	ESB	No	Dead	28
3	5	M	Superior	Osseous	none	ESB	Yes (bone marrow, retroperitoneal lymph nodes)	Dead	6
4	20	F	Temporal	Osseous	Intracranial, temporal fossa	ESB	Yes (bone marrow)	Dead	2
5	2	F	Superior	Extraosseous	none	EES	No	Dead	8
6	6	F	Temporal	Osseous	Temporal fossa, nasal cavity, maxillary sinus, anterior ethmoid sinus	ESB	No	Dead	11
7	26	F	Superior	Osseous	Intracranial	ESB	Yes (renal lesions)	Dead	3
8	6	M	Inferior	Osseous	Intracranial, temporal fossa	pPNET	Yes (bone marrow)	Dead	1
9	7	M	Medial	Osseous	Intracranial, nasal cavity	pPNET	No	Dead	23
10	11	M	Superior	Extraosseous	none	EES	No	Dead	7
11	8	F	Superior	Osseous	Intracranial	ESB	No	Dead	6
12	0.4	F	Inferior	Osseous	Maxillary sinus	ESB	No	Alive	152

Abbreviations: EES, extraosseous Ewing sarcoma; ESB, Ewing sarcoma of the bone; F, female; M, male; pPNET, peripheral primitive neuroectodermal tumor.

Eye Institute, Hyderabad, from January 1996 to October 2016. Inclusion criteria were histopathologically confirmed cases of primary ESFT. Those with inadequate data or with orbital metastasis of Ewing sarcoma from elsewhere were excluded.

Medical records were analysed for age at presentation, gender, laterality, symptoms, duration of symptoms, clinical features, radiological features, treatment, histopathological features, and outcome. Computed tomography (CT) images of the orbit were reviewed from the photography archives. The tumor epicenter, predominant osseous or extraosseous component, and extent of the lesion were noted. All patients were examined by the medical oncologist at initial presentation and systemic work-up (bone marrow biopsy, contrast enhanced CT chest, ultrasound/CT abdomen, and bone scan) was done.

All patients underwent incision biopsy/debulking of the lesion to confirm the diagnosis of ESFT. The lesions with indistinct neural differentiation on histopathology with predominant osseous lesion clinicoradiologically were classified as ESB and those with exclusive extraosseous component clinicoradiologically were classified as EES. The tumors with evidence of neural differentiation and rosettes/pseudorosettes were classified as pPNET. After the histopathology confirmation of the diagnosis, the treatment was initiated. The treatment protocol included four to five cycles of neoadjuvant chemotherapy with vincristine, adriamycin, and cyclophosphamide alternating with etoposide and ifosfamide, local therapy of surgical excision/debulking, and/or radiotherapy followed by continuation of chemotherapy with similar agents, to complete a duration of 49 weeks.

Follow-up was done every 3 weeks during chemotherapy and every 3 months thereafter for the next 1 year, and every 6 months thereafter. A detailed systemic evaluation was done at each follow-up visit by the medical oncologist. Any event of metastasis or death was noted.

Results

Fourteen cases with orbital ESFTs were identified during the study period. One patient was initially diagnosed with primary orbital ESFTs but on further evaluation, was detected to have the primary site of origin at right tibia with secondary orbital involvement. Another patient was a diagnosed case of ESFT of the left tibia with spinal metastasis and presented to us with secondary orbital involvement. Both these patients with secondary orbital involvement were excluded from the study.

A total of 12 cases met the inclusion criteria (Table 1). The mean age at presentation was 12 years (median, 8

