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RESEARCH ARTICLE

UNUSUAL SITES OF EWING SARCOMA: A SERIES OF 3 CASES

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ABSTRACT

Ewing sarcoma (ES)/primitive neuroectodermal tumours (PNET, together defined as Ewing sarcoma [ES]) is a primary neoplasm of the skeletal system, first described by James Ewing in 1921 (Gupta *et al.*, 2009). ES is the second most common bone cancer, most often occurring in Caucasian children, adolescents and young adults. we are presenting two cases of ewings sarcoma maxilla and one case of ewings sarcoma scapula. Ewing's sarcoma is a radiosensitive tumour (Infante-Cossio *et al.*, 2005). Multimodality therapy consisting of an initial biopsy, aggressive combination of surgery, chemotherapy and localized radiotherapy is the treatment of choice for Ewing's sarcoma of the head and neck region and may result in long-term survival (Vikas Prasad *et al.*, 2008). 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 (Ross *et al.*, 2013; Regezi *et al.*; Davido *et al.*, 2011; Brazão-Silva *et al.*, 2010). Systemic disease is the most important predictive factor towards disease-free survival followed by the clinical response to chemotherapy (Zheng *et al.*, 1998).

INTRODUCTION

Ewing sarcoma (ES)/primitive neuroectodermal tumours (PNET, together defined as Ewing sarcoma [ES]) is a primary neoplasm of the skeletal system, first described by James Ewing in 1921 (Gupta *et al.*, 2009). ES is the second most common bone cancer, most often occurring in Caucasian children, adolescents and young adults. It is considered a high-grade malignancy. The neoplasm is thought to arise from immature reticulum cells or primitive bone marrow cells. The current reports have suggested the role of mesenchymal stem cells (MSC) in Ewing tumor proliferation (Ross *et al.*, 2013). Its occurrence in head and neck region is less frequent and majority of them are found in mandible as compared to maxilla (Mukherjee *et al.*, 2012). We are presenting two cases of ewings sarcoma maxilla and one case of ewings sarcoma scapula.. The ES usually arises in the metaphysis or diaphysis of long bones of extremities. The lungs, bones and bone marrow are the most common sites of metastasis. An extensive review of the literature showed only few reported cases of the extra-osseous ES in patients under the age of 10 years. This report describes a case of extra osseous ES of the scapular region in a 11 years old child. Although the prognosis is poor but early diagnosis and long term follow up can improve the survival.

Case 1: A 9 year old female child presented with swelling left cheek and upper jaw for a duration of one year. CECT findings

were expansile lytic lesion (35x20) involving left maxilla extending from left alveolus into maxillary antrum with breach in cortex. CEMRI findings were left maxillary lesion (predominantly cystic) with infiltration into alveolus and into the anterolateral wall of maxilla into the subcutaneous planes. BONE SCAN showed local pathology without any metastasis. She was diagnosed as malignant round cell tumor on biopsy and was found positive for EWSR1 gene translocation. Patient underwent VAC-IE therapy. Partial maxillectomy was performed. Cut section of the Gross show cystic area measuring 2.5x2.1 cm (Figure 1), on histopathological examination (Figure 2) of the specimen tumor regression was noted in the form of fibrosis and inflammation. All the resection margins

Case 2: A 7 year old female patient presented with diffuse swelling left side of face. MRI findings were nasal cavity lesion extending into left maxillary sinus, in contact with orbital wall but integrity of wall is maintained. PET-CT shows a mildly metabolically active lesion in the left maxillary sinus extending into nasal cavity without any metastasis. Histopathology was done with histopathological features of malignant round cell tumor and IHC markers (markers positive were CD99, Vimentin, NSE, FLI1 and Synaptophysin). EWS-FLI1 gene rearrangement was present and the tumor was diagnosed as Ewings Sarcoma. Patient was put on VAC-IE Therapy. Medial maxillectomy (Figure 3) was performed after therapy, all the bony resection margins were free of tumor.

Case 3: A 12 year old boy presented with progressively increasing swelling right shoulder since 1 year .NCCT Chest show lytic lesion involving right scapula with large extraosseous soft tissue density seen measuring 5x4 cm (Figure 4). Histopathology (Figure 5 & 6) and immunohistochemistry of the tissue biopsy was done IHC markers (Figure 7) positive were CD99, Vimentin, NSE, FLI1 and Synaptophysin. Ki67 was 30%. EWS-FLI1 gene rearrangement was present and the tumor was diagnosed as Ewings Sarcoma.

