Primary Ewing's sarcoma of the ethmoid sinus with orbital extension in a young child: A rare case and review of literature

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Key words: Ethmoid sinus, Ewing sarcoma, orbital extension

The Ewing's sarcoma family of tumors (ESFT) is a highly malignant, small round cell neoplasm derived from primitive neuroectodermal cells with variable grades of neuronal differentiation.[1] The two primary forms are skeletal and extraskeletal ESFT. It represents the second most primary bone malignancy accounting for more than 10% of all bone tumors and 4% of head and neck tumors. The commonly affected sites are long bones of the extremities and pelvis. The extraskeletal variety primarily affects the soft tissues of the lower extremities, paravertebral tissues, chest wall, and retroperitoneum.[2] Primary Ewing's Sarcoma (ES) originating from the ethmoidal sinus is rare. Only a few such cases have been published to the best of our knowledge [Table 1].[3–10] We report a young boy who presented with orbital proptosis with reduced vision and was diagnosed as primary ES of the ethmoidal sinus with orbital extension; it was managed successfully with chemotherapy and radiotherapy alone.

A 13-year-old boy presented with proptosis and reduced vision of the right eye (RE) with anosmia and nasal obstruction for two months. General and systemic examination was unremarkable. Ophthalmic examination showed significant abaxial proptosis with downward (11 mm) and temporal (5mm) displacement of the RE [Fig. 1a]. Extraocular movements were limited in supraduction and adduction. A 3 × 2 cm firm, non-compressible, tender mass was palpable in the

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Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_236_22

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Received: 26-Jan-2022 Revision: 22-Feb-2022
Accepted: 01-Mar-2022 Published: 30-Jun-2022

Cite this article as: Kasturi N, Sarkar S, Gokhale T, Ganesh RN. Primary Ewing's sarcoma of the ethmoid sinus with orbital extension in a young child: A rare case and review of literature. Indian J Ophthalmol 2022;70:2741-4.

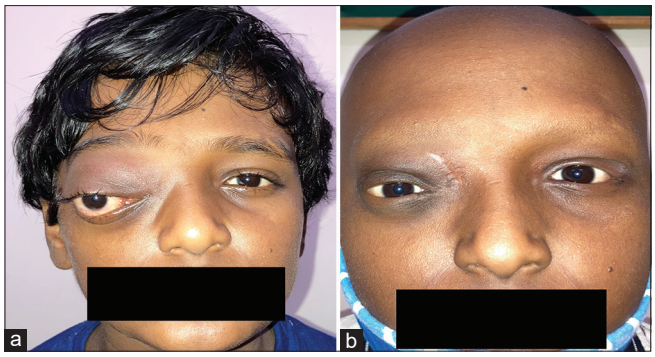

Figure 1: (a) Clinical photograph showing right eye proptosis with dystopia and mass in the superonasal orbit; (b) Clinical photograph showing resolution of proptosis following chemotherapy

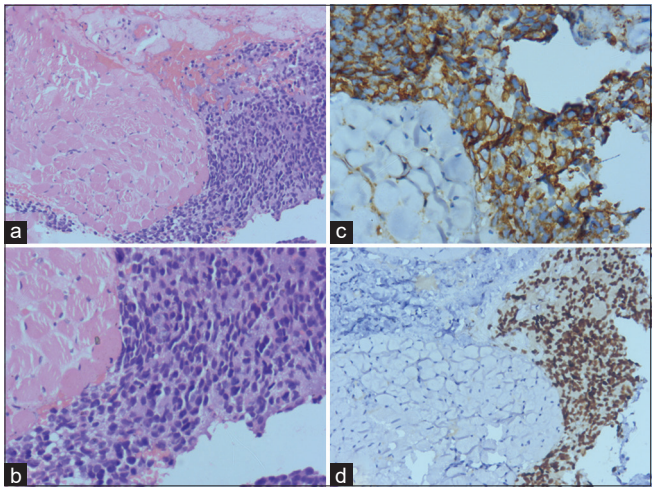

Figure 3: (a) Section shows a small round cell tumor infiltrating the skeletal muscle bundles (Hematoxylin and Eosin (H and E) stain, ×40); (b) Section shows higher magnification of small round tumor cells with stippled chromatin, and cells are arranged in rosettes (H and E stain, ×400); (c) Section shows tumor cells highlighted in the cell membrane by CD99 primary antibody from DAKO antibody, USA (Diaminobenzidine stain with hematoxylin, ×400); (d) Section shows tumor cells highlighted in the nucleus by NKX2.2 primary antibody from DAKO antibody, USA (Diaminobenzidine stain with hematoxylin, ×40)

superomedial region above the medial palpebral ligament. The retropulsion test was negative, and the posterior extent of the mass was not determined clinically. The best-corrected visual acuity (BCVA) was 6/60 in RE and 6/6 in the left eye (LE), and intraocular pressure was normal in both eyes. Slit-lamp examination revealed exposure keratitis inferiorly in RE. The anterior segment of LE and the dilated fundus examination of both eyes were unremarkable.

