EWING SARCOMA IN MANDIBLE WITH INVOLVEMENT OF SYMPHYSIS – AN EXTREMELY RARE ENTITY

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ABSTRACT

Ewing's sarcoma is uncommon round cell tumor affects most often in the bone and soft tissues of children and young adults. It has poor prognosis because of aggressive local spread and uncontrolled metastatic potential necessiting early diagnosis and intervention critical for survival of the patient. It primarily affects long bones, seldom occurs in the head and neck region. We report such a case of Ewing's sarcoma that affects mandible of a 13 years girl child.

Keywords: Ewing Sarcoma; PNET; Askin Tumor; Orthopantomogram; extraskeletal ES; round cell tumor, PET CT

Introduction

Ewing's sarcoma (ES) is a rare malignant primitive round cell tumor that was first described by James Stephen Ewing, an American pathologist in 1921.[1] It can occur in any bone but commonly it is found in the diaphysis of long bones and pelvic girdle. In the head and neck region predilection is toward mandible followed by maxilla.[2]

ES is an aggressive tumor showing rapid growth with local infiltration and metastasis. It is a part of the ES family of tumors (ESFT), which also includes peripheral neuroectodermal tumor (PNET), neuroepithelioma and Askin's tumor.[3] They are grouped based on shared clinical, morphologic, biochemical and molecular features. They share common karyotyping translocation t (11;12) (q24;q12) in approximately 90% cases.[4] This has made the diagnosis further complex. Thus immunohistochemistry and molecular assays for chromosomal translocation seem to be the main stay of diagnosis.[5] ES has the most unfavorable prognosis of all primary musculoskeletal tumors. Even with early diagnosis and intervention, patients with metastasis have approximately 20% chance of 5-year survival. Here we report a case of ES involving mandible in a 13-year-old girl to make the clinicians aware of the clinical and histopathological spectrum of this rare tumor.

Case Report

A 13-year-old girl visited the Dental Clinic with 3-month history of a painless, gradually increasing swelling in the mandibular left lateral region. Extraorally, a hard nontender swelling (4 cm × 2 cm) was observed on the middle one third of the ramus of the mandible which was covered by normal appearing skin. Intraoral examination revealed involvement of mandibular alveolar ridge with expansion of the outer cortical plates. Overlying mucosa was normal. The mass was hard in consistency. The patient was apparently healthy with no sign of paresthesia or lymphadenopathy at the time of presentation. But there was history of fever. Routine hemogram and biochemical examination was unremarkable.

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OPG (Fig. 1) revealed an ill-defined radiolucent lesion with adjoining sclerosis seen extending from left first

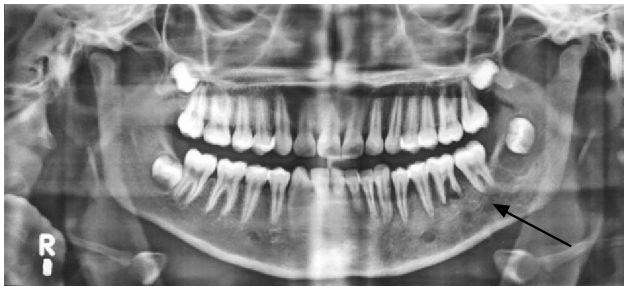

Figure - 1: Orthopantomogram of the 13 year girl child show ill-defined radiolucent lesion (arrow) with adjoining sclerosis seen extending from left first molar to left second molar teeth. Adjoining soft tissues are unremarkable.

molar to left second molar. Cortical plates are intact. Clinical and radiological features suggested a destructive lesion. CT scan (Fig. 2) with 3D reconstruction shows bony break and periosteal reaction

