Diagnosis of extraskeletal small cell osteosarcoma in cytology specimen. Report of a case of rare tumor and review of the literature

Kollin Kahler*Alexander Garcia, Jenna Jarrell, Rona Bakri, Savanna Craib, Karina Leyva, Christian Green, and Mohamed Aziz

Department of Pathology- American University of the Caribbean, School of Medicine, USA

Abstract

Extraskeletal small cell osteosarcoma (ESCOS) is a rare tumor which may present a challenging primary diagnosis on cytologic assessment. The cytomorphology of this tumor is similar to other small round blue cell tumors (SRBT), and in potential absence of osteoid material in cytology specimens, diagnostic error may not be avoided. The diagnostic challenge is even greater with extraskeletal location. The most important reason to be able to differentiate ESCOS from other SRBT is the effect of this diagnosis on guiding appropriate therapy. We present a case of a 62 year old male with the diagnosis of ESCOS based solely on cytologic specimen evaluation.

KEYWORDS: Sarcoma, Extraskeletal; Immunohistochemistry; Molecular; Translocation; Treatment

INTRODUCTION

Osteosarcoma is the most common primary malignant tumor of bone in adolescents and young adults. One rare variant of osteosarcoma is the small cell type, which accounts for less than 1% of all cases of osteosarcoma. Extraskeletal small cell osteosarcoma (ESCOS) is even rarer and very few cases have been noted in the literature. ESCOS presents as a challenge for diagnosis on cytology specimens due to its rarity and similarity to other small blue cell tumors. Common cytological features include relatively small to intermediate sized cells, high nuclear/cytoplasmic ratios, round nuclei, and presence of osteoid. ESCOS can closely resemble other small blue cell tumors such as Ewing’s sarcoma/primitive neuroectodermal tumor (ES/PNET), non-Hodgkin lymphoma, mesenchymal chondrosarcoma, myositis ossificans, desmoplastic small round cell carcinoma, and neuroblastoma.

CASE PRESENTATION

We present a case of a 62 year old male with the diagnosis of ESCOS based solely on cytologic specimen evaluation. Patient presented with severe lower abdominal pain and feeling of a mass in his pelvic area.

Radiographic imaging revealed a 15 cm infiltrating soft tissue pelvic mass. Multifocal scattered tumor masses in the pelvic area were also identified. MRI with and without intravenous gadolinium revealed an enlarging enhancing mass within the pelvic region in addition to multiple smaller pelvic masses. Cystic and hemorrhage components were identified with several fluid-fluid levels, however the solid component of the mass demonstrated marked enhancement concerning for a soft tissue sarcoma. There was no involvement of any pelvic bones.

A CT-guided fine needle aspiration material was obtained from the largest pelvic mass. The cytology sample was sufficient for diagnostic and the preparation included a cell block to be utilized for immunohistochemistry and molecular studies. Cytomorphology showed sheets of small round to oval cells with moderate atypia and abundant abnormal mitotic figures. (Figure 1A). Foci of osteoid formation were identified in the cell block preparation (Figure 1B). The main differential diagnosis included ESCOS and ES/PNET. Immunocytochemistry studies performed on the cellblock showed the tumor cells positive for EMA, CD99, Vimentin (Figure 1C) and Synaptophysin (Figure 1D), while negative forAE1/AE3, CAM5.2, HMW-CK903, Calponin. S100, Desmin, Myogenin, CD34, CD31, and SMA. To rule out possible ES/PNET molecular genetic studies were performed and the tumor was negative for t(11;22) (q24;q12) translocation. The histomorphologic features, together with the immunohistochemistry profile and genetic molecular studies were diagnostic for ESCOS. The presence of osteoid, event in only rare foci was essential for making the diagnosis.

The patient underwent neoadjuvant chemotherapy treatment followed by large en bloc excision. Due to the massive presence of the tumor in the pelvic area, the surgical margins were not free in multiple foci. Post-operative pathological examination showed...
the presence more than 40% viable tumor. Patient received postoperative chemotherapy/radiation, which was not completed due to side effects, but was free of recurrence of metastasis for nine months. Patient expired eighteen months from the initial diagnosis due to massive pulmonary metastasis and respiratory failure.

Our case highlights the importance of the close correlation with clinical and radiologic presentation, with utility of available ancillary resources such as immunocytochemistry studies, and molecular studies to make the diagnosis of ESCOS in small cytology specimens.

