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A CLINICO CYTOLOGICAL STUDY OF EWING SARCOMA IN A TERTIARY HOSPITAL FROM SOUTH INDIA

Pathology

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ABSTRACT

Ewing sarcoma family include typical, atypical ES, Peripheral primitive neuro ectodermal tumour and Askin tumour occuring during first two decades of life , the most frequent sites,being femur,tibia, ilium and fibula.

Materials and methods: A Prospective,descriptive study with 3444 fine needle aspirates revealed 61 bone lesions . Primary malignant bone tumours 37 (61%) and ES were 9 cases (15%).

Results: The median age of the patients were 17years ,M: F ratio 1.2: 1, with swelling and pain mimicking osteomyelitis.Aspirates showed dispersed cells with an admixture of large pale andand small round cells.

Histopathology revealed sheets , lobules and pseudo rosettes of small uniform round cells separated by thin fibro vascular septae.In two cases with metastases, an intense membranous positivitywith CD 99 and NSE was positive in Askin tumour.

Conclusion: An accurate, specific cytodiagnosis supplemented with IHC and Cytogenetics helps an early therapeutic protocol to be implemented.

KEYWORDS

Ewing Sarcoma, Cytology, Diagnosis

INTRODUCTION

Ewing sarcoma (ES) family of tumours include typical and atypical ES, Peripheral primitive neuro ectodermal tumour and Askin tumour.This tumor was first described by Ewing in 1921 as “diffuse endothelioma of bone”. The soft tissue counterpart was first reported byAngervall and Enzinger in 1975. In 1979, Askin *et al*.reported identical tumors in the thoracopulmonary region, known as Askin tumor.

ES are one of the most aggressive malignant small round cell tumors occurring as osseous or soft tissue tumors that usually occur during the first two decades of life , more frequently in boys than girls. The most frequent sites are femur(20 to25%), tibia, ilium, fibula, humerus ,pelvis, mandible and clavicle. 30% of these tumours are multicentric and metastases are often seen.Localized pain is typically the first symptom followed by a swelling reported in many paediatric patients.Fever is present in 28% of patients at the time of diagnosis. Patients seek medical attention due to metastases which are seen in approximately 26% of patients at initial diagnosis and frequent sites are lungs and other bones.

MATERIALS AND METHODS:

A prospective descriptive study was done.During a period of 6 months from January to June 2008 ,3444 fine needle aspirates were performed in Govt. Rajiv Gandhi General Hospital , Madras Medical College. Out of 61 bone lesions , primary malignant bone tumours were 37 (61%) and ES group contributed 9 cases (15%) .The hospital case files were analyzed. Surgical specimens of these tumors from open, needle biopsies, Resection specimens were subjected to meticulous gross and microscopic examination. The specimens were fixed in 10% neutral buffered formaldehyde. Extensive sampling was done , processing and paraffin blocks (number of blocks depending on the size of the tumor) were made. Histologic Sections (5 to 6 µm) were stained with Hematoxylin and Eosin and additional sections for Immuno histochemistry Panel. Ethical clearance was obtained from the Institutional ethics committee. Microsoft excel was used for the statistical analysis.

Clinical Presentation:

The age at presentation ranged from 11 to 30 years with M: F ratio being 1.2: 1.Most of the patients presented with swelling and pain. Radiology revealed lytic lesions in 6 cases and 3 cases were mimicking osteomyelitis. MRI scan for a 11 year old female showed a large, lytic lesion involving a major portion of scapula with the attached soft tissue component extending intra articularly.

No	Age	Sex	Site	Recurrence
1	11	F	Fibula	-
2	17	M	Ilium	-
3	13	F	Scapula	-
4	18	F	Humerus	-
5	30	M	Chest wall(Askin tumour)	-
6	15	M	Femur	-
7	24	M	Femur	Recurrence
8	11	F	Scapula	Skull, Clavicle metastasis
9	17	M	Scapula	-

The 11 year year old girl had Scapulectomy followed by radiotherapy and chemotherapy for 33 cycles with Cyclophosphamide , Actinomycin and Dexamethasone,but presented again with metastases in the skull and clavicle. 17 year old male patient had Left hip disarticulation for Ewing Sarcoma in left proximal femur but the tumour recurred 6 months after a cycle of chemo and radiotherapy which measured 25 x 20 cm involving the scar .

CYTOLOGY:

Fine Needle Aspiration (FNA) plays a pivotal role in the prompt and accurate diagnosis of Ewing s Sarcoma of bone.Ewings Sarcoma mimicks Osteomyelitis of bone both clinically and radiologically . FNA is of great help to differentiate between the two lesions thereby avoiding unnecessary incisional biopsies.

Aspirates from 7 cases were highly cellular showing predominantly dispersed cells with some clustering. Most of the smears showed an admixture of both large pale cells and small dark cells. Large cells had nuclei with fine chromatin and 1 – 2 nucleoli having moderate eosinophilic cytoplasm and small cells had dark round nuclei with scanty cytoplasm. Rosettes were seen in five cases.

Two cases who presented with recurrencesand metastases had predominant large cell population with nuclear pleomorphism and prominent nucleoli in a necrotic background.

HISTO PATHOLOGY:

Ewings tumours are primitive mesenchymal neoplasms with limited capacity for multidirectional differentiation. About 80% of cases exhibit classic Ewing morphology and up to 20% display atypical features including large cell, adamantinoma-like, spindle cell sarcoma-like, sclerosing, clear cell, or vascular-like patterns.

