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Extraosseous Ewing Sarcoma – Cytological Diagnosis of a Rare Entity

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Abstract: *Extraosseous Ewing Sarcoma (EES) is rare, aggressive, rapidly growing soft tissue tumor that shares morphological features with its osseous counterpart. EES has a wide age range, from infancy to the elderly and can involve soft tissues at any location, common sites being paravertebral and intercostal regions, followed by extremities. The osseous tumor is a relatively uncommon primary malignant bone tumorthat occurs often in children and adolescents. It is known to be more common in men.With the recent advances in EES treatment protocols, cytology has gained importance for rendering an early and accurate diagnosis, thereby avoiding a more invasive open surgical biopsy.Here we discuss the cytological appearance of EES in three middle aged patients, two of whom were females. These patients presented with soft tissue mass at different locations, without the involvement of the underlying bone.*

Keywords: *Cytology, Ewing sarcoma, Extraosseous.*

I. Introduction

Ewing sarcoma (ES) is defined as an undifferentiated small, round to oval cell sarcoma, occurring most often in children and adolescents.[1, 2] It is the second most common primary malignancy of bone in children. Extraosseous Ewing sarcoma (EES) arises in soft tissues of trunk or extremities, but has also been reported to occur in sites such as larynx, nasal fossa, neck, lung, retroperitoneum, perineum, and mediastinum. [3, 4]It is known to be more common in men and has a wide age distribution, from 8 months to 60 years or more. [2,3]

EES shares histologic, immunohistochemical and molecular features with its osseous counterpart. [5] Microscopically, EES is composed of poorly differentiated small round cells. Due to the lack of characteristic morphologic features, it is difficult to distinguish EES from similar looking small round cell tumorslike neuroblastoma, alveolar rhabdomyosarcoma, malignant lymphoma and poorly differentiated synovial sarcoma. [1, 2]With the advances in therapeutic protocols, fine needle aspiration cytology (FNAC) is being increasingly used in the evaluation of bone and soft tissue tumors to avoid an open surgical biopsy. We report three cases of EES diagnosed on FNAC and confirmed by histopathology and immunohistochemistry.

II. Case Report

Three patients in the age group of 20-40 years, presented to the out-patient department with soft tissue swelling which had progressively increased in size over a short duration of time and was painful.

Of the three patients, one was a male aged 40 years with a soft tissue swelling over the left knee and was treated with intrasynovial steroid injections, with no relief. A clinical diagnosis of osteomyelitis was given but subsequent radiographs revealed a soft tissue mass. (Fig 1)

One of the remaining two patients was a female aged 23 years with a swelling over the sternum and the third patient was a 39 year old female with a swelling on the lateral aspect of left lower chest wall.

FNAC in all these three cases revealed cellular smears showing two populations of cells, one with cells having thin rim of pale cytoplasm, large nuclei, and prominent nucleoli with dispersed chromatin. The other population of cells comprised of relatively small cells with round to elongated nuclei and coarse chromatin. Some of these cells were arranged in rosettes. These small cells formed the predominant population.The background was clean. (Fig 2a and 2b)

The above features led to the cytological diagnosis of malignant small round cell tumor, most likely Extraosseous Ewing Sarcoma.

Histopathological sections revealed sheets of small uniform cells with round nuclei and scanty cytoplasm. Occasional perivascular Homer-Wright rosettes were identified. Immunohistochemistry was performed, in which tumor cells exhibited diffuse membranous staining for CD99. (Fig 3a and 3b)
The above features led to a confirmative diagnosis of Extraosseous Ewing Sarcoma in all the three cases.

III. Discussion

EES is a highly malignant, undifferentiated round cell tumor with an aggressive clinical behaviour and high rates of local recurrence and distant metastasis.[4]EES occurs commonly in the paravertebral region, lower limbs, and chest wall, with few reported cases of EES in the pelvic cavity, retroperitoneal region, upper limb, head and neck. [2,4]

The primary osseous ES affects children and young adults, involving the diaphysis or metaphyseal-diaphyseal regions of long bones. Less frequently, ES can demonstrate a primary soft tissue origin and the neoplasm is classified as extraosseous ES. [6]

EES has a low incidence rate and accounts for 1.1% of malignant soft tissue tumors, most often occurring in young people ranging in age from 15 to 30 years. Rarely, it can occur in adults more than 40 years of age. It has been reported to be more common in men. [2]

