

# Aggressive high-grade Ewing's sarcoma of maxilla: A rare case report

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## Abstract

Ewing's sarcoma (ES) is an uncommon malignancy of childhood and adults that constitutes 6%–8% of all primary malignant tumors and the third-most common tumor after osteosarcoma and chondrosarcoma, frequently involves the mandible among jaw bones. This article presents a rare case of ES of maxilla in a 22-year-old male patient showing extensive lesion into skull base which was confirmed with computed tomography, dilemmatic histopathologic features in H and E which is not a frequent presentation. Histopathologic features showed monotonous round cells with hypo- and hyper-cellular areas, intralesional hemorrhage and necrosis with lesional cells positive for CD99. Although the prognosis is poor, early diagnosis and long-term follow-up can improve the survival. The diagnosis was confirmed by immunohistochemistry where lesional cells were positive for CD 99 and vimentin. ES of maxilla is a rare and aggressive tumor. Hence, early diagnosis, combined therapy, and long-term follow-up are suggested in such cases.

**Keywords:** CD99, Ewing's sarcoma, maxilla, round cells

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## INTRODUCTION

Ewing's sarcoma (ES) is a rare malignant round cell tumor occurring as a primary neoplasm of bone sarcoma which was named after James Ewing who first described it in the year 1921.<sup>[1]</sup> It belongs to the ES family of tumors (ESFT) which is an aggressive form of childhood malignancy. The other malignancies in ESFT include peripheral primitive neuroectodermal tumor (PNET), neuroepithelioma and Askin's tumor (neoplasm involving thoracopulmonary region).<sup>[1-3]</sup> ES is considered as the second-most common tumor in children and adolescents.<sup>[2]</sup> Although it may involve any bone, diaphysis of long bones and pelvic girdle are involved most commonly.<sup>[4]</sup> ES constitutes about

6%–8% of all primary malignant tumors and represents the third-most common bone neoplasm preceded by osteosarcoma and chondrosarcoma.<sup>[5]</sup> It has now been documented as a distinct entity of primitive mesenchymal stem cells that have undergone reciprocal translocation of chromosomes 11 and 22.<sup>[3,6]</sup>

## CASE REPORT

A 22-year-old male reported with a chief complaint of pain and swelling in the upper left tooth region for 9 months. The swelling involved the orbital floor. There was no compromise in vision of the left eye. The swelling was initially small in size measuring around 3 cm, which

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then gradually increased to the present size [Figure 1]. Pain started 9 months back, and it was associated with mobility of tooth. Pain was dull and intermittent in nature, aggravated while sleeping on left side and relieved spontaneously. The patient gave a personal history of smoking two cigarettes per day for the past 3 years.

Intraorally, the patient presented with a solitary, well-defined, sessile swelling on the left side of the palate measuring 5 cm × 3 cm in size extending from 23 up to 28 region, displacement of tooth to the buccal side was seen with respect to 27. There was grade II mobility with respect to 27 and 28 [Figure 2].

On radiographic examination, orthopantomogram reveals displacement of 27 and 28, haziness of the left maxillary sinus along with loss of lamina dura; paranasal sinus view reveals break in continuity of superior wall of maxillary sinus. For determining the extent of the lesion, computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed.

CT scan revealed a large destructive lesion involving maxillary sinus and maxilla on the left side. Lesion involved alveolar process of maxilla involving hard palate with thinning and elevation of the left orbital floor along with destruction of wall of the maxillary floor. Lesion showed moderate heterogeneously enhancing mass. Small necrotic areas were seen, extended into the left nasal cavity. There was partial destruction of nasal septum and destruction of pterygoid plate on the left side [Figure 3]. The mass was extending in the left ethmoid sinus. Intraoral extension with mild destruction of zygoma is seen. Mass measured around 6.8 cm × 5.5 cm × 7.5 cm. Mucosal thickening was seen in left frontal and left ethmoidal sinuses. The left orbital cavity was compromised with normal intraorbital contents [Figure 4].

### HEMATOLOGICAL INVESTIGATIONS

Hb – 14.2 g%, red blood cell (RBC) – 4.7 cells/mm<sup>3</sup>; TC – 14,000 cells/mm<sup>3</sup>, erythrocyte sedimentation rate – 16 mm/h, packed cell volume – 43%; bleeding time – 3 min 30 s, clotting time – 6 min; differential count-neutrophils–65%, lymphocytes–35%, eosinophils–0%, monocytes and basophils–0%; blood Group-B, Rh Type-+ve, HIV-negative (tridot), HBSAg– negative.