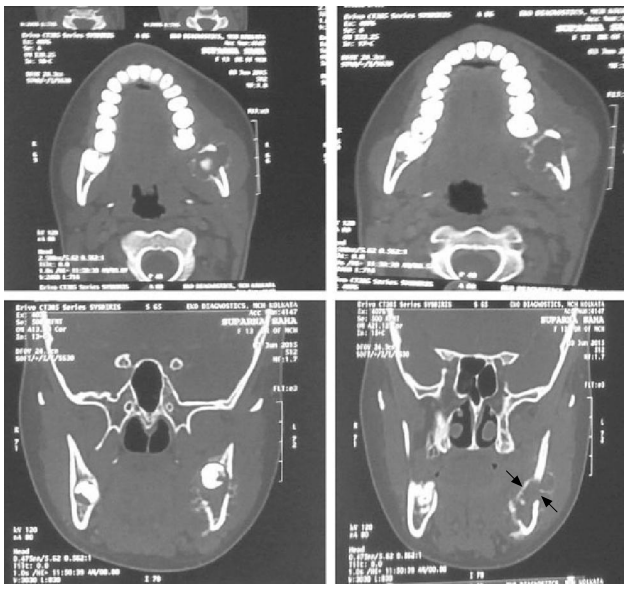

Figure - 2: Expansileluscent lesion seen in left hemimandible at molar area with mild soft tissue prominence with bony break and periosteal reaction. Soft tissue involvement seen in inward and superficial part (arrow).

with involvement of surrounding firbroadipose tissue and muscle both inward and superficial part. Excisional biopsy with left sided mandibulectomy was done followed by mandibular reconstruction with fibula after obtaining consent (3D CT image of reconstructed mandible shown in (Fig. 3). Microscopy revealed soft tissue mass composed of nest of squamoid appearing round tumor cell having hyperchromatic nuclei and

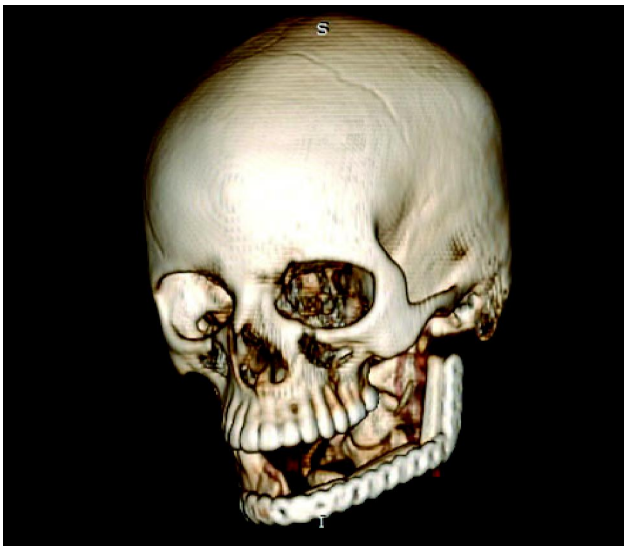

Figure - 3: 3D reconstructed image of CT scan shows reconstructed left hemimandible with prosthesis.

scanty cytoplasm and have mitotic figure admixed with few mucin producing cells without cystic areas or bony trabeculae. Tumor is highly vascular. Immunohistochemistry showed strong positivity for CD99 and cytokeratin & weak positivity for synaptophysin but negativity for myogenin, chromogranin and desmin. Surgical margins were free from lesion and regional lymph node show evidence of metastasis without perinodal extension. Post-operative chemotherapy is being continued, till date 3 cycles of chemotherapy have been given. After 3 cycle of chemotherapy patient is advised whole body FDG-PET CT scan to assess any residual disease or recurrence, but found to be negative (Fig. 4).

Discussion

ES is uncommon round cell tumor with aggressive course affecting mainly children and young adults. Although uncommon among other round cell tumors, it is 2nd most common primary malignant tumor of both children and adolescent after osteosarcoma. ES affecting jaws is uncommon among Indian population. Potdar in 1970 first reported nine cases of ES involving jaws. The tumors showed male preponderance and commonly affected mandible.[6] Present case is rare where symphyseal region of mandible is involved.