The Ewing sarcoma family includes, Ewing sarcoma of bone, Extraosseous Ewing sarcoma, peripheral primitive neuroectodermaltumor (pPNET) and Askintumor (thoraco-pulmonary PNET). These tumors are now known to arise from a common precursor cell, with each entity representing a distinct expression of the same neoplasm. [7]

The non-osseous or extraosseous Ewing sarcoma has been recognised as a distinct entity, since the time it was first described by Tefft et al in a series of five patients with round cell tumor arising from paravertebral soft tissue. The authors believed that four of the tumors were related to Ewing sarcoma but were unusual due to paucity of bone changes on plain film. [3]The tumor usually presents as a painful, deep seated, rapidly growing mass. Pain as a presenting symptom is seen in one-third of the cases, as was seen in our patients. Progressive sensory or motor disturbances are noted with the involvement of peripheral nerve or spinal cord. However, the patients in the current report did not present with any sensory loss. Movement was restricted to a minimal degree due to painin the patient with swelling over left knee. Cytology and histopathology provide a definitive opinion in conjunction with radiographs (CT or MRI). [4]

EES has no specific clinical manifestation, so a timely pathologic investigation is essential to clarify the diagnosis. The tumor shows rich vascularity with abundant thin walled vessels within fibrovascularseptae. The vessels get compressed and obscured by closely packed tumor cells. These cytological features provide necessary clues for diagnosis.[4]

According Xie et al,[2] clinical diagnosis of EES is fraught with the following short-comings:

- Low incidence of the tumor
- No specific characteristics in symptoms, signs or imaging
- No distinct histological features can cause pathologic misdiagnosis.

The exact diagnosis of EES relies on pathology with use of ancillary techniques like cytogenetic analysis, reverse transcriptase polymerase chain reaction and fluorescence in situ hybridisation. Demonstration of t(11;22)(q24;q12) chromosomal translocation (EWS-FLI1 gene rearrangement) is highly specific for ES/PNET since it is seen in more than 90% of the tumors. On immunohistochemistry, these tumorsexpress CD99/MIC 2, which is a cell membrane glycoprotein. In our study, all three cases showed strong membrane staining with CD99.[2, 6]Due to lack of characteristic morphologic features, ES/PNET is difficult to distinguish from other round cell tumors like rhabdomyosarcoma, lymphoma, metastatic neuroblastoma, and poorly differentiated synovial sarcoma. [2, 4, 6]

In adults, Non-Hodgkin's lymphoma can be excluded on histopathology by the presence of marked cell dissociation, scant blue cytoplasm, lymphoglandular bodies and tingible body macrophages in the background.

The five year survival rate for skeletal Ewing sarcoma is around 75% as against a low of 38% in the extraskeletal counterpart. [4] A retrospective study of 24 patients with extraskeletal Ewing sarcoma showed an overall 5-year survival rate of 61%. A wide tumor-free resection margin with multi-agent chemotherapy has been shown to give good clinical outcome. [6]

However with the advent of new advances in EES treatment protocols, preoperative chemotherapy is given to a significant proportion of patients. Thus, it is essential to render a specific cytologic diagnosis, thereby avoiding a more invasive open surgical biopsy. [5]

IV. Figures

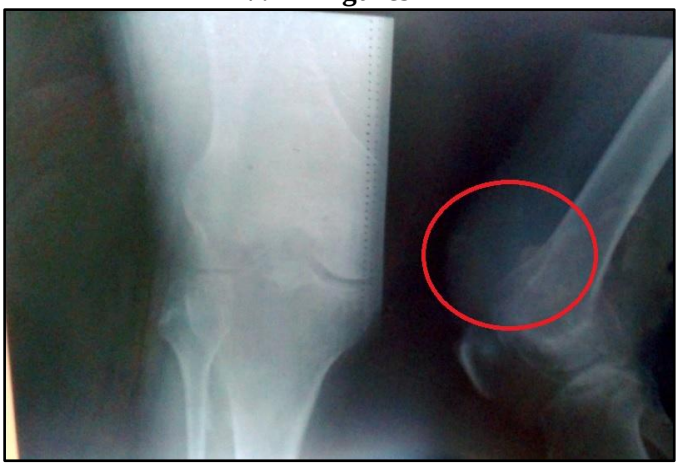

Figure 1: Roetgenogram showing a soft tissue mass at the lower end of left femur near the knee joint.