Histopathological correlations were obtained in 6 cases.

Multiple sections showed solid sheets and distinct lobules of small uniform round cells separated by thin fibro vascular septae. Some of the cells were arranged in pseudo rosette pattern. Cells had round to ovoid nucleus with distinct nuclear membrane, fine chromatin and 1-2 small nucleoli. Two cases had extensive areas of necrosis.Neuronal differentiation and CD99 positivity were used to differentiate Ewing sarcoma and peripheral primitive neuroectodermal tumors (pPNETs).

IMMUNO HISTOCHEMISTRY

A panel of immunomarkers such as CD99, leukocyte common antigen (LCA), cytokeratin, desmin, and neural markers such as neuron specific enolase (NSE),S100, and synaptophysin are usually used to distinguish the different tumors with small round cell morphology. CD99 is an important and "traditionally used" one. Among the other markers, the most commonly expressed are the markers for neuroectodermal differentiation, which includes Synaptophysin, NSE and S100.

In our study, two cases where CD 99 was done, an intense membranous immuno reactivity was presented with metastases seen. Neuron specific enolase was positive in Askin tumour.

CYTOGENETICS:

EFTs are characterized by pathognomonic EWSR1 gene translocation with a member of the ETS transcription factor family and genomic studies have shown that the number of additional mutations or genomic alterations increased with age which suggests increasing genomic instability with age.

Clinical presentation and outcomes of patients diagnosed with EFTs at age over 50 years are different from pediatric population. The differences in clinical presentation underline possible differences in tumor biology. In 85–90% of EFTs cases, the tumor is characterized by a translocation involving the EWSR1 (EWS RNA-Binding Protein 1) gene on chromosome 22, and an ETS (E26 transformation-specific)-family gene such as FLI-1 or ERG.

CONCLUSION:

Ewing's sarcomas (EWS) and peripheral primitive neuroectodermal tumours (PNET) are small round cell tumours . The cytological diagnosis of ES entails an accurate assessment of the cytomorphological features. Diagnosis also requires histopathological examination, immunohistochemistry and cytogenetics. Clinical management is based on the combined evaluation of clinical data, radiographic findings and cytological examination An accurate, specific cytodiagnosis supplemented with IHC and Cytogenetics helps an early therapeutic protocol to be implemented. At present, limb salvage therapy is replaced by chemo therapy and radiotherapy. The advent of multimodality treatment, which includes local control by surgery and radiotherapy and systemic control by chemotherapy, has improved the overall survival.

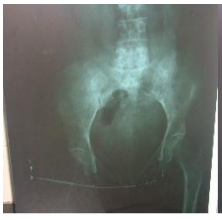

FIG:1LYTIC LESION-ILIUM, 17 / M

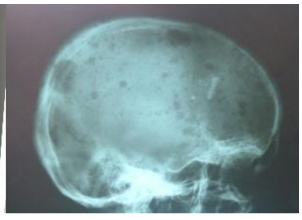

FIG:2 SKULL- MULTIPLE METASTASES, 11 / F

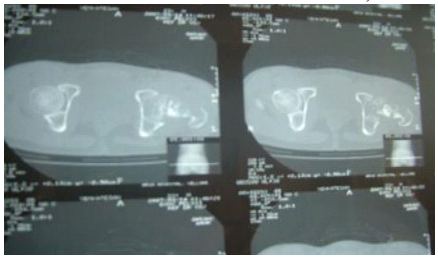

FIG 3 : MRI – LYTIC LESION ILIUM

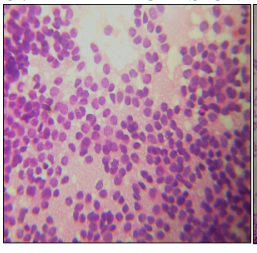

FIG : 4. ROSETTES , 10 X 40

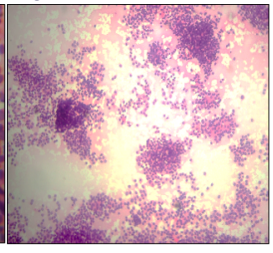

FIG : 5 .10x10 , Small and large cells

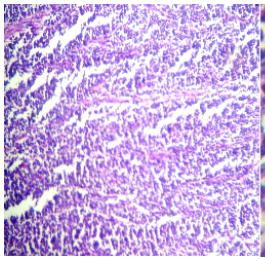

FIG 6. HPE- SHEETS OF SMALL ROUND CELLS 10 x 10

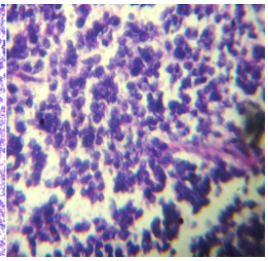

FIG 7. SMALL ROUND CELLS,10X 40,

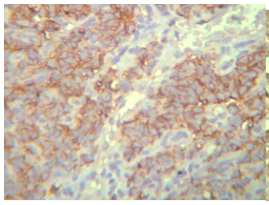

Fig 8, Strong and diffuse Membranous CD 99 positivity 10 X 40

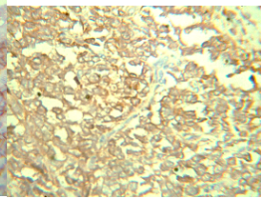

Fig 9, Strong and Diffuse membranous NSE positivity

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