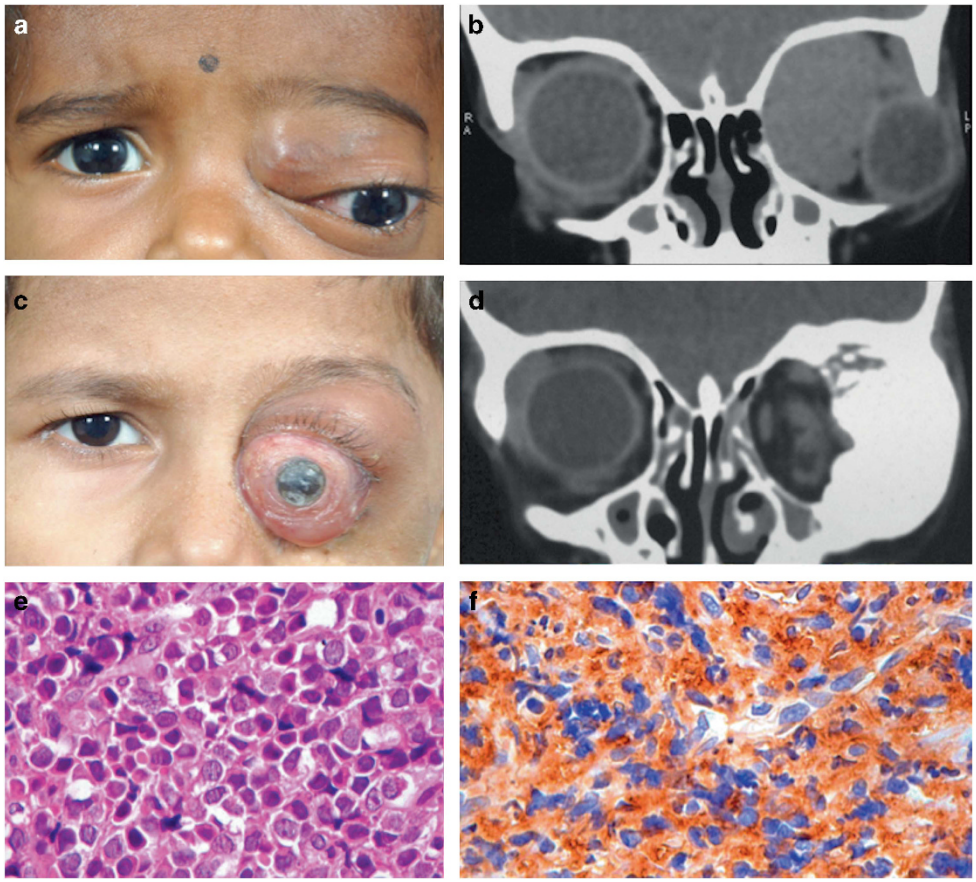

Figure 1 Clinical presentation, radiological features, histopathology, and immunohistochemistry of primary orbital Ewing family of tumors. (a) A 2-year-old child with superior orbital mass in the left orbit with inferior globe dystopia. (b) Computed tomography (CT) orbit revealed a soft tissue lesion in the superonasal orbit without bony erosion. (c) A 6-year-old child with left eye proptosis with inferior globe dystopia. (d) CT orbit revealed bony lesion involving the lateral orbital wall. (e) Photomicrograph shows sheets of small round cells with scanty cytoplasm and mitotic figures (hematoxylin and eosin stain, original magnification ×40). (f) Immunohistochemistry revealing strong positivity of tumour cells with anti-CD99 antibodies (original magnification ×40).

years; range, 5 months to 28 years). Seven (58%) of the 12 patients were younger than 10 years of age. There were seven (58%) females and five (42%) males. All of them had unilateral disease with the left eye being involved in 10 (83%) and right in 2 (17%). The presenting complaints included proptosis ($n=10$; 83%) and swelling in the upper eyelid ($n=2$; 17%). The mean duration of symptoms was 9 weeks (median, 5 weeks; range, 2–24 weeks). Tumor epicenter was located in the superior orbit ($n=6$; 50%), lateral orbit ($n=3$; 25%), inferior orbit ($n=2$; 17%), and medial orbit ($n=1$; 8%). Regional lymphadenopathy was present in two patients including submandibular lymph nodes ($n=1$, 17%) and upper deep cervical lymph nodes ($n=1$; 17%).

CT orbits (Figure 1) revealed predominant osseous lesion in 10 (83%) patients, whereas 2 (17%) patients presented with isolated soft tissue/extraosseous lesion without signs of bone erosion/ destruction. At presentation, extraorbital extension was noted in 10 (87%) patients including intra cranial extension ($n=7$; 58%), extension into the temporal fossa ($n=4$; 33%), nasal cavity ($n=2$; 17%), maxillary sinus ($n=2$; 17%), and ethmoid sinus ($n=1$, 8%). Among the 12 patients, systemic metastases at presentation were detected in 5 (42%) patients involving the bone marrow ($n=4$; 33%), kidney ($n=1$; 8%), and retroperitoneal lymphnode ($n=1$; 8%). No extraorbital extension or systemic metastasis was detected in the two patients with extraosseous ESFTs.

Ten patients with locoregional tumor extension underwent incision biopsy from the lesion for histopathological diagnosis and two patients with isolated well-defined extraosseous lesion underwent tumor debulking/excision biopsy. Light microscopic examination revealed sheets of small, round, uniform cells with scant clear cytoplasm, indistinct cell membranes, round nuclei with indentations, and small nucleoli. Homer–Wright rosettes or pseudorosettes were present in three (25%) patients. Immunohistochemistry

demonstrated CD 99/ MIC-2 positivity in all the patients confirming the diagnosis of ESFTs. Based on clinicoradiological features, histopathology, and immunohistochemistry, the final diagnosis was made as ESB in seven (58%), EES in two (17%), and pPNET in three (25%) patients. Systemic chemotherapy was given to all patients and only six patients received adjuvant external beam radiotherapy of 50 Gy to the orbit, as six patients died while on chemotherapy early in the follow-up before the commencement of radiotherapy.