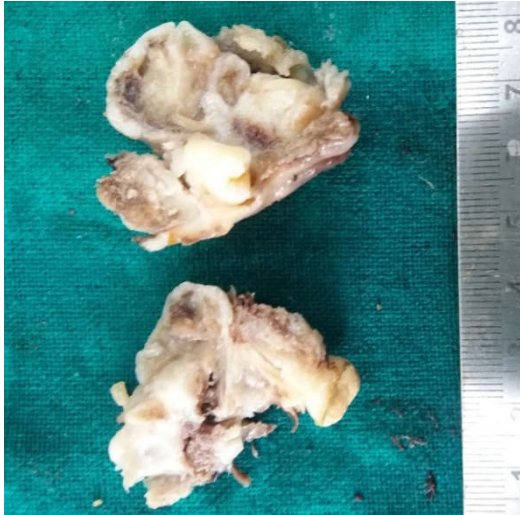


Figure 1. Photomicrograph shows cystic area measuring 2.5x2.1 cm in the left maxillary sinus

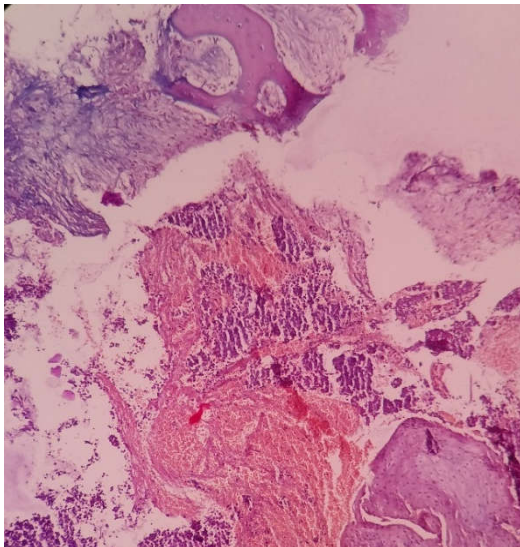


Figure 2. Photomicrograph shows small round tumor cells infiltrating the bony trabeculae (H & E 40 x10)

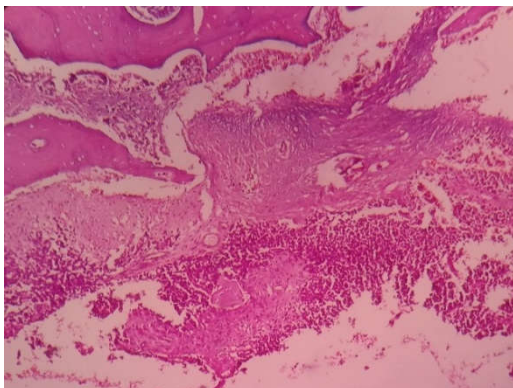


Figure 3. Photomicrograph shows small blue round tumor cells infiltrating the maxillary cortical bone. (H&E, 40x10)

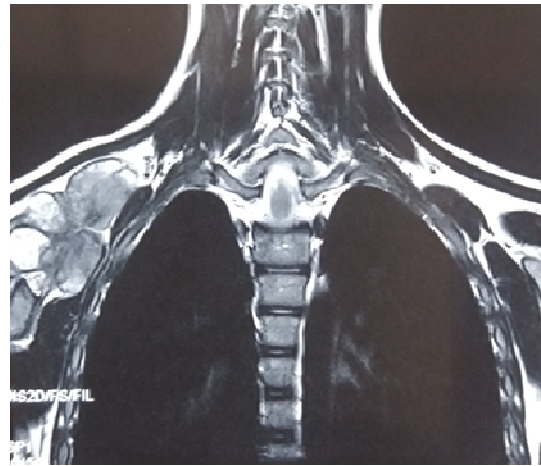


Figure 4. NCCT Chest showing lytic lesion involving right scapula with large extra osseous soft tissue density seen measuring 5x4 cm)



Figure 5. Photomicrograph shows Gross specimen of scapula with multicystic areas filled with necrosis

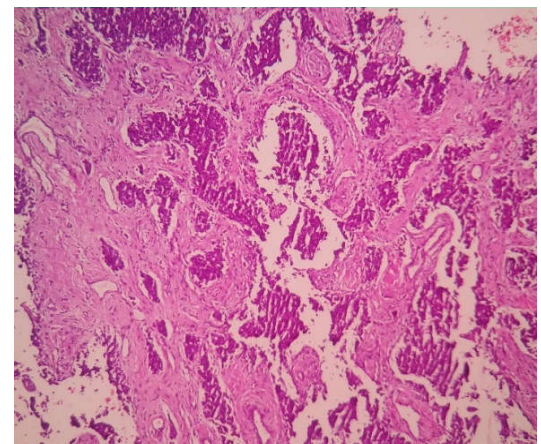


Figure 6. Photomicrograph shows small round tumor cells arranged in nests infiltrating the surrounding tissue (H&E, 40x10)