### BIOCHEMICAL INVESTIGATIONS

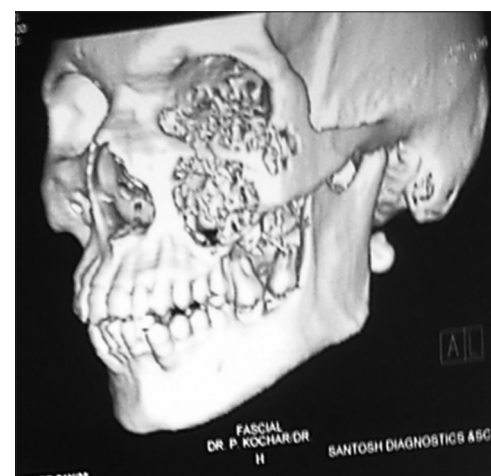
Using autobiochemistry analyzer (Robonik Prietest, Robonik India Private Limited, Mumbai, India), the following were investigated: blood sugar – 125 mg/dL, urea, SGOT,



**Figure 1:** Extraoral well-defined swelling on the left mid-face region



**Figure 2:** Intraorally, well-defined, sessile swelling on the left side of the palate.



**Figure 3:** Computed tomography scan showing three-dimensional view of the extent of the lesion, revealing large destructive lesion involving maxillary sinus and maxilla on the left side

SGPT, K, Na and Ca. The above parameters were within the normal range. Urine analysis revealed pH – 6.0; specific

gravity – 1.030; albumin – Nil; sugar – Nil; pus cells – 2 to 3 cells/high power field; epithelial cells – 1 to 2 cells/high power field and RBC – Nil.

An incisional biopsy was performed, and the specimen was subjected to histopathological examination. During biopsy, extensive bleeding was noted which is controlled with cautery. Grossly, the specimen was grayish white, soft to firm in consistency. Sections were stained with H and E. On microscopic examination, sections revealed areas of connective tissue devoid of epithelium. The lesional connective tissue showed hypo- and hyper-cellular areas, [Figure 5a] intralesional hemorrhage and necrotic areas, with some pleomorphic, hyperchromatic and monomorphous round cells. Perivascular hyalinization along with extensive vascularity with hemangiopericytoma like areas was also seen [Figure 5b]. The present case was also positive for intracytoplasmic glycogen with periodic acid–Schiff (PAS) reagent [Figure 6]. Histopathologically, it was confirmed as a high-grade sarcoma and subjected to panel of IHC markers.

The tissue sections were subjected to a panel of immunohistochemical markers. The neoplastic cells were positive for CD99 [Figure 7], FLI-1, Vimentin [Figure 8] and were negative for cytokeratin smooth muscle actin, muscle-specific actin, Desmin, B-Catenin, Calponin, CD31, epithelial membrane antigen (EMA), S100, synaptophysin, chromogranin, glial fibrillary acidic protein (GFAP) and CD56. The overall features were suggestive of ES.

## DISCUSSION

ES is a highly malignant neoplasm of neuroectodermal origin composed of small, round, generally uniform cells with small, round, lightly stippled nuclei and glycogen-rich cytoplasm. Until recently, ES and PNET were classified as

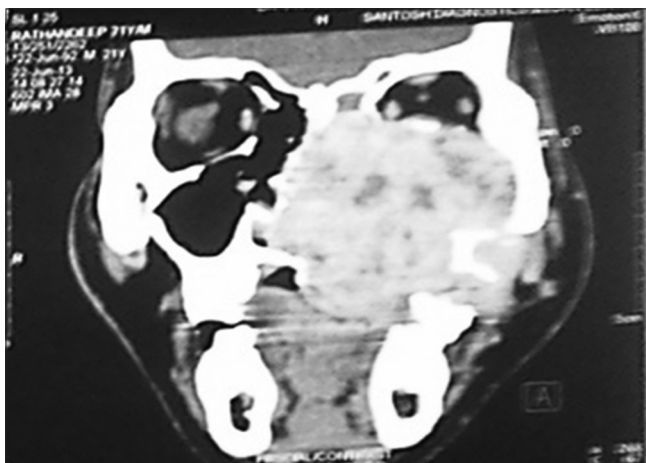
separate neoplasms. Those tumors that were characterized by sheets of uniform primitive cells with scant cytoplasm and cytoplasmic glycogen were classified as ES whereas tumors featuring cells with more nuclear variability, more abundant cytoplasm and Homer-Wright rosette formation were classified as PNET.<sup>[7]</sup>