Non-contrast computed tomography (NCCT) revealed a solid mass occupying the right ethmoidal sinus extending into the superomedial extraconal space with medial and superior orbital wall erosion. A sunburst pattern of periosteal reaction was noted with loss of fat planes near the superior and medial recti. Magnetic resonance imaging (MRI) showed large circumscribed expansile lobulated T1 isointense and T2/FLAIR heterogeneously hyperintense lesion with an epicenter

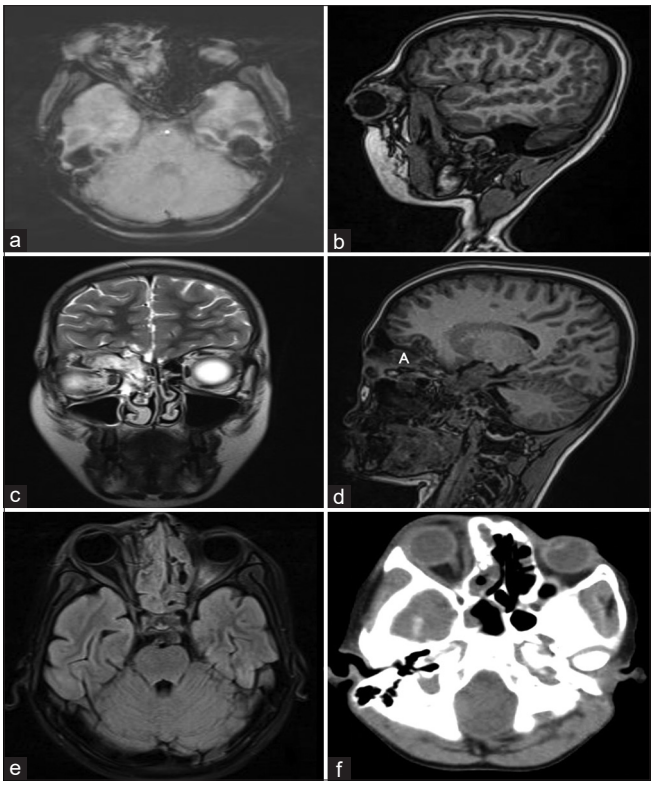

Figure 2: (a and b) MRI showing large circumscribed expansile lobulated T1 isointense, and T2/FLAIR heterogeneously hyperintense lesion with an epicenter around the medial wall of right orbit, and ethmoid cells noted measuring about 32 × 39 × 53 mm with heterogeneous enhancement and no restricted diffusion; (c and d) MRI showing expansile heterogeneously enhancing lesion with epicenter in the medial wall of right orbit and ethmoid sinuses, with the remodeling of the floor of anterior cranial fossa with compression on the right frontal lobe; (e) MRI and (f) CT scan images showing mild proptosis with no evidence of residual mass or recurrence

around the medial wall of right orbit and ethmoid cells. There was a remodeling of the anterior cranial fossa floor with compression on the right frontal lobe and extension into the right orbit [Fig. 2a–d]. Nasal endoscopy showed an avascular solid mass in the anterior ethmoidal sinus. An incisional biopsy was performed through the right upper eyelid crease. The histopathological section showed predominantly fibromuscular tissue with separately lying tiny fragments of malignant small round cell tumor infiltrating the fibrous tissue [Fig. 3 a–d]. The tumor cells were positive for NKX2.2, CD99, vimentin, and focally for pan-cytokeratin while negative for EMA, CD34, chromogranin, MyoD1, TLE-1, and LCA. Based on the above evidence, the diagnosis of primary ES of the ethmoid sinus with right orbital extension was established. The metastatic workup did not reveal any signs of distant metastasis.

The child was treated with combined chemotherapy and radiotherapy. The chemotherapy regimen (VAC/IE) included vincristine, adriamycin, cyclophosphamide alternating with ifosfamide (2450 mg/m^2 on days 1–5) and etoposide (140 mg/m^2 on days 1–5) every two weeks for a total of 10 cycles. After completion of the chemotherapy, the child received 55.8 Gy in 31 fractions radiotherapy to the residual tumor volume using volumetric modulated arc therapy (VMAT).

