Cellular variant of extraskeletal myxoid chondrosarcoma with Ewing's sarcoma-like areas: a diagnostic pitfall in core needle biopsy

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Extraskeletal myxoid chondrosarcoma (EMC) is a rare mesenchymal soft tissue tumour that poses diagnostic difficulty as it lacks a characteristic immunophenotype, in addition to its wide morphological spectrum. Microscopically, EMC shows strands and cords of relatively small cells with acidophilic cytoplasm that are occasionally vacuolated. Small cells with scant cytoplasm may comprise some EMC. We describe a rare and challenging case of EMC, which shows an unusual morphology with small blue cells, raising the possibility of PNET/Ewing's sarcoma. The small cellular variant of EMC usually poses diagnostic difficulty, particularly during its evaluation in a core needle biopsy. Consideration of EMC, small cell variant, in evaluation of a blue cell tumour, may avoid a potential diagnostic pitfall. Proper diagnosis of EMC and its differentiation from PNET/Ewing's sarcoma is crucial due to a difference in management protocols and prognostic outcome.

Introduction

Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft tissue tumour that poses diagnostic difficulty as it lacks a characteristic immunophenotype, in addition to its wide morphological spectrum. We describe a rare case of EMC, which shows an unusual morphology with small blue cells, raising the possibility of PNET/Ewing's sarcoma. Awareness of the small cellular variant of EMC, particularly during evaluation of a core needle biopsy, may avoid a potential diagnostic pitfall. Proper diagnosis of EMC and its differentiation from PNET/Ewing's sarcoma is crucial due to a difference in management protocols and prognostic outcome.

Case report

A fifty-four year old female presented with a non-painful right thigh lump of a chronic onset and progressive course. Physical examination revealed a hard, non-mobile and non-tender mass situated in the anterior compartment of the thigh with no evidence of skin ulceration, limitation of movement, regional lymphadenopathy, or organomegaly. There was no previous radiology for comparison. CT scan with contrast of the abdomen and pelvis was performed and showed a large soft tissue mass in the right proximal thigh which was located within the tensor fascia a lot of muscle (Fig. 1). It showed evidence of central necrosis. The lymph nodes as well as the thoracic and abdominal organs were uninvolved. There was a big soft tissue mass at the anterolateral aspect of the upper femur. MRI revealed this mass to be lobulated with a spindle-shaped appearance (Fig. 2). Core biopsy was performed which showed undifferentiated high-grade sarcoma with features of a blue cell tumour (Fig. 3 and 4). A wide immunohistochemical panel including S100, HMB45, Melan A, Cam5.2, AE1/AE3, LCA, desmin, actin, and myogenin was negative in the tumour cells. EMA, CD56, CD99 (Fig. 5), and NSE
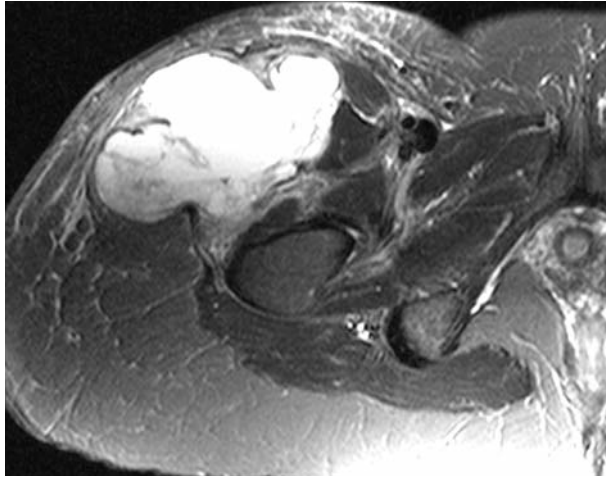
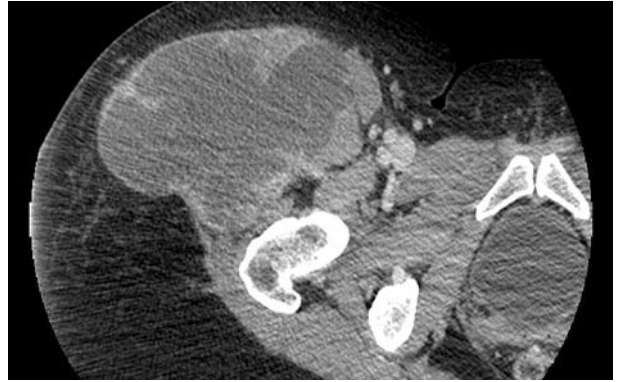**Fig. 1.** Computer tomography scan with contrast showing the radiological characteristics of the mass