Over a mean follow-up period of 21 months (median, 7 months; range, 1–152 months), disease-related death occurred in 11 (92%) cases. Among the 11 patients who died, the mean survival time was 10 months (median, 7 months; range, 1–30 months).

Four (33%) patients survived for <6 months after diagnosis of ESFTs. At presentation, all these patients were >5 years of age at presentation, had predominant osseous lesion with intracranial tumor extension, and systemic metastasis at presentation (bone marrow metastasis = 1; renal metastasis = 1). At the time of this manuscript preparation, only one patient was alive. This patient presented at 5 months of age with ESB with tumor extension into the maxillary sinus but with no evidence of metastasis at presentation or during the follow-up period. The patient responded well to treatment and is disease free at 12 years of follow-up.

Discussion

ESFT is a highly malignant tumor of the bone and soft tissue and is most commonly seen in children and young adults under the age of 20 years.[1] The mean age at presentation in males is 10–14 years and in females is 5–9 years.[1] In our series, 9 (75%) patients were ≤ 20 years at presentation and the mean age at presentation was 13 years in females and 11 years in males.

ESFTs most commonly involves the central axis including pelvis (17–20%) and chest (20–21%).[1,3] ESFTs involving head and neck is seen in only 3–9% cases.[1,3,22] In an analysis of large series of 183 cases of head and neck ESFTs, orbit involvement was evident in only 3 (2%) cases, suggestive of its rarity.[23] There are only 41 cases of primary orbital ESFTs published in the literature.[4,24] Based on the available data, the mean age at presentation of these published cases was 7 years (median, 7 years; range, 0.5–20 years).[4,24] In our series, the mean age at presentation was higher at 12 years, whereas the median age at presentation was comparable at 8 years.

Of all ESFTs, osseous lesions with/without soft tissue component (85%) are more common compared with soft tissue/extraosseous lesions (15%).[3] ESB most commonly involves upper or lower extremity (44–52%).[1,3] EES commonly involves extremities (26%), head and neck (18%), and retroperitoneum (16%).[25] pPNET commonly involves chest (44%), pelvis and abdomen (26%), extremities (20%), and head and neck (6%).[1] ESFTs of head and neck commonly involves bones of the skull and face, including mandible in 49% and soft tissues of head and neck in 30% cases.[23] In our series of primary orbital ESFTs, an osseous lesion was noted in 10 (83%) and soft tissue/extraosseous lesion in 2 (17%) cases. Based on histopathology, immunohistochemistry, and clinicoradiological features, the lesions were classified as ESB in seven (58%), EES in two (17%), and pPNET in three (25%) patients.

Ewing sarcoma has a better prognosis than pPNET. Schmidt *et al*[26] studied 81 cases of Ewing sarcoma and 36 cases of pPNET, and reported a disease-free survival rate of 60% in Ewing sarcoma and 45% in pPNET patients at 7.5 years follow-up. However, this study included ESFTs at any site but not limited to the orbit. In our study of primary orbital ESFTs, only one patient survived over a mean follow-up period of 21 months and this patient had ESB. All patients with pPNET died within 2 years of diagnosis.

Histopathologically, ESFTs are composed of small, round, hyperchromatic cells with varying degrees of neural differentiation. Differential diagnosis of small round cell tumors include ESFT, neuroblastoma, rhabdomyosarcoma, lymphoma, osteogenic sarcoma, and mesenchymal chondrosarcoma.[4,27] Immunohistochemical and/or ultrastructural techniques are useful to establish the diagnosis. Immunostaining with CD99 is the keystone in the diagnosis and is a common feature of ESFTs.[4] In our study, CD99 was positive in all cases. Fluorescence *in situ* hybridization studies to detect chromosome (11;22) translocation can also be used for definite diagnosis of ESFTs.[4]

ESFTs exhibits rapid progression and have poor prognosis. Local tumor extension and clinical metastases are often found during initial diagnosis of ESFTs. Overt metastatic disease is evident in 20–25% cases.[1] It is assumed that most patients with ESFTs have a subclinical metastatic disease at presentation due to its association with high relapse rate in patients treated with only local treatment without systemic chemotherapy. In patients with no clinically detectable metastatic disease, bone marrow micrometastases has been detected by reverse transcription-polymerase chain reaction in 20–30% patients.[1,28,29] In our series, local tumor extension was evident in 10 (83%) and overt metastasis at presentation in 5 (42%) cases.

