

## Presentation Of Ewing's Sarcoma In Unlikely Age Group At Unusual Location -

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**Abstract :** Ewing's sarcoma is a highly malignant, round cell neoplasm of uncertain origin. It is the sixth most common malignant tumor of bone. It must be distinguished from chronic osteomyelitis and other malignant round cell tumors like lymphoma, metastatic neuroblastoma and small cell osteosarcoma. Most patients are between 10 to 25 years old; rarely patients are younger than age 5 years and older than age 40 years. We report a 55 years female who presented with swelling over right shoulder with pain and inability to move right shoulder later diagnosed as Ewing's sarcoma of proximal part of humerus right side. The earlier diagnosis at this age may help in better management of the condition and prevent further complications and have better prognosis.

**Keywords :** Ewing's sarcoma, Primitive neuroectodermal tumor (PNET), Ewing family of tumors (EFT), Round cell tumor.

**Introduction :** Ewing's sarcoma is a highly malignant, round cell neoplasm of uncertain origin. It is the sixth most common malignant tumor of bone <sup>[1]</sup>. Most patients are between 10 to 25 years old; rarely patients are younger than age 5 years and older than age 40 years <sup>[1]</sup>. In 1918, a tumor composed of small round cells with rosettes in ulnar nerve was described by Arthur P Stout <sup>[2]</sup>, later on it became known as Primitive neuroectodermal tumor (PNET). James Ewing described a tumor of diaphysis of long bones composed of undifferentiated cells and the tumor was radiosensitive <sup>[3]</sup>. Earlier Ewing's sarcoma (ES) & PNET were described as two separate entities, but in 1975 Angervall and Enzinger described extraskelatal tumor resembling to ES <sup>[4]</sup> and Jaffe et al. wrote an article on "the neuroectodermal tumor of bone" in 1984 <sup>[5]</sup>. Now it is known that ES and PNET have similar translocations and are the two ends of histological spectrum of Ewing's family of tumors (EFT). Analysis of molecular techniques not only provided better understanding of biology but also help in developing better techniques in diagnosis and prospective potential treatment. The

present report is about rare presentation of Ewing's sarcoma in a 55 years old female who presented with swelling over right shoulder with severe pain and inability to move right shoulder.

**Case Report :** A 55 years old female, housewife, was presented with progressive swelling over right shoulder and difficulty in shoulder movements. Swelling was accompanied with severe pain which increased gradually over a period of 6 months.

On examination, she was an average built female with swelling over right shoulder and upper part of right arm. Swelling was of 25x20cm size. It was a solitary swelling with local rise of temperature over swelling. Swelling was tender and variable in consistency. It was a non-mobile swelling. Redness and prominent superficial veins were visible over swelling over right shoulder and upper part of arm (Fig.1). Her hemoglobin levels were decreased and she had elevated erythrocyte sedimentation rate (ESR). Her renal function tests and liver function tests were towards lower normal range.

X-ray right shoulder with arm shows round lytic lesion in head and upper part of humerus (Fig.2). MRI of right shoulder joint was suggestive of a 8.7x6.7x6.5 cm well defined, lobulated, expansile, lytic, lesion involving head and proximal shaft of right humerus, causing thinning and erosion of the cortex with breach at few places and narrow zone of transition, adjacent soft tissue extensions with edema and moderate right shoulder joint effusion. These findings are suggestive of Neoplastic mass involving proximal humerus with pathological fractures (Fig. 3)

Histopathology report shows sheets of small round cells with hyperchromatic nuclei, condensed chromatin and scanty eosinophilic cytoplasm with vacuisations with unremarkable bony trabeculae (Fig.4). Immunohistochemistry is suggestive of Vimentin, CD99, S 100 positive and AE1/AE3 focally positive. Cytology report was suggestive of cytomorphological features positive for malignancy.



Fig. 1: Clinical photograph of patient showing right shoulder swelling.