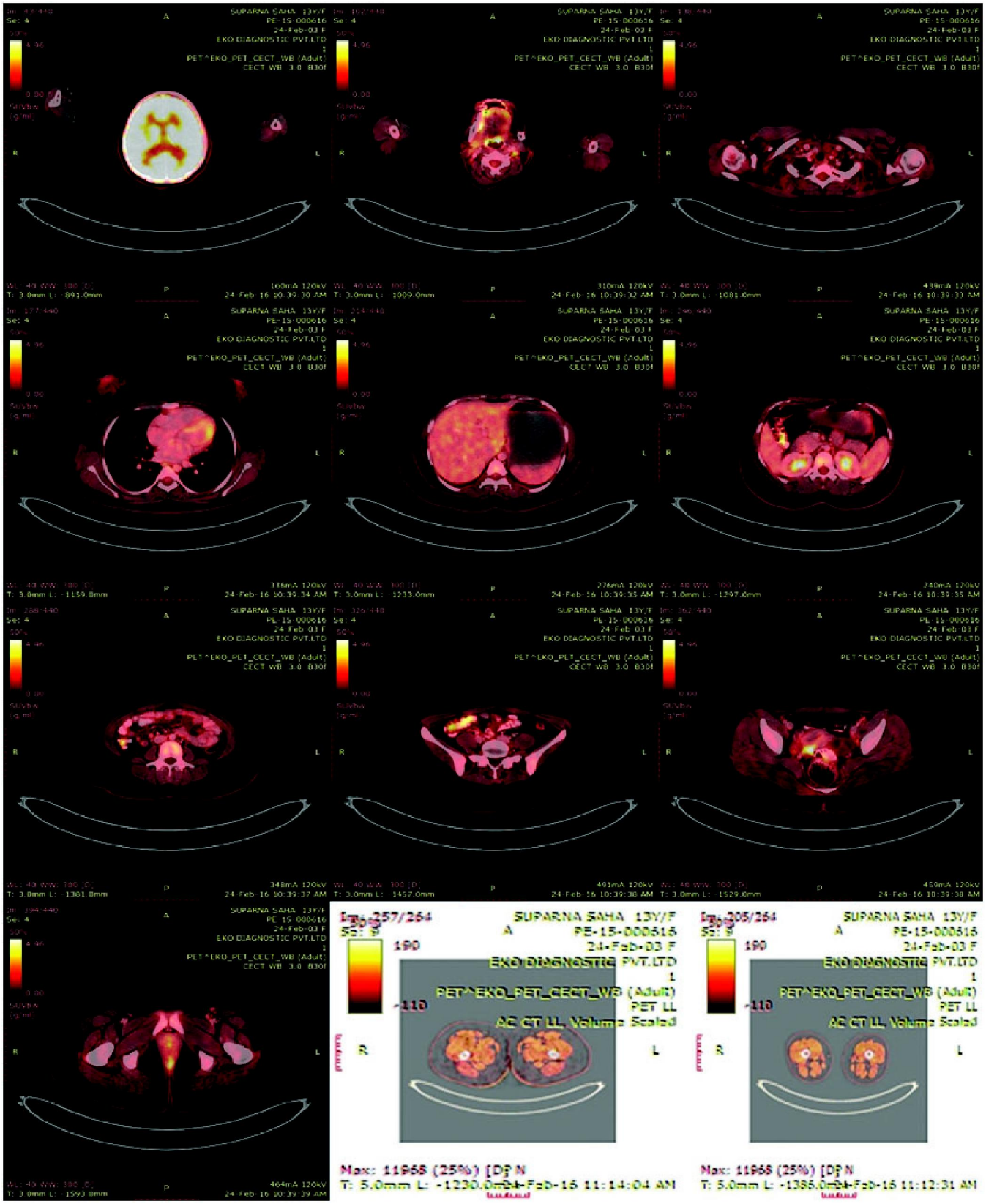

Figure 4: PET CT Imaging show no metastatic involvement.

It accounts for 6% of all primary bone cancers affecting adolescents and young adults and it is found most commonly in the 10 to 25 year age range, with a peak at 15 years. ES generally affects white population in 95% cases and rare in blacks (0.5% - 2%).[7] It is male predominant tumor (male/female ratio, 2:1). Age is very important for diagnosis. 20-30% cases occurs in 1st decade of life. When presentation in > 30 years occurs, first possibilities of other round cell tumor like small cell carcinoma and large cell lymphoma should be considered before final diagnosis of ES. In patients < 5 years, metastatic neuroblastoma and acute leukemia should be ruled out.