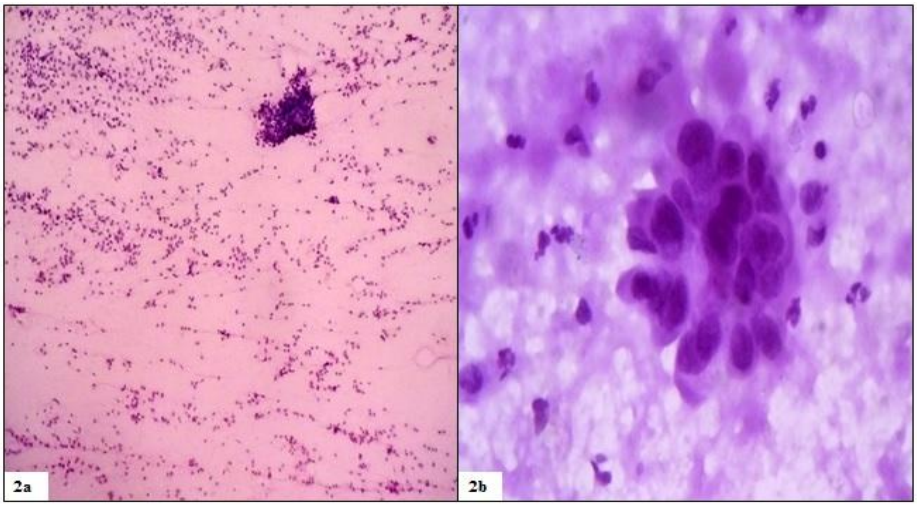

Figure 2a: Photomicrograph showing cellular FNA smear composed of dissociated cells and clusters of small uniform round cells with rounded bland nuclei. (H&E; x100)
Figure 2b: Photomicrograph showing FNA smear with round dark cells forming a rosette, in a background of hemorrhage and necrosis. (H&E; x1000)

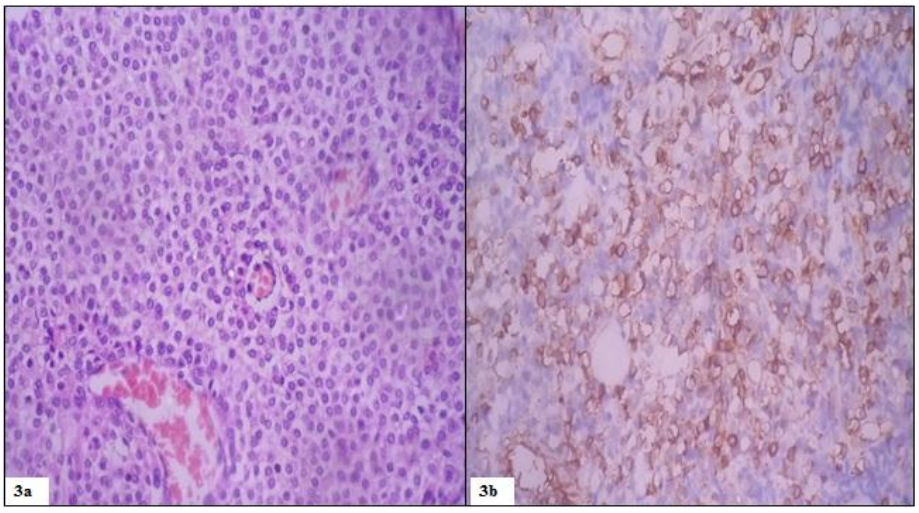

Figure 3a: Photomicrograph of histopathological section showing small round cells with round nuclei containing fine chromatin, scant clear or eosinophilic cytoplasm and indistinct cell borders. Homer-Wright rosettes in perivascular distribution are seen. (H&E; x400)
Figure 3b: Photomicrograph showing diffuse membranous staining for CD99. (H&E; x400)

V. Conclusion

Fine needle aspiration cytology has distinct advantages over open biopsy, the former being safe, economical, relatively painless, which can be performed as an outpatient procedure. With the advent of new treatment protocols and use of preoperative chemotherapy to minimize surgical intervention in the management of EES, a quick and minimally invasive diagnostic modality like FNAC, has proved to be of importance. FNAC is also useful in long term follow up of these cases to diagnose recurrence or an intercurrent second malignancy. This is especially true in places where monetary funds are limited.

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