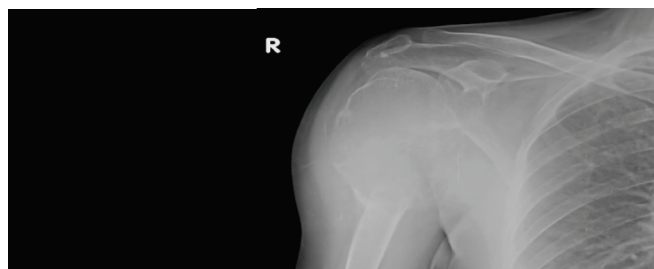


Fig.2:X-ray right shoulder showing round lytic area in upper end of humerus.

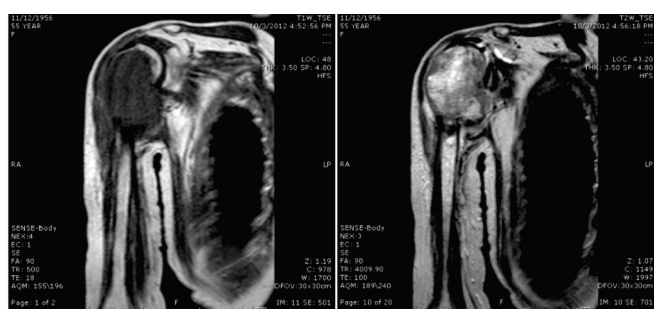


Fig. 3: MRI right shoulder - T1W,T2W and STIR images showing expansile, lobulated, lytic lesion involving head and proximal part of humerus.

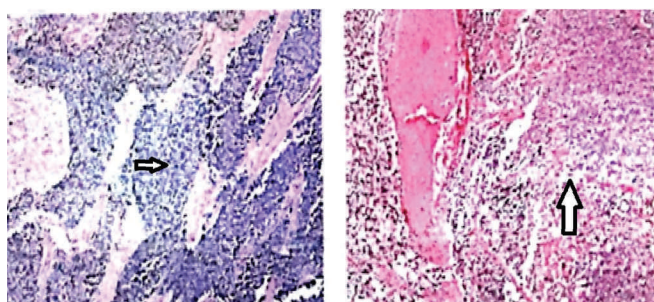


Fig.4: Microscopic picture (40X) showing sheets of small round cells with hyperchromatic nuclei (arrow), condensed chromatin and scanty eosinophilic cytoplasm.

## Discussion :

**Epidemiology :** EFT comprises 5 to 10 % of total bone tumors and is the 2nd most common tumor of childhood [6]. It occurs predominantly in young adults and children and shows a slight predilection for males [7]. 75% cases are seen between 10 to 25 years age of life. Youngest case reported so far was of 4.5 months old [8] and oldest case reported was 61 years old. Infancy cases are to be differentiated from metastatic neurofibroma.

**Sites :** In 55% long bones it is usually diaphyseal lesion but also metaphyseodiaphyseal lesion can be seen. Flat bone (pelvis and ribs) involvement can also be seen. Less common sites of occurrence are skull, vertebra and scapula.

**Presentation of Ewing's sarcoma :** Pain, Swelling and fever are the presenting symptoms. X-ray shows permeative pattern of bone involvement (boundary between uninvolved bone and area of bone destruction and bone is broad, vague & imperceptible). All types of periosteal reactions seen like onion peel, moth eaten, honey combed, fine and reticulated [1].

**Biopsy :** Ideally core biopsy is done, if repeated attempts of core biopsy fails open biopsy is done. FNAC not recommended in case of Ewing's sarcoma. Frozen section studies opted in selected cases only as freezing of tissue distorts the morphology. Fixation of tissue is done in 10% formalin. Inadequate fixation leads to loss of antigen, so inconclusive results on immunohistochemistry and also causes autolysis and degeneration of DNA thus making molecular analysis difficult. Ratio of specimen to formalin is 1:10.

**Histology :** It is prototype of small round cell tumor growth. It shows sheets of small cells with increased nuclear to cytoplasm ratio. Cytoplasm is scanty, eosinophilic, and detected by periodic acid Schiff (PAS), contains glycogen and diastase degradable. Occasional rosette formation are seen and frequently undergoes necrosis and residual viable cells show peritheliomatous or perivascular distribution. EFT tumor cells can be large with irregular nuclear membrane and prominent nucleoli [9]. EFT cells show membrane expression of CD99 /MIC 2 on immunohistochemistry [10]. Antibody against FLI-1 is seen in nucleus of tumor cells which is specific for diagnosis of EFT [11]. Tumor cells may show neuron specific enolase (NSE), synaptophysin and s-100 protein [12].