DISCUSSION

After osteosarcoma, ES/Peripheral Neuro-Ectodermal Tumor (PNET) is the second most frequent primary malignant tumor occurring in bone. However, it is rare for ES/PNET to be found in the head and neck region (Gupta *et al.*, 2009; Ross *et al.*, 2013). PNET is a rare malignant tumor of ES family of tumors which include ES, PNET and Askins tumor (Ross *et al.*, 2013). ES and PNET share a common karyotype translocation t(11;12) (q24;q12).

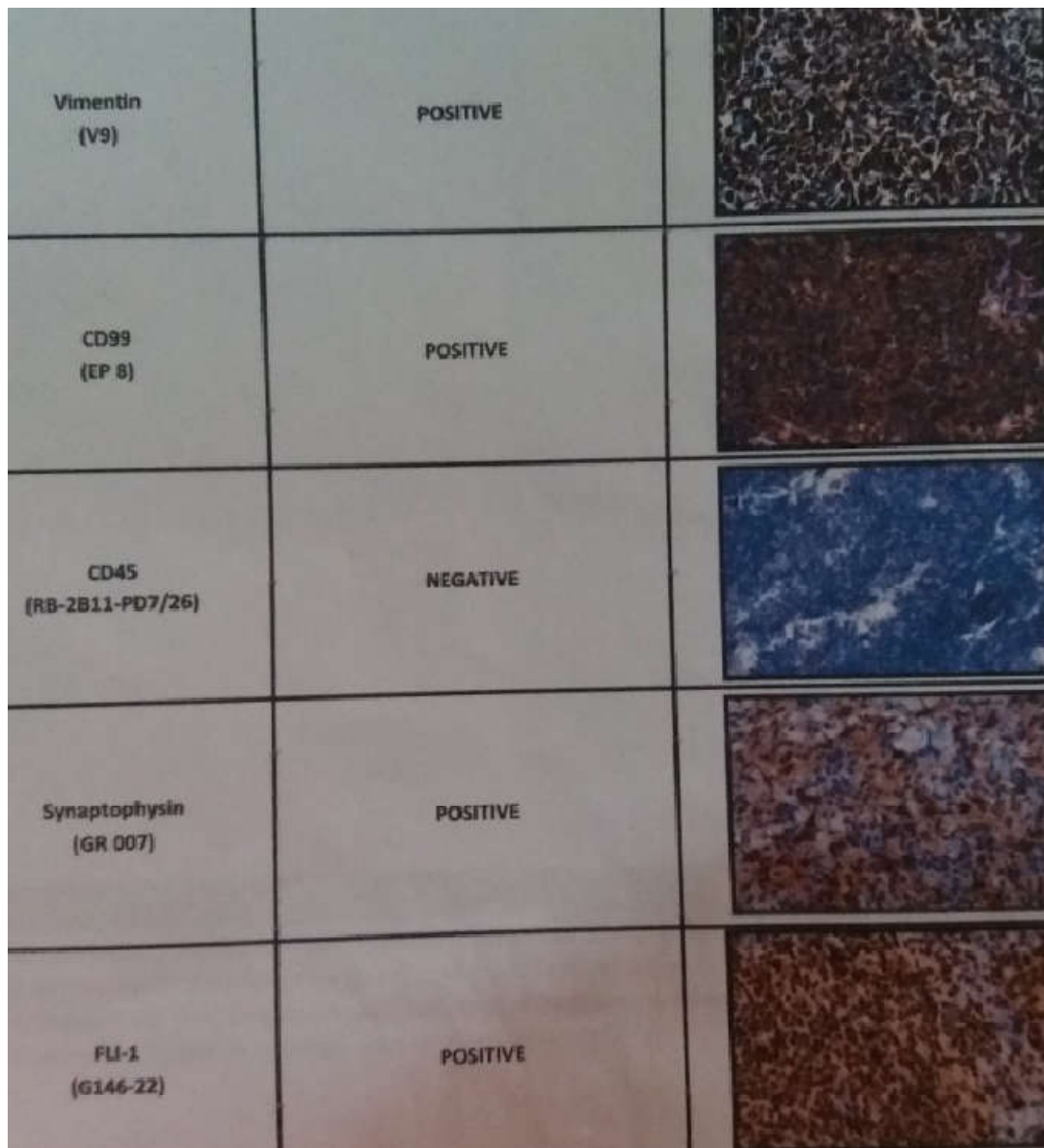


Figure 7. Photomicrograph shows IHC positive for vimentin ,CD99, synaptophysin and FLI1