Localized pain with swelling at the site of the lesion is main presenting features. A soft tissue mass is palpable in more than one third of the cases. The pain initially is dull in nature and may increase before presentation. Systemic symptoms of slight to moderate fever, secondary anemia, leukocytosis and increased ESR are common in Ewing's sarcoma. Local temperature elevation with dilated veins and associated tenderness accompanies the lesion, thereby suggesting an inflammatory condition.[8] The inflammatory like symptoms of Ewing's sarcoma may be explained by the fact that the tumor characteristically outgrows its blood supply, resulting in extensive ischemic degeneration and necrosis.

Ewing's sarcoma is seen most frequently in the diaphyseal region of long tubular bones (50%) and in the flat bones (40%).[9] The lower extremity encompasses the largest portion of the tubular involvement. The femur is most commonly involved (23%) followed by the tibia, fibula, and humerus (9%). Of the flat bones the most frequently affected site is the pelvis (21%). 10% of all malignant rib lesions are Ewing's sarcoma. Involvement of the scapula occurs in approximately 5% of cases. Spinal involvement is uncommon, occurring in only 3.5-7%. The sacro-coccygeal is most common sites followed by dorso-lumber vertebrae. 4% of ES arises in the bones of head neck region with 1% in the jaws with predilection for ramus of the mandible. When involved posterior portion is favored than anterior portion.[10] Few cases involving maxilla have also been reported.

According to anatomical site of occurrence it is classified as: (a) intraosseous (most common) (b) extraskeletal (less common) and (c) periosteal (rare) type.

The classic presentation is that of a diaphyseal lesion (usually in the lower extremity), permeative (72 -80%) in its appearance, with a wide zone of transition (96%). Cortical saucerization is an early and characteristic sign (19-42%). Geographic border seen in 15%. Purely lytic lesions are uncommon, with a mixed lytic and sclerotic pattern predominating in the tubular bones. Approximately 30 - 42 % of cases affecting flat bones demonstrate diffuse sclerosis.[11] This diffuse sclerosis represents normal bone formed as a reaction to the tumor cells rather than actual tumor bone. Pathologic fracture is noted in approximately 5% of cases.[12]

ES originates in central medullary canal with early involvement of soft tissue in 80 - 100% of cases. Soft tissues are usually large and circumferential around the involved bone. They may exceed the intraosseous compartment in 2-15% of cases. The communication between the medullary canal & soft tissue component may be through focal cortical destruction.

Periosteal reactions are the reactive osteogenesis of the periosteum caused by intraosseous invasion of the tumor. Several types of periosteal reaction (58 – 84%) seen (1) onion peel appearance: it is multilayered reaction. (2) a sunburst: perpendicular reactions, also known as groomed or trimmed whiskers effect.[13] (3) Codman's triangle: is a triangular lifting of periosteum from the bone at the site of attachments.

Other less common radiographic features of ES include cortical thickening (21%), pathological fracture (15%), expansile bone remodeling (13%). Unusual findings are soft tissue calcification (7.9%), extrinsic cortical erosion or saucerization (6%), honey comb appearance (6%), vertebra plana (6%), well marginated lesion (4%).

ES has propensity to metastasize to the other bones characterized by extensive bone destruction. It is the most common primary malignant bone tumor to metastasize to bone. The spine is a common site for metastasis.[14] Multiple lesions in the one bone occur and are with normal bone in between, described as skip lesions.[15] So, the possibility that the jaw involvement represents metastatic disease from another skeletal site always be considered. Secondary spread to the lungs is also a common occurrence, with the lung parenchyma and pleura being the favored locations (38% cases). Sometime mediastinal lymphadenopathy seen in 25% of cases. Local recurrence

typically occurs within 5 years after diagnosis in 85-90% of cases. The prognosis in patients with recurrence or progressive disease is poor with <10% survival. The risk of secondary malignancy in patients with ES is significant with 1-2% of survivors. Secondary AML and myelodysplastic Syndrome are common secondary malignancy. There is 20% cumulative risk of development of other sarcoma.