The current treatment strategy for ESFTs is combined neoadjuvant chemotherapy with surgical resection or radiotherapy followed by adjuvant chemotherapy.[1] The treatment plan consists of three stages, which includes initial cytoreduction with chemotherapy to eradicate

micro metastatic disease and facilitate effective local tumor control measures, definitive radiation or surgical therapy to eradicate all known disease, and consolidation therapy for eradication of occult residual disease to reduce the likelihood of tumor recurrence. Multiagent chemotherapeutic protocols using doxorubicin, cyclophosphamide, vincristine, dactinomycin, ifosfamide, etoposide, topotecan, irinotecan, and cisplatin have been used in various clinical trials.[1,3,30–32] Alternating courses of vincristine, doxorubicin, and cyclophosphomide, with ifosfamide and etoposide, are most commonly used, similar to our series. There are no proven benefits of bone marrow transplantation, stem cell transplantation, and targeted therapy. The treatment of metastatic disease is similar to localized ESFTs with multimodal treatment; however, the cure rate is poor.[33,34] In an analysis of 975 patients with ESFTs, it was noted that the 5-year relapse-free survival in patients with no metastasis at presentation was 55 versus 22% for patients with metastasis at presentation.[35]

The poor prognostic factors for ESFTs are metastatic disease at presentation, large tumor >5 cm, older age, male gender, central tumor location including skull, clavicle, ribs, pelvis, vertebrae, and the upper extremities.[35,36–38] Orbital ESFT is considered to be less aggressive than ESFT at other locations in the body,[4–23,39] as the survival has been more than 6 months in majority of the reported cases. Although extraorbital extension is frequently reported with primary orbital ESFTs, systemic metastases at presentation or during follow-up duration is rare as per the available literature.[4–23,39] However, in our series, systemic metastases was detected in five (42%) patients at presentation and the most common site of metastasis was the bone marrow (33%). Of the reported 41 cases in the literature, disease-related mortality was noted in 9 (22%) patients over a mean follow-up period of 27 months (median, 17 months; range, 3–84 months).[4–23,39] However, in our series, disease-related mortality was noted in 11 (92%) patients over a mean follow-up period of 21 months (median, 7 months; range, 1–152 months) despite using a standard treatment protocol. The high rate of mortality in our series could be attributed to referral bias or advanced disease including intracranial extension ($n=7$), and/or systemic metastasis ($n=5$) at presentation. In our series, all patients with systemic metastasis at presentation died due to the disease before completion of treatment.

In our series, complete surgical debulking could not be achieved in cases ($n=10$) with extensive locoregional involvement of the tumor. Of these 10 patients, only 1 patient survived following subsequent systemic chemotherapy and orbital radiotherapy. Only two patients with isolated well-defined extraosseous lesions underwent complete surgical debulking/excision biopsy, but both died due to the disease in less than one year. As this is a retrospective study, it is difficult to predict whether complete/near-total surgical debulking in cases with extensive locoregional tumor could influence the final outcome. However, it should be noted that, in cases with extenive orbital disease with tumor extension into paranasal sinuses, brain, and surrounding vital structures, complete tumor resection remains a challenge. Combination of systemic chemotherapy and radiotherapy may be an effective alternative to surgical resection in selected cases for local tumor control, where surgical resection results in significant cosmetic mutilation and/or physical handicap.[21,40] However, a combination of surgical resection, chemotherapy, and radiotherapy is associated with better locoregional control and survival rate compared with those without surgical resection.[40]

In a study of 1039 localized ESFT patients who underwent treatment, the 5-year overall event-free survival estimate for extraosseous ESFTs was 76% compared with 69% for patients with osseous ESFTs.[41] However, patients with systemic metastasis at presentation have a poor prognosis with survival rate of only 20%.[42] In our study, seven patients had intracranial extension and five had systemic metastasis at presentation, and all of them died due to the disease. The only patient who survived had an osseous lesion with no evidence of intracranial extension or systemic metastasis at presentation.

In summary, primary ESFTs of the orbit is a rare tumor, which poses a diagnostic challenge and demands a very high index of suspicion. Older age at presentation (>1 year), intracranial tumor extension, and systemic metastasis at presentation are poor prognostic features in primary orbital ESFTs.

Summary

What was known before

- Ewing family of tumors in the orbit is rare and less information known about its prognosis, as <50 cases have been published in the literature.

What this study adds

- The clinical presentation of Ewing family of tumors in the orbit and the prognosis of this rare tumor.

Conflict of interest

The authors declare no conflict of interest.

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