Diagnostic Enigma of an Extraskeletal Ewing’s Sarcoma/PNETT

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Introduction

An eleven-year-old girl was seen in December 2001 because of a tender swelling on the medial aspect of her left great toe. She related the swelling to a trivial trauma happened six month ago. The personal medical history revealed no relevant information and the family history was negative for important congenital or hereditary diseases.

Physical examination of the left great toe showed a localized swelling over the dorsal aspect of the toe, which was tender, reddish and warm. Range of motion of the toe was normal and neurovascular examination did not reveal any abnormality.

Plain radiograph of the toe showed no fracture or bony abnormalities. Laboratory investigations consisting of full blood count, blood sugar, serum electrolytes and urinalysis showed a leucocytosis of 11,200/ml and the other features were within the normal range.

The provisional diagnosis of this swelling was a soft tissue abscess, for which she was taken to the theatre for incision and drainage. Under general anesthesia and without using tourniquet the lesion was incised directly. There was no pus collection and two lobulated, bluish soft tissue masses appeared over the proximal phalanx of the great toe, having no attachment to tendons, bone or other adjacent structures. The specimens were sent for histopathology examination to two different laboratories. The wound healed within 10 days postoperatively.

The histopathology reports were received six days later with the following details:

Macroscopic examination: Five irregular brownish white nodular tissues, largest measuring 1.8×1.0×0.5, smallest measuring 1.0×0.5×0.3 cm.

Microscopic examination: Section reveals highly necrotic hemorrhagic nodular lesion composed of diffuse proliferation of spindle or oval cells or foamy cells with dense nuclei. There are few multinucleated and floret-like cells and gapping spaces simulating vascular channels seen. Areas of hemorrhage, foci of myxoid change and patchy inflammatory cell infiltrate mainly lymphocytes, plasma cells and histiocytes seen. Resection margins are normal. No evidence of malignancy identified.

Special stains: Elastic Van Gieson (negative), Reticulin Stain (positive). Immunocytochemistry stains were done. Vimentin (negative), EMA, CK, CEA, Desmin, Myoglobin, Myosin, S 100, NSE and SMA (negative).

Diagnosis: Consistent with highly vascular soft tissue lesion.
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Comment: From the age of the patient and site of the lesion, so the possibility of Giant Cell Fibroblastoma cannot be excluded.

The patient was discharged from the clinic’s follow-up and was feeling no problem until the next September (one year later) who found swelling and tenderness of the same toe. She was again operated for an incisional biopsy of the lesion and its underlying bone. The new histopathology examination showed the following result:

Macroscopic examination:
1. Labelled as cystic lesion of the big toe measuring 1.8\(\times\)1.0\(\times\)0.4 cm, reveal brownish yellow nodule.
2. Bone pieces from swelling big toe, small pieces of tissue measuring 0.5\(\times\)0.4\(\times\)0.3 cm

Microscopic examination:
1. Sections reveal encapsulated tumor similar to previous biopsy composed of sheets and clusters of small uniform round to oval cells with little cytoplasm and vesicular nuclei with arterial nuclei. The tumor cells are arranged around blood vessels as a peritheliomatous pattern. Small focus of necrosis and areas of hemorrhage seen. Surrounding tissue shows hyalinized fibrocollagenous tissue.

Special stains: PAS stain shows cytoplasmic positivity. Reticulin stain shows fibrillary fibers surrounding the tumor cells. Immunohistochemistry stains were done: Vimentin (positive), Ewing’s tumor marker, CD99 (strongly membrane positive), S100 and Neurillament (some cells are positive), NSE (few cells are positive), EMA, CK, S100 myosin, CD68 Lyosyme (negative), Synaptophysin and HMB45 (negative)
2. Sections reveal fragments of bony trabeculae with areas of hemorrhage and marrow cells. No evidence of tumor cells infiltration seen.