PNET is thought to be arising from soft tissues and ES in bone. Both ES and PNET share a high level of expression of the CD99 antigen (MIC-2 gene product). Because of these findings many investigators now believe that ES and PNET belong to same spectrum of tumors with different morphological patterns (Hafezi *et al.*, 2011; Allam *et al.*, 1999; Regezi *et al.*). Approximately 4% of Ewing's sarcoma cases have arisen in the bones of head and neck with 1% occurring in the jaws. When the jaws are involved it frequently involves the mandible than maxilla (Kaler and Sheriff , 2013; Varshney *et al.*, 2007; Hafezi *et al.*, 2011; Allam *et al.*, 1999; Regezi *et al.*). The lesion is predominantly seen in children and young adults. It has characteristic radiographic picture described by some authors as “onion skin appearance” especially in the long bones, but such pattern is less commonly seen in lesions of jaws (Kawabata *et al.*, 2008; Regezi *et al.*). With respect to teeth, some of the radiological features noted include periodontal space widening, loss of lamina dura, root resorption, displacement or more commonly destruction of unerupted tooth follicles. MRI is considered to be an important tool to determine the extent of the lesion and for monitoring the effects of chemotherapy on the tumor (Lopes *et al.*, 2007; Coskun *et al.*, 2005). Soft tissue ES is a rapidly growing, round-cell, malignant tumour which can reach 10 cm size by the time

diagnosis is made. Commonly affected extra-osseous sites are the paravertebral spaces, lower extremities, head and neck, and pelvis. A few cases of extraosseous ewings sarcoma scapula are reported in literature. Ewing's sarcoma is composed of uniform small, round, undifferentiated tumour cells with round or oval nuclei exhibiting a fine chromatin pattern, small nucleoli and scanty cytoplasm usually crowded in sheets or segregated in lobules by fine fibrovascular septa (Regezi *et al.*). 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 Ewing's sarcomas are usually vascular; hemorrhagic areas and extensive necrosis are common (Ross *et al.*, 2013; Mukherjee *et al.*, 2012; Regezi *et al.*). Histopathologically the tumor must also be differentiated from other small round cell tumor such as mesenchymal chondrosarcoma, rhabdomyosarcoma, malignant lymphoma, eosinophilic granuloma, neuro-endocrine tumors and metastatic neuroblastoma (Vikas Prasad, 2008). The use of immunohistochemistry has helped in the diagnosis of this tumor (Infante-Cossio *et al.*, 2005). In general, the tumor cells are positive for vimentin and CD99 and negative for neural, skeletal, vascular and lymphoid cell markers (Fiorillo *et al.*, 1996; Davido *et al.*, 2011; Brazão-Silva *et al.*, 2010).

Regarding Mic-2 antigen, recently published data have confirmed the high sensitivity of the Mic-2 gene product (CD99) for all ES family tumors with over 95% of the cases showing positivity for this marker (Ross *et al.*, 2013). Both ES/PNET are no longer considered a distinct entity because of histological and molecular similarities. More than 90% show a clear translocation t (11; 22) (q24; q12) resulting from the fusion of EWS and FLI gene. The gene rearrangement causes a fusion product which functions as an oncogene aberrant transcription factor with structural variability and potential prognostic impact. The neuroepithelial differentiation is varied, Ewing's sarcoma shows a minimum degree of differentiation and PNET shows obvious degree of differentiation (Ross *et al.*, 2013; Lopes *et al.*, 2007). Ewing's sarcoma is a radiosensitive tumour (Infante-Cossio *et al.*, 2005). Multimodality therapy consisting of an initial biopsy, aggressive combination of surgery, chemotherapy and localized radiotherapy is the treatment of choice for Ewing's sarcoma of the head and neck region and may result in long-term survival (Vikas Prasad *et al.*, 2008). 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 (Ross *et al.*, 2013; Regezi *et al.*,; Davido *et al.*, 2015; Brazão-Silva *et al.*, 2010). Systemic disease is the most important predictive factor towards disease-free survival followed by the clinical response to chemotherapy (Zheng *et al.*, 1998).

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