Cytological diagnosis of small cell osteosarcoma of the bone

ABSTRACT
Small cell osteosarcoma (OS) is a rare histological variant of OS that poses unique diagnostic difficulties. We present a case of a 10-year-old child who underwent fine needle aspiration cytology (FNAC) from a mass in the right thigh. The cytological findings were those of a malignant small round cell tumor, closest to small cell OS. The FNAC findings were confirmed on histopathology.

Key words: Bone; fine needle aspiration; small cell osteosarcoma

Introduction
Small cell osteosarcoma (OS) of the bone is an unusual variant of OS. It may present a diagnostic challenge on cytological assessment owing to its rarity and its morphologic similarity to other small round cell tumors, including Ewing’s sarcoma (ES), peripheral neuroectodermal tumor (PNET), malignant lymphoma, metastatic neuroblastoma, rhabdomyosarcoma and mesenchymal chondrosarcoma. In particular, ES poses the greatest difficulty. Distinguishing these tumors from each other is important clinically as optimal therapy differs according to the tumor type. Only rare accounts of the cytopathological findings of small cell OS on fine needle aspiration (FNA) exist in the literature.[1,2] This article highlights the features that help in diagnosing this distinctive microscopic variant of OS on FNA cytology.

Case Report
A 10-year-old male child presented with complaints of pain and swelling in the lower third of the right thigh for 6 months. The swelling was diffuse and measured 5 cm × 6 cm. Radiograph showed a tumor involving the metaphysis and diaphysis of the femur with soft tissue extension and periosteal reaction. Magnetic resonance imaging (MRI) revealed both intraosseous and extraosseous extension; however, there was no intra-articular involvement.

FNA was performed using a 22 gauge needle attached to a 10 mL syringe on Cameco handle after careful anatomic localization of the tumor with the help of the radiograph and MRI films. Smears were air dried and stained with May-Grünwald-Giemsa (MGG) and also wet fixed and stained with hematoxylin and eosin (H and E).

The cytological smears were moderately cellular and showed clusters and singly scattered tumor cells [Figure 1]. The cells were small and pleomorphic and had a high N/C ratio with round hyperchromatic nuclei and inconspicuous nucleoli and the cytoplasm showed vacuolations that were Periodic acid-Schiff (PAS) positive [Figure 1, inset]. Many atypical mitotic figures, a few tumor giant cells and osteoclastic giant cells were noted. On careful search, a focal area showing presence of pink/metachromatic osteoid-like material was identified. Based on these findings, a diagnosis of malignant small round cell tumor closest to small cell OS was made and biopsy was advised.

The FNA diagnosis was subsequently confirmed on trucut biopsy, which showed small round malignant cells directly laying down pink lacy osteoid. The patient received neoadjuvant chemotherapy for 3 months, which was followed by resection of the right femur. The sections from the resected
specimen showed large areas of necrosis and fibrosis. Only a few areas showed viable tumor with morphology of small cell OS. The chemotherapy was continued but the patient succumbed to neutropenia-related complications 6 months after the surgery.

**Discussion**

OS is the most common primary malignant tumor of the bone. Small cell OS is a distinctive microscopic variant of OS, originally described as a neoplasm having microscopic features of both OS and ES.\(^3\) This is a rare form of OS with an incidence of 1.3% of all OSs. The clinical features including age, sex and skeletal distribution are similar to those of conventional OS. Most of the cases are found in the metaphysis of a long bone.\(^4\) The radiological features are not consistently typical for small cell OS because there is very little production of mineralized matrix.\(^5\) However, if the mineralization is identified within the tumor and in areas of soft tissue extension, it favors OS.\(^1\)

The widespread use of pre-operative FNA of bone lesions necessitates recognition of the various bone tumors as this may drastically alter the management. Small cell OS poses unique diagnostic difficulties as it may be difficult to distinguish from other small cell malignancies. Primary small round cell tumors of the bone include small cell OS, ES/PNET, lymphoma and mesenchymal chondrosarcoma.\(^6,7\) Metastatic neuroblastoma and rhabdomyosarcoma are the other differential diagnoses in the younger age group.

On cytology, small cell OS is composed of small- to intermediate-sized cells. The cells are mostly dyscohesive oval to round having a high N/C ratio. Chromatin can be fine to hyperchromatic and nucleoli can be inconspicuous to prominent. Focal pleomorphism and cytoplasmic vacuolations can be present. Osteoid production is variable.\(^1\)

The most difficult differential diagnosis is between small cell OS and ES/PNET. Sheets of monotonous small round cells with minimal cytoplasm are seen in either of the tumors. A diagnosis of small cell OS can be rendered if osteoid production is noted. The amount of osteoid produced however is often scanty, making the diagnosis difficult, as was noted in the current case. In addition, it may be difficult to differentiate osteoid from hyalinized collagen that can be seen in ES/PNET. Osteoid is seen as clumps of amorphous or finely fibrillar material that is faintly eosinophilic in H and E and bright red or pink in MGG. In contrast with collagen, osteoid has a more wispy and lacy quality with ill-defined borders and lacks naked fibroblastic nuclei.\(^5\) In the absence of osteoid, another feature to suspect OS is cellular pleomorphism. The presence of Homer Wright rosettes and pseudorosettes supports the diagnosis of ES/PNET.\(^1,4,8\) Although cytoplasmic glycogen is a feature of ES, its positivity does not rule out a diagnosis of small cell OS. In a histopathologic series of OS, 10/21 cases of small cell OS were positive for glycogen, which was highlighted by the PAS stain.\(^9\)

ES/PNET is usually strongly positive for CD99; however, small cell OS can also be immunoreactive, adding to the difficulty in diagnosis. A negative result however supports the diagnosis of small cell OS over ES/PNET. Molecular testing can be very useful as the t (11;22) (q24;q12) is diagnostic for ES/PNET.\(^1,4,8\) Staghorn hemangiopericytoma-like vessels are usually present. The chondroid foci stain for S100 protein and the primitive mesenchymal cells are positive for CD99.\(^1\) Mesenchymal chondrosarcoma occurs in the older age group and is characterized by two cell populations: A small round cell component and lacunar cells associated with chondroid matrix.\(^7\) Staghorn hemangiopericytoma-like vessels are usually present. The chondroid foci stain for S100 protein and the primitive mesenchymal cells are positive for CD99.\(^4\) The cells of lymphoma as compared with small cell OS generally have larger nuclei with vesicular chromatin and prominent nucleoli and show presence of lymphoglandular bodies.\(^1\) Leukocyte common antigen can help in establishing the diagnosis. Metastatic neuroblastoma shows characteristic rosettes of tumor cells with finely fibrillar pink staining material. In addition, neuroblastomas are immunoreactive for synaptophysin and chromogranin but are virtually never immunoreactive for CD99.\(^1\) In rhabdomyosarcoma, eccentric, triangular, strap-shaped rhabdomyoblasts with dense eosinophilic cytoplasm may be recognized.\(^8\) The cells show positivity for Desmin, myogenin and MyoD1.\(^4\)
Conclusion

To conclude, the diagnosis of small cell OS is challenging on cytology. The diagnosis rests primarily on the identification of osteoid production by the malignant cells, and this should be carefully searched for. In the absence of osteoid, cellular pleomorphism favors a diagnosis of small cell OS. Correlation with radiographic findings and ancillary tests can aid in a definitive diagnosis.

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