**Family of EFT includes -1)non hodgkin's lymphoma 2)rhabdomyosarcoma 3)synovial sarcoma**

4)mesenchymal chondrosarcoma 5)desmoplastic small round cell tumor (DSRCT) 6)retinoblastoma.

False positive cd99 screening is seen in other cases as well hence CD99, FLI1 and NSE to be positive for diagnosis of EFT/PNET.

**Molecular genetics :** Translocation t (11:22) (q24;q22) is seen in 85 % cases. Fusion of EWS gene on 22q12 with FLI-1 on 11q24 results in chimeric fusion transcript EWS-FLI1<sup>[13]</sup>. EWS-FLI1 induces insulin like growth factor (IGF-1). Phospholipase D2 (PLD2) and Protein tyrosine phosphatase 1 (PTPL1) are expressed in increased levels. Thus tumor cells escape from apoptosis and growth inhibition.

**Therapeutic targets :** EWS-FLI1 fusion is to be targeted and split. Monoclonal antibodies against IGF - 1 are being tried as it is associated with EFT growth<sup>[14]</sup> and PLD2, PTPL1 are other conceivable candidates as both are highly expressed in EFT<sup>[15]</sup>.

**Chemotherapy in ES :** There is no universally accepted staging. American joint committee on cancer (AJCC) suggests that primary bone or extra skeletal Ewing's sarcoma may be included with their respective bone or soft-tissue sarcoma staging (STS) systems<sup>[16]</sup>. Although AJCC staging includes metastatic disease and tumor size greater or less than 8 cm; nodal status and grade are irrelevant for ES because it rarely spreads by lymph nodes and by definition of ES is high grade tumor<sup>[16]</sup>. Presence or absence of metastasis at the time of diagnosis is used as main tool for planning the treatment strategy<sup>[16]</sup>.

**Prognostic factors :** 1) tumor site and size 2) age and gender 3) serum LDH levels

ES in distal extremity has better prognosis than proximal extremity. ES in central location (pelvis) has worst prognosis<sup>[17] [18] [19]</sup>. Tumor volume <100-200ml-small tumor has better prognosis and tumor volume >100-200ml-large tumor has bad prognosis. Girls have better prognosis than boys<sup>[19]</sup>. Increased serum LDH levels at time of diagnosis with large tumor with metastatic disease has worse prognosis. Metastasis in lungs alone has prognosis better than metastasis in extra-pulmonary sites. Patient with minimal tumor or no residual tumor after preoperative chemotherapy incline towards better prognosis.

Evolution of chemotherapy: Adjuvant therapy: Vincristine + Actinomycin D + Cyclophosphamide (VAC).

**Intergroup Ewing's sarcoma study (IESS) :** VAC +

doxorubicin. IESS trial –II demonstrated that intermittent high doses of VAC + doxorubicin was better than continuous moderate dose therapy with this agents<sup>[20]</sup>. VAC+ doxorubicin alternating with Ifosfamide and Etoposide (IE) has better prognosis. There is no role of dose intensification.

**Current trend :** Alternating cycles of VAC IE every 3 weeks<sup>[21]</sup> for 48 weeks with local control at 9-12 weeks is to be administered. There is no role of dose compression (decrease in duration of cycles). There is some role of stem cell in preliminary stage of management.

**Local therapy :** Surgical resection with or without limb salvage followed by Radiotherapy and then chemotherapy is given.

**Conclusion :**

Chemotherapy remains back bone of the treatment for Ewing's sarcoma, local treatment with surgery &/or radiotherapy has important role in management of ES. The outcome of management is better in localized ES as compared to elusive outcome in metastatic disease or local recurrence.

This case is presented in view of rarity to increase suspicion index for the presence of Ewing's sarcoma. Early detection of Ewing's sarcoma as chemotherapy and radiotherapy can limit further damage and progression of the disease can be done.

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