DISCUSSION

Osteosarcomas are the most common primary malignant tumors of bone in adolescents and young adults, comprising about 15% of all primary bone tumors (1,2). The most common variant of osteosarcoma is the osteoblastic variant, followed by the fibroblastic, chondroid, telangiectatic, small cell, and well differentiated types (1). Osteosarcoma has a bimodal age distribution, having the first peak during adolescence and the second peak in older adulthood. The first peak is in the 10–14-year-old age group while the second osteosarcoma peak is in adults older than 65 years of age. The incidence of osteosarcoma has always been considered to be higher in males than in females. The most common sites are the femur (42%, with 75% of tumors in the distal femur), the tibia (19%, with 80% of tumors in the proximal tibia), and the humerus (10%, with 90% of tumors in the proximal humerus). Other likely locations are the skull or jaw (8%) and the pelvis (8%) (3).

Extraskkeletal osteosarcoma (ESOS) is defined as a rare malignant mesenchymal neoplasm that produces osteoid, located in the soft tissues and is without (or with minimal) skeletal or periosteal attachment (4,5). ESOS accounts for <4% of all osteosarcomas and approximately 1.2% of all soft tissue sarcomas (6,7). The most common location for primary extraskeletal osteosarcoma is the soft tissues of the thigh (46%), followed by the upper extremity (20%) and the retroperitoneum (17%), but can occur in any part of the body (7). Uncommon sites include larynx, tongue, mediastinum, spermatic cord, penis, pleura, lung, heart, colon, and central nervous system. ESOS occurs in patients older than 40 years, with mean age of 50.7 years (range 23-81 years) and with slight male predominance (8). The prognosis of ESOS is poor when compared to conventional, de novo, intraosseous osteosarcoma. More than 80–90% of patients develop local recurrences and metastasis to the lungs and bones (7,9).

Among the extraskeletal osteosarcomas, the small cell type is extremely rare. The small cell osteosarcoma (SCOS) variant was first described by Sim et al. as an extremely rare and distinct variant of osteosarcoma, estimated to account for less than 1% of all cases of osteosarcoma (10,11). The demographics of SCOS are similar to those of conventional osteosarcoma (11,12). Only seven cases of ESCOS have been presented in the literature. According to Zhang’s literature review of 3 cases, “small-cell extraskeletal OS occurs most often in middle-aged patients (at 30 years, 31 years and 40 years respectively), with 1 male-to- 2 female. Tumor sizes ranged from 3.6 cm to 10 cm. Presentation was usually with a growing, painless, soft tissue mass, occasionally with swelling or tenderness, but this depended on tumor size and
location. Without exception, the reported anatomical locations involved the left lower extremities, including thigh, leg and foot.” The malignant potential of ESCOS is relatively high, and little is known about the variables that may affect its prognosis (13).

The increasingly widespread use of preoperative fine needle aspiration cytology (FNAC) of bone lesions necessitates the recognition of even rare primary osseous neoplasms. In Bishops review of 5 cases of SCOS, common cytomorphologic features observed on FNAC included relatively small to intermediate sized cells, high nuclear/cytoplasmic ratios, round nuclei, minimal anisonucleosis, hyperchromasia, finely granular nuclear chromatin, fine cytoplasmic vacuoles, and only rare osteoid. All cases displayed numerous mitoses and abundant karyorrhectic nuclei reflecting high cell turnover and rapid tumor growth. Frank cellular necrosis was not observed. The typical cytomorphic features of osteosarcoma that were not observed in SCOS included macronucleoli, prominent spindled morphologic features, plasmacytoid morphologic features, cellular necrosis, and relatively abundant osteoid (14). Histologically, SCOS shows sheets of uniform, round nuclei and minimal cytoplasm with at least focal presence of lace-like mineralized osteoid (6, 14, 15). Although classified as an osteosarcoma based on its production of osteoid, the histomorphologic features of SCOS differ from those of conventional osteosarcoma- the cells of SCOS are smaller with less cytoplasm and more uniform than conventional osteosarcoma (14). The presence of osteoid is required for diagnosis of SCOS; but it is often focal, making the diagnosis often extremely difficult (11, 12, 16). Immunohistochemically, the tumor shows CD99 and neuron specific enolase positivity and is negative for S100 protein, smooth muscle actin, chromogranin, Ki-67, leukocyte common antigen, epithelial membrane antigen, CD30 and desmin (6, 14, 15).

The differential diagnosis of SCOS includes other small round blue cell tumors- including ES/PNET, non-Hodgkin lymphoma, mesenchymal chondrosarcoma, desmoplastic small round cell carcinoma, and neuroblastoma (11, 12, 17).