Various cases were reported involving different sites by Lucke (1866) in bone, Stout (1921) in ulnar nerve, Angervall and Enzinger (1975) in soft tissue (extraskelatal ES) followed by reports by Jaffe *et al.* in the bone and Askin *et al.* in the thoracopulmonary region. Skeletal ES, extraskelatal ES, PNET and Askin's tumor showed many overlapping histopathological, ultrastructural and immunohistochemical features suggestive of a common origin. To confirm this, subsequent cytogenetic studies were performed which demonstrated that all these tumors contained a common karyotypic change, i.e.,  $t(11;22)(q24;q12)$ . It was thus evidently supported that ES and PNET represent a single entity in which ES represents the undifferentiated and most primitive and uncommitted member of the spectrum, whereas PNET is the more neurally differentiated counterpart.<sup>[7]</sup>

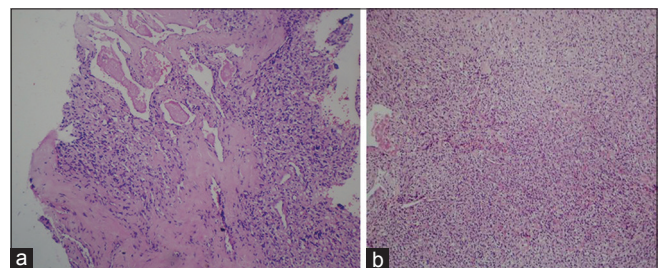
In childhood malignancies, ES/PNET is the second-most common sarcoma of bone, after rhabdomyosarcoma. Tumors of head and neck account for about 8% of ES/PNET, involving skull bones and jaws. In jaw bones, mandible is affected twice as often as the maxilla.<sup>[7,8]</sup>

Primary bone lesions are much more common than metastatic lesions in the jaws (14:1). Pain and swelling in the involved area are the most common symptoms. In jaws, pain, loose teeth and paresthesia are common. Hematological changes associated are anemia, leukocytosis and increased erythrocytic sedimentation rate.<sup>[7]</sup>

Radiographically, CT scans and MRI scans are helpful to determine the site from where the tumor arises, the extent of the lesion as well as the involvement of adjacent

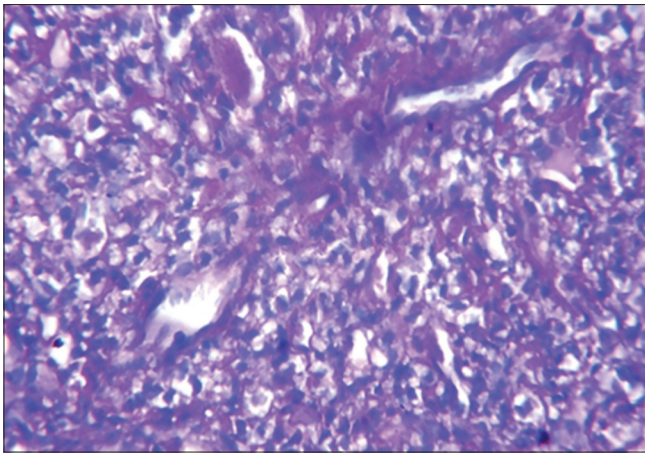


**Figure 4:** Magnetic resonance imaging scans showing the extent of the lesion, involving the floor of the left orbit and maxillary bone

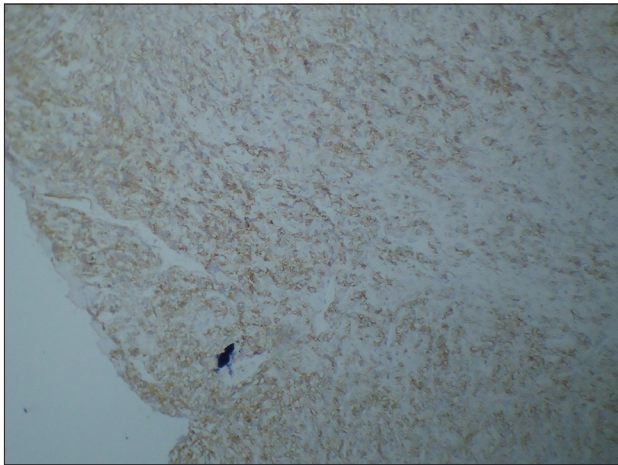


**Figure 5:** (a) Microscopic examination of H&E stained lesional tissue (low magnification) lesion devoid of epithelium, showing densely packed cells throughout the tissue with focal areas of hemorrhage. (b) higher magnification showing monotonous sheets of round cells densely packed throughout the lesional tissue