Impression:
1. Excisional biopsy: Extraskeletal Ewing’s sarcoma/PNET
2. Bone pieces: Bony tissue with degenerative changes

With this histopathology report she was referred to a cancer center that was operated by left great toe amputation and resection of the first metatarsal head. She is now taking chemotherapy under the care of the same center.

Discussion
Pediatric solid tumors, especially small round cell tumors remain a diagnostic challenge, mainly due to their undifferentiated or poorly differentiated features. Ewing’s sarcoma / PNET (Primitive Neuroectodermal Tumor), rhabdomyosarcoma and neuroblastoma are included in this group of tumors. Ewing’s sarcoma/PNET is the second most common bone/soft tissue tumor in the pediatric age group. In fact Ewing’s sarcoma/PNET is a tumor with variable degrees of neural differentiation which happens in bone or soft tissues. Before James Ewing’s description (1921) of his undifferentiated tumor in the diaphysis of long bones, Arthur Purdy Stout described (1918) a tumor of ulnar nerve having gross features of a sarcoma, composed of small round cells and rosettes. He called this tumor neuroepithelioma and subsequently it was named as peripheral primitive neuroectodermal tumor (pPNET). Later a new type of tumor which caused confusion about histogenesis and terminology was reported. This type, named as ‘extra skeletal Ewing’s sarcoma’ or ‘soft tissue Ewing’s sarcoma’ shows a neural differentiation which can be demonstrated by immunohistochemical and ultrastructural methods. This tumor was reported by Tefft et al in 1989 and the pathological features were described by Angervall et al in 1975. There is no sex predilection for this condition and patients are older; unlike the osseous form
where the median age of occurrence is about 20 years.Extraskeletal Ewing's sarcoma has been described in almost all sites where every other sarcoma is found. Distant metastases to the lung are usually found.

Similar to Ewing's sarcoma and PNET, these tumors have positivity in some neural markers such as neuron specific enolase, 70 kd neurofilament and also neuroendocrine marker positivity such as chromogranin. Also, in some extraskeletal Ewing's sarcoma cases, focal positivity of keratin and MIC-2 gene products are detected and such cases are classified as a separate clinicopathological group and referred to as Akin tumor. These tumors are generally localized in the thoracopulmonary region.9,10,11

In fact extraskeletal Ewing's sarcomas are uncommon soft tissue neoplasms. They are rare in all parts of the body and few cases have been reported in the literature.12 Ahmad R, et al. reported 24 cases of extraskeletal Ewing's sarcoma happened mostly in trunk with two cases in foot.12 They also believe that the incidence of this tumor is even distributed among the genders but they found the age at the time of diagnosis, unlike its osseous counterpart, to have a wide range, from infancy to the elderly.

Added to H & E and immunohistochemical staining they did immunohistochemistry stains included high and low molecular weight cytokeratin (AE1/AE3 and CAM5.2), Vimentin, Leukocyte Common Antigen (LCA), desmin, actin, Neuron Specific Enolase (NSE), HBA-71, and S-100. Finally, they reviewed by electron microscopy the presence of neural differentiation, Neural Secretary Granules, and Cytoplasmic processes. Tumors that had these features and were HBA-71 positive were designated as PNET. The remaining tumors were reported as Ewing's sarcomas with differentiated electron microscopy findings, were positive on HBA-71 staining, or had no evidence of rosette formation on light microscopy.

**Conclusion**

Added to the rarity of extraskeletal Ewing's sarcoma and very few cases of this tumor reported in foot and no case of toes to the extent of the authors' knowledge, the complexity of the diagnosis has no utmost importance. The main reason for this complexity seems to be due to the unusual locations placing it out of the list of differential diagnosis. Due to the nature of the extraskeletal Ewing's sarcoma that is soft tissue tumor growing out of bony structures, both the surgeons and pathologists are recommended to consider it as a probable tumor for all range of patients' age in all parts of the body.

**References**


