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Case report

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 tumour of bone. It must be distinguished from chronic osteomyelitis and other malignant round cell tumours 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 a better prognosis.

Keywords: Ewing's sarcoma, Primitive neuroectodermal tumour (PNET), Ewing family of tumours (EFT), Round cell tumour.

INTRODUCTION

Ewing's sarcoma is a highly malignant, round cell neoplasm of uncertain origin. It is the sixth most common malignant tumour of bone¹. Most patients are between 10 to 25 years old; rarely, patients are younger than age 5 years and older than age 40 years¹. In 1918, a tumour composed of small round cells with rosettes in ulnar nerve was described by Arthur P Stout², later on it became known as Primitive neuroectodermal tumour (PNET). James Ewing described a tumour of diaphysis of long bones composed of undifferentiated cells and the tumour was radiosensitive³. Earlier Ewing's sarcoma (ES) & PNET were described as two separate entities, but in 1975 Angervall and Enzinger described extraskelatal tumour resembling to ES⁴ and Jaffe et al. Wrote an article on "the neuroectodermal tumour of bone" in 1984⁵. Now it is known that ES and PNET have similar translocations and are the two ends of the histological spectrum of Ewing's family of tumours

(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 a 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 haemoglobin levels were decreased and she had an elevated erythrocyte sedimentation rate (ESR). Her renal function tests and liver function tests were towards the 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). Immuno-histochemistry 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 a patient showing right shoulder swelling.



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

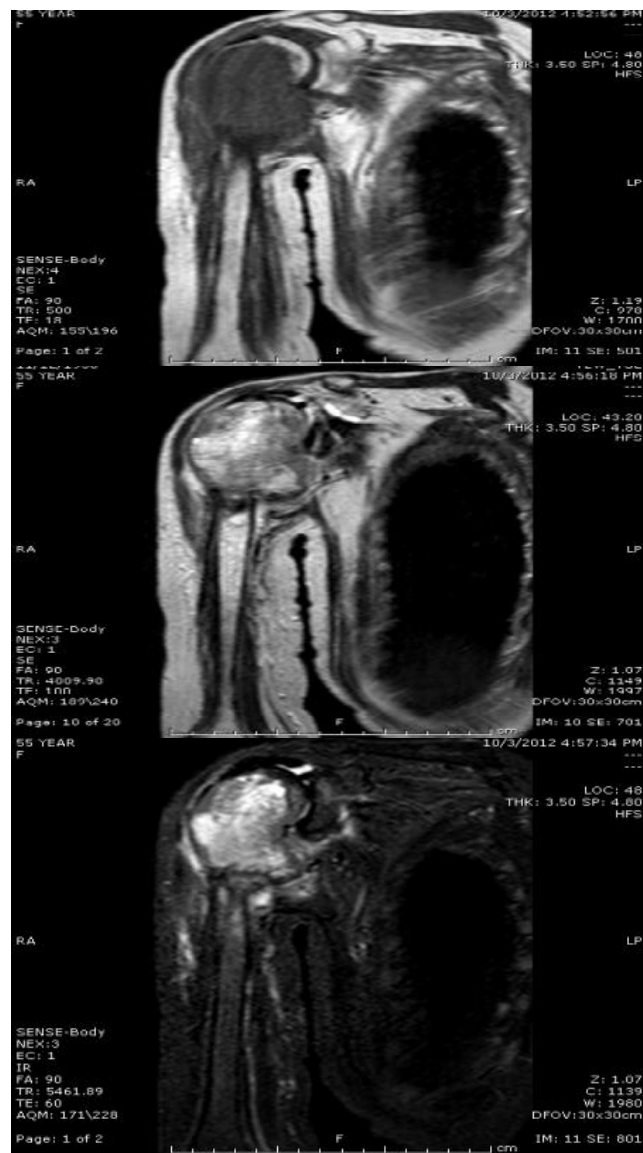


Fig 3: MRI right shoulder - T1W,T2W and STIR images showing expansile, lobulated, lytic lesion involving head and proximal part of humerus.

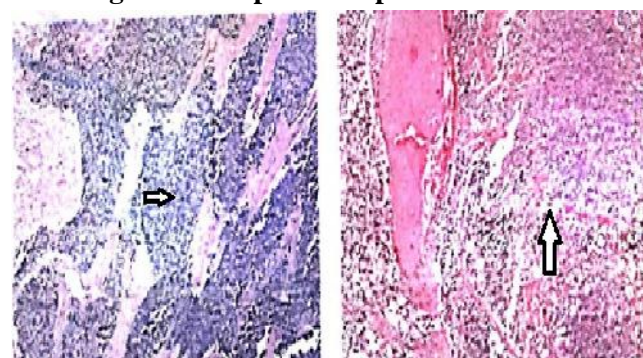


Fig 4: Microscopic picture (40X) showing sheets of small round cells with hyperchromatic nuclei (arrow), condensed chromatin and scanty eosinophilic cytoplasm.

DISCUSSION

Epidemiology: EFT comprises 5 to 10 % of total bone tumour and is the 2nd most common tumour 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:** At 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 an onion peel, moth eaten, honeycombed, fine and reticulated ¹.

Biopsy: Ideally core biopsy is done, if repeated attempts of core biopsy fail 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 of 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 tumour 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 is seen and frequently undergoes necrosis and residual viable cells show peritheliomatous or perivascular distribution. EFT tumour 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 the nucleus of tumour cells, which is specific for the diagnosis of EFT ¹¹. Tumour 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 ¹³. EWS-FLI1 induces insulin like growth factor (IGF-1). Phospholipase D2 (PLD2) and Protein tyrosine phosphatase 1 (PTPL1) are expressed in increased levels. Thus tumour 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 ¹⁴ and PLD 2, PTPL1 are other conceivable candidates as both are highly expressed in EFT ¹⁵.

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 ¹⁶. Although AJCC staging includes metastatic disease and tumour 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 the ES is high grade tumour ¹⁶. Presence or absence of metastasis at the time of diagnosis is used as the main tool for planning the treatment strategy ¹⁶.

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

ES in distal extremity have better prognosis than proximal extremity. ES in a central location (pelvis) have worse prognosis ^{17,18,19}. Tumour volume <100-200ml-small tumour has better prognosis and tumour volume >100-200ml- large tumour has a bad prognosis. Girls have better prognosis than boys ¹⁹. Increased serum LDH levels at time of diagnosis with large tumours with metastatic disease has a worse prognosis. Metastasis in lungs alone have prognosis better than metastasis in extra-pulmonary sites. Patient with minimal tumour or no residual tumour 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 agents²⁰. 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 weeks²¹ to 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 stages of management.

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

CONCLUSION

Chemotherapy remains the backbone of the treatment for Ewing's sarcoma, local treatment with surgery &/or radiotherapy has an important role in the management of ES. The outcome of management is better in localized ES as compared to the 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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Conflict of Interest: None

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