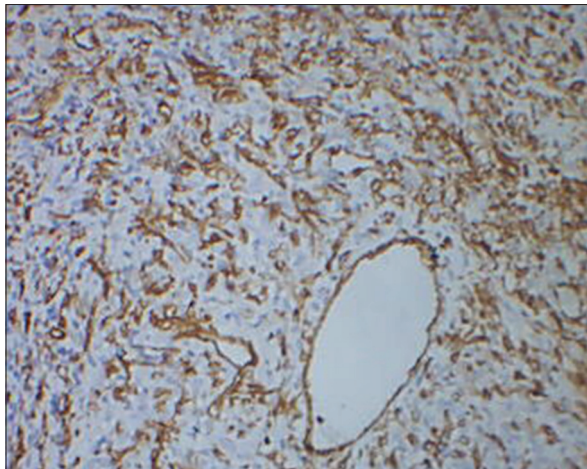




**Figure 6:** Periodic acid–Schiff stained section showing intracytoplasmic glycogen positivity



**Figure 7:** Lesional tissue expressing strong CD99 positivity



**Figure 8:** Lesional tissue expressing strong positivity for Vimentin

tissues. It usually exhibits osteolytic appearance, periosteal spiculated or laminated reaction called “onion skin appearance” in long bones. However, in jaw lesions the onion skin or sunray appearance is very rare.<sup>[7-9]</sup>

Histopathologically, small uniform round cells which appear bland and undifferentiated, with scanty cytoplasm present closely packed in little stroma, arranged in diffuse sheets in lobulated, alveolar, angiomatoid or fascicular pattern. Intracytoplasmic glycogen is commonly present and demonstrated by PAS stain. The diagnosis of ES is based on the immunohistochemical expression of the tumor and confirmed by cytogenetics. H and E features are helpful to select the panel of immunohistochemical markers.<sup>[1]</sup>

As the present lesion was in the palatal region, a clinical differential diagnosis of mucoepidermoid carcinoma was considered along with high-grade sarcomas. However, H and E histological pattern along with negativity of IHC markers calponin, GFAP, CK and EMA excluded the diagnosis of mucoepidermoid carcinoma.

The histopathological differential diagnosis of ES includes lymphoblastic lymphoma, neuroblastoma, poorly differentiated synovial sarcoma (PDSS), alveolar rhabdomyosarcoma, mesenchymal chondrosarcoma, small cell osteosarcoma, small cell carcinoma and small cell variant melanoma.<sup>[9]</sup>

All the lymphomas except the lymphoblastic lymphoma are usually CD45 positive whereas ES is generally CD45 negative.<sup>[7]</sup> The lymphoblastic lymphoma may occur both in bone and soft-tissue locations, invariably express both CD99 and FLI1 and is commonly CD45 negative. Hence, IHC for terminal deoxynucleotide transferase, CD43 and CD10 (common acute lymphoblastic leukemia antigen) is required to differentiate this entity from ewings sarcoma (EWS).<sup>[9]</sup> Nonhodgkin's lymphoma show lack of uniformity of nuclei. Furthermore, ES shows glycogen-rich cytoplasm and lack of reticulin fibers in the tumor lobules. The intracytoplasmic glycogen may be demonstrated by PAS stain in 75% of the cases, but it is not pathognomonic and conclusive because other small round cells may show the presence of glycogen as well. Since ESs are usually vascular, hemorrhagic areas and extensive necrosis are common.<sup>[7]</sup> The present case showed intracytoplasmic glycogen which stained positive with PAS staining [Figure 7] with areas of hemorrhage and necrosis.

Esthesioneuroblastomas and neuroblastomas usually comprise more uniform round cells within a neurofibrillary background and are CD 99 negative, and strongly positive for CD56, synaptophysin and neuron-specific enolase (NSE).<sup>[9,10]</sup> Furthermore, they secrete catecholamines and show N-MYC expression, and ultrastructurally neurosecretory granules and neurites are evident. In contrast, ES shows varying immunopositivity for NSE