MRI facilitates the staging of Ewing's sarcoma and is better than CT for demonstrating bone marrow and soft tissue involvement. MRI accurately defines the medullary infiltration and soft-tissue extension that is of intermediate signal intensity on T1-weighted and intermediate/high signal intensity on T2-weighted and STIR sequences relative to skeletal muscle. Skip metastases (12%) and distant metastases (<20%) in lungs and bone may be identified on initial imaging performed for surgical staging. FDG-PET is more sensitive than bone scintigraphy in the detection of osseous metastases with a performance similar to that of whole-body MRI. FDG-PET may also be used in the assessment of response to adjuvant chemotherapy and detection of recurrence.

Presence of soft tissue mass, age of presentation, hematological menifestation and radiological appearance can facilitate differential diagnosis. Histopathologial appearance and immunohistochemistry enables final diagnosis. In Ewing sarcoma Family share a karyotype abnormality with translocation involving chromosome 11 & 22. Histologically they demonstrate crowded sheet of small round blue cells.

Combined therapy including surgery, radiotherapy and chemotherapy is the best approach for ES. Multidisciplinary treatment protocols have dramatically improved the 5-year survival rate of patients from 16 to 75%. Radiotherapy can treat nonresectable primaries and chemotherapy can suppress micrometastasis and reduce tumor load before surgery. The chemotherapeutic agents commonly used are vincristine, doxorubicin, cyclophosphamide, ifosfamide and actinomycin-D. ES has poor prognosis because of hematogenous spread and lung rapid metastases. Age of presentation < 10 years, pelvic location, presence of metastasis, large tumor (>8 cm at presentation), radiolucency, high mitotic figure in HPE, systemic symptoms, high erythrocyte sedimentation rate, elevated serum lactate dehydrogenase levels, thrombocytosis, presence of metastasis at presentation, recurrence within 2 years, poor response to chemotherapy are poor prognostic indicator.[16] However, tumors in jaws have a better prognosis than those in long bones as tumor in facial bones are detected earlier. After the confirmatory diagnosis, the patient undergone surgery and chemotherapy. Early diagnosis and judicial management ensure good prognosis of this enigmatic malignancy!

In 1956 Sherman reported three cases of periosteal ES (PES) of long bones.[17,18] Later Angervall and Enzinger in 1975 reported the first case of extraskeletal ES.[19] Askin in 1979 and Jaffe in 1984 reported malignant small round cell tumor of the thoracopulmonary region and 'PNET of bone', respectively.[20] Extraskeletal ES is rare compared to ES of bone (15 – 20% of that of ES or bone). Most common location is paravertebral region (32%), lower extremities (26%), chest wall (18%), pelvis & hip (11%), retroperitoneum (11%), upper extremities (3%). In contrast to skeletal ES, extraskeletal ES is characterized by equal M:F ratio, average age of presentation 20 years, more common in trunk rather than limbs. Askin tumor (in 1979) – extraskeletal ES involving chest wall.

Conclusions

1. ES is highly aggressive tumor with rapid growth and metastasis. Early diagnosisis crucial for the survival of the patient. ES of mandible has better prognosis than long bone ES due to early diagnosis.

2. In lesion of the mandible the differential diagnosis of lymphoma, lytic type of osteogenic sarcoma, osteomyelitis, neuroblastoma & histiocytosis X are to be considered, before the possibility of Ewing Sarcoma.

3. Age of presentation and radiological image helps in the provisional diagnosis. HPE and immunohistochemistry are necessary for fixed diagnosis.

4. ES has property to metastasis to other bones. So involvement of jaw either due to metastasis from ES seen at the other site or the primary involvement should be rechecked and excluded. PET CT scan is the ideal to localize the primary as well as secondaries. It is also suitable for follow up to monitor the relapse and recurrences.

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