The most difficult differential diagnosis is between SCOS and ES/PNET as both are made up of small round cells (10). However, immunohistochemistry is not reliable for distinguishing SCOS from ES/PNET (13). Indeed, the histologic appearance of ES/PNET—sheets of monotonous, small round cells with minimal cytoplasm— can be identical to that of SCOS. The presence of convincing osteoid or bone is a key component for diagnosing SCOS and represents a unique feature for differentiation from ES/PNET but, in the absence of mineralization, true osteoid of SCOS can be very difficult to differentiate from collagen or fibrin that can be seen in ES/PNET (13, 17). ES/PNET is composed by more uniform cells and nuclei and lacks osteoid formation. The diagnosis of ES/PNET is supported by presence of Homer Wright rosettes, pseudorosettes, and CD99 positivity; however, it is important to note that CD99 positive staining is not always helpful in distinguishing the two (10, 12, 14, 15). Although Righi et al found that CD99 expression was consistently negative in their cases, findings from Bishop, Machado, and Kilpatrick demonstrated that CD99 could be positive in some SCOS patients and thus should not be used to distinguish SCOS from ES/PNET (18, 14, 19, 20). In addition, if molecular testing can be performed, the t(11;22) (q24;q12) translocation is diagnostic for ES/PNET. However, in the absence of osteoid, it may not be possible to definitively differentiate SCOS and ES/PNET in limited material obtained by FNAC (14).

Malignant lymphoma generally shows larger nuclei than SCOS with vesicular chromatin, irregular nuclear membranes and prominent nucleoli. Moreover, lymphomas are common leukocyte antigen positive (LCA) and lack osteoid; SCOS is negative for LCA.

Mesenchymal chondrosarcoma (MC) has areas of small round blue cell morphologic features that may arise from either bone or soft tissue (11, 12). Histologically, MCs are composed of a mixture of immature cartilage and small round or spindled cells; the small round blue cell component mimics other round cell sarcomas, such as Ewing’s sarcoma, and frequently contains a prominent “hemangiopericytoma-like” vascular proliferation (21, 22). The small cell component stains positively for SOX9 and negatively for FLI-1, which may help distinguish the tumor from an Ewing’s sarcoma (21). However, if these features are not present on the smears owing to sampling, mesenchymal chondrosarcoma can be very difficult to differentiate from SCOS (14).

Myositis ossificans is a benign extra osseous bone forming lesion located in muscles of extremities in 80% of cases often following local trauma (15). It also presents as painful, enlarging lesion but has characteristic radiological picture of circumferential calcification with a lucent center and a radiological cleft that separate lesion from cortex of adjacent bone along with typical histological zonal organization in form of peripheral well organized mature lamellar bone, intermediate osteoid region and central immature non osteoid cellular focus (23).

Desmoplastic small round cell tumor consists of small round cells of primitive appearance with vimentin, synaptophysin, CD99 (MIC2 protein), and FLI-1 positivity and detection of the reciprocal chromosomal translocation, t(11;22)(p13;q12), which is uniquely associated with this tumor (15). Additionally, the most common symptoms are abdominal pain and weight loss (24). Constipation due to mass effect caused by the tumor and bowel obstruction have also been reported. Due to a significant burden of peritoneal disease, some patients will present with an abdominal mass alone, but the most common presentation is abdominal distension from ascites (25).

Neuroblastoma metastasis mimics the histological features of SCOS as both possess small blue cell morphology and affect young patients, but the presence of Homer Wright rosettes or pseudorosettes supports a diagnosis of neuroblastoma over SCOS. Neuroblastomas are immunoreactive for synaptophysin and chromogranin and are virtually never immunoreactive for CD99 (14). Also, Because of its neuroendocrine properties, neuroblastoma has the potential to secrete catecholamines, which results in early-onset hypertension and tachycardia. Patients may also experience paraneoplastic syndromes. Examples include intractable diarrhea with electrolyte disturbances due to release of vasoactive intestinal peptide (VIP), encephalomyelitis, or sensory neuropathy (26).
The most important reason to be able to recognize SCOS is the effect of this diagnosis on guiding appropriate therapy (14). The prevailing therapeutic approach to ESCOS is a radical en bloc excision with negative margins, which may even include total amputation. Although surgical excision is followed by postoperative chemotherapy to help control metastasis, such therapeutic efficacies are not well established because of the rarity of cases of ESCOS (13). Although the treatment of SCOS has not been optimized (owing to its rarity), SCOS is most often treated like conventional osteosarcoma, with neoadjuvant chemotherapy followed by surgical resection (11, 17).

It is our hope that this report raises awareness of including this uncommon tumor in the differential diagnosis of soft tissue masses presented in the pelvic area. We report this case to show how imperative a correct diagnosis is for this uncommon tumor in order to guide appropriate treatment options. Our case also shows that cytology fine needle aspiration sampling alone including cellblock preparation can solely make definitive diagnosis of extraskeletal osteosarcoma even with the rare small cell variant.

ACKNOWLEDGEMENT

Special thanks to Samer Berry, Ekaterini Kostakos, and Sam Amiri, MD candidates, American University of the Caribbean for their assistance in reviewing the final manuscript.

REFERENCES