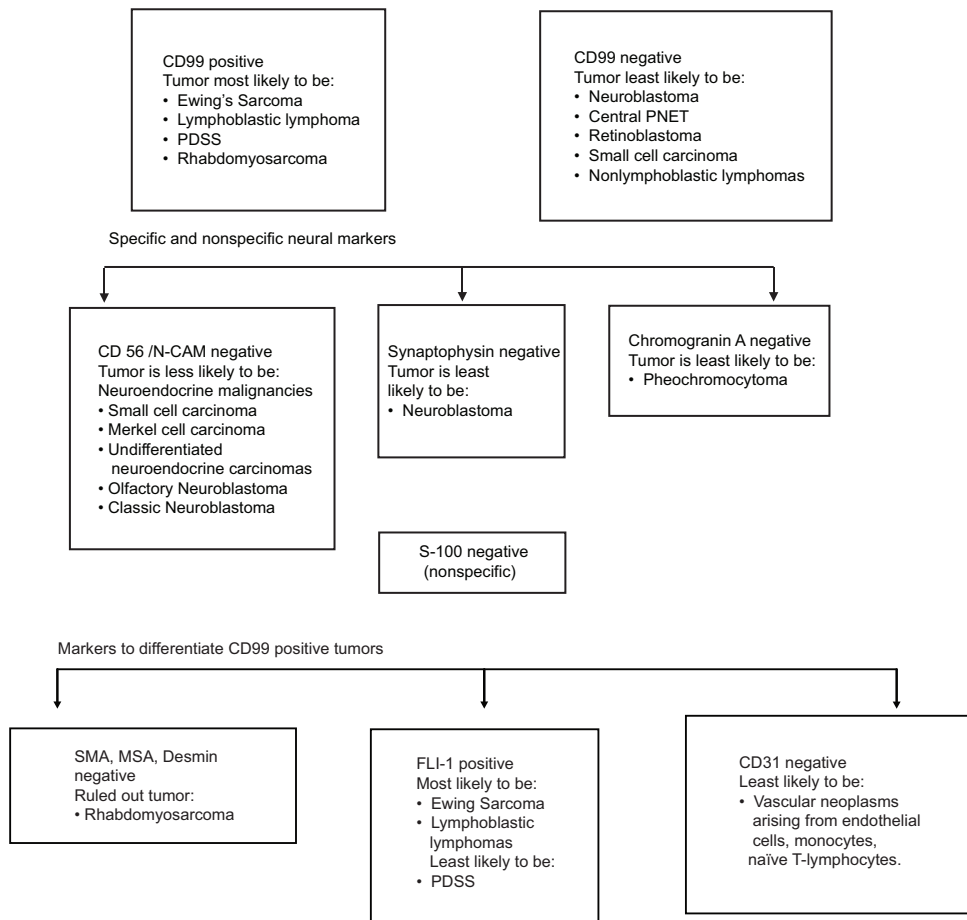


Figure 9: Immunohistochemical Flowchart for diagnosis<sup>[10,11]</sup>

and synaptophysin and usually negative for chromogranin which is a less-specific neuroendocrine marker.<sup>[7,11]</sup>

PDSS usually show at least focal areas of more typical monophasic synovial sarcoma (MSS) or biphasic synovial sarcoma, and although they are CD99 positive, they lack FLI-1 expression.<sup>[9]</sup> MSS shows expression of cytokeratins in the absence of S100 protein although 20% may show S-100 protein positivity and CD34 is the most characteristic of MSS.<sup>[9]</sup>

Mesenchymal chondrosarcoma contains chondroid and small cell osteosarcomas contain osteoid areas along with reticulin meshwork and vascular pattern which is not seen in EWS.<sup>[7,9]</sup> Small cell carcinomas generally lack CD99 expression and show much stronger expression of cytokeratins and neuroendocrine markers [Figure 9]. Small cell variants of melanoma are only focally positive for S-100 protein but are strongly positive for human melanoma black 45 (HMB-45) and/or Melan-A.<sup>[9]</sup>

ES is a radiosensitive tumor. Multimodality therapy consisting of an initial biopsy, aggressive combination of

surgery, chemotherapy and localized radiotherapy is the treatment of choice for ES of the head and neck region and may result in a long-term survival. The prognosis of ES is poor because hematogenous spread and lung metastases occur within a few months after diagnosis, although the tumor burden is considered today as an important factor of prognosis.<sup>[12]</sup>

**CONCLUSION**

Malignant sarcomas pose a diagnostic difficulty. To arrive at a diagnosis, a correlation between clinical, radiological, histopathological and immunohistochemical with cytogenetics is needed. Of further help would be cytogenetics and molecular studies such as Southern blot, reverse transcription-polymerase chain reaction and fluorescence *in situ* hybridization for the detection of EWS-FLI-1 fusion characteristic of ES/PNET, to differentiate it from heterogeneous group of small round cell tumors. Thus, the diagnosis of ES/PNET traditionally depends on the exclusion of other small cell neoplasms by light microscopy, histochemical stains or ultrastructural studies on the basis of lack of histological and biochemical

characteristics of neuroblasts, primitive skeletal muscle, epithelial cells or lymphocytes.

### 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.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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