Table 1: Summary of all ethmoidal Ewing's sarcoma cases

Author	Age/Sex	Location	Treatment	Course	Follow up
Suzuki *et al*.[3]	23 y/M	Mass involving the left nasal cavity, maxillary antrum, and ethmoid sinus	Surgical resection+Chemotherapy (VDC/IE) + RT (50.4 Gy)	No evidence of further disease and metastasis	30 months
Li M *et al*.[4]	39 y/F	Ethmoid sinus with intracranial and orbital extension	Chemotherapy (VDC/IE) regimen + RT (55.8 Gy)	Patient fully recovered without any recurrence	32 months
Neguru ME *et al*.[5]	33 y/M	Ethmoid sinus, sphenoid sinus with intracranial extension	Chemotherapy (Vincristine + Doxurubicin+Ifosamide + G-CSF) + RT (54 Gy)	Patient fully recovered without any recurrence	15 months
Aferzon *et al*.[6]	14 y/M	Ethmoid sinus	Surgical excision+Chemotherapy (VDC/IE regimen) - 12 cycles + RT (5040 cGy)	Fully recovered without any recurrence or metastasis	Last follow up period not mentioned
Whaley *et al*.[7]	9 y/F	Ethmoid sinus	Biopsy+Chemotherapy (Actinomycin D, Cyclophosphamide, Vincristine) + RT (55.8 Gy)	No evidence of disease	10 years
Gray *et al*.[8]	15 y/F	Ethmoid sinus involving the skull and orbit	Chemotherapy (VDC/IE) + RT (59.4 GyE of proton)	Fully recovered without any recurrence or metastasis	12 months
Meccariello G *et al*.[9]	6 y/Boy	Left ethmoidal sinus with orbital extension	Neoadjuvant chemotherapy+Wide surgical excision + Brachytherapy + RT	Disease free	14 months
Velche-Haag *et al*.[10]	Not mentioned	Ethmoid sinus	Exision + Chemotherapy + RT	Full recovery	Not specified

Chemo, Chemotherapy; RT, Radiotherapy; M, Male; F, Female V, Vincristine; D, Doxorubicin; C, Cyclophosphamide; I, Ifosfamide; E, Etoposide

Sequential boost technique, and subsequently, 6 MV photons were also delivered. On completion of chemo- and radiotherapy, mild proptosis with no evidence of residual mass or recurrence was observed on repeat MRI [Fig. 2e] and CT scan [Fig. 2f]. No metabolic activity was noted on positron emission tomography-computed tomography (PET-CT). The BCVA improved to 6/6 with complete resolution of proptosis [Fig. 1b]. The child has been on follow-up after completion of therapy for the last 32 months and has been disease-free to date.

Discussion

ESFT includes skeletal or soft tissue ES, peripheral primitive neuroectodermal tumors of bone (pPNET), and Askin's (thoracopulmonary) tumors.[1,3] Primary ES commonly occurs in early childhood or adolescence with male gender predominance. Histopathologically, ES comprises of uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic cytoplasm, and PAS-positive intracytoplasmic glycogen granules.[4] Other small round cell tumors such as ESFT, neuroblastoma, rhabdomyosarcoma, lymphoma, osteogenic sarcoma, and mesenchymal chondrosarcoma share similar characteristics. Hence, clinical, radiological, histopathological, and cytogenetic analyses are needed for diagnosis.

ES is characterized by the fusion of FLI1, ERG genes with the EWS gene, and translocation of the EWS gene at 22q12 position. The EWS gene is fused with the FLI1 gene located on 11q24, causing a translocation at t(22;11), finally leading to an EWS–FLI1 fusion gene found in more than 85% of the cases of ES.[1] Sinonasal ES can affect the frontal, ethmoidal, maxillary sinuses, or the nasal cavity presenting as an increasing mass, nasal blockage, rhinorrhea, epistaxis, and proptosis due to orbital extension.[4,9] The maxillary followed by the ethmoid are most commonly affected sinus. Ethmoidal sinus ES can extend towards the maxillary sinus, sphenoid sinus, nasal cavity, orbits, and intracranial. Ethmoid sinus has minimal space and thin, bony lamina papyracea causing direct tumor extension into the orbits.[4] About 18% of ES patients present with metastasis as an initial presentation, with lungs and bones being the commonest site.[5] The prognosis varies with the patient's age, location, the presence of distant metastasis, and associated comorbidities. The recent advances in the treatment protocol of ES have improved the survival rate in patients without metastatic diseases.[3] A multidisciplinary treatment protocol with chemoreduction followed by debulking surgery, adjuvant chemotherapy, and radiotherapy is required for a favorable outcome. The recommended chemotherapy regimen is alternating cycles of vincristine-doxorubicin, cyclophosphamide, and ifosfamide, etoposide.[2] In our case, the patient responded well to chemotherapy and radiotherapy. Surgical resection of the tumor was not needed as it showed complete resolution on a repeat CT scan following complete therapy. Similar to ours, few cases of ethmoid sinus ES were managed with chemotherapy and radiotherapy alone, with favorable outcomes reported.[4] We have been following this child for 32 months and have been disease-free since then. Our case shows that successful outcomes can be achieved in these cases with timely diagnosis and treatment with chemotherapy and radiotherapy only.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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