Fig. 2. Magnetic resonanse imaging showing the radiological characteristics of the mass
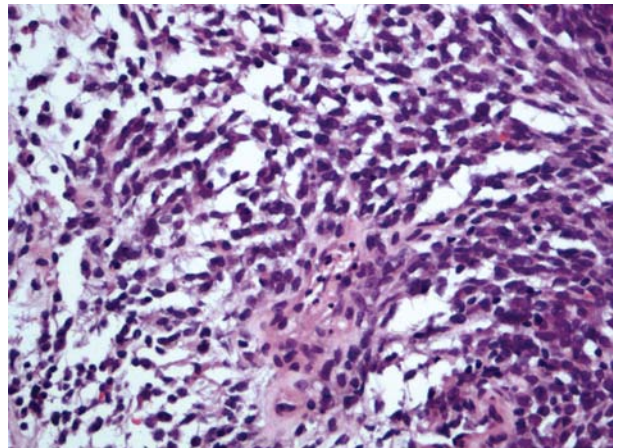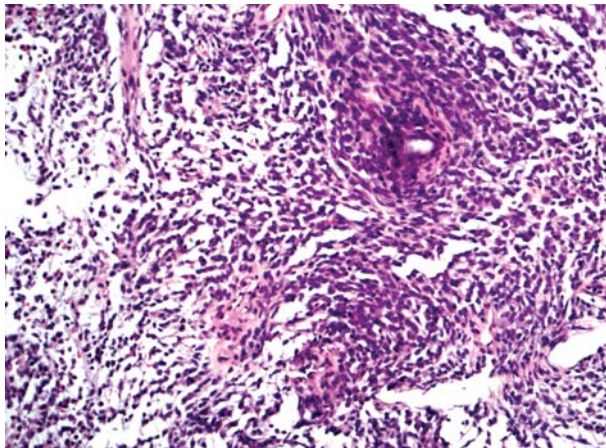

Fig. 3 and 4. Extraskeletal myxoid chondrosarcoma as presented in core biopsy as undifferentiated high-grade sarcoma with features of a blue cell tumour (HE, magnification 100× and 200×)

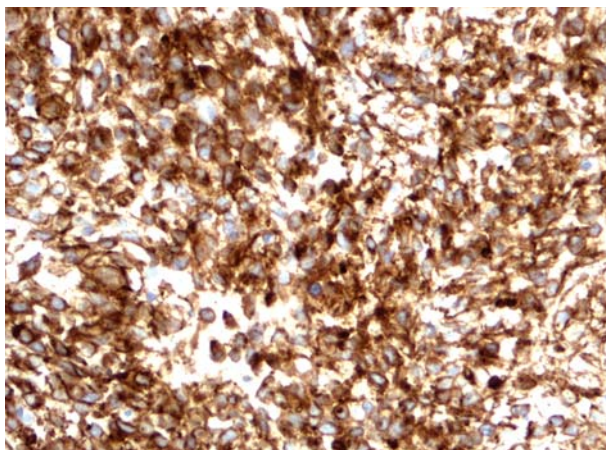**Fig. 5.** Extraskeletal chondrosarcoma showing focal expression of CD99 in the tumour cells (CD99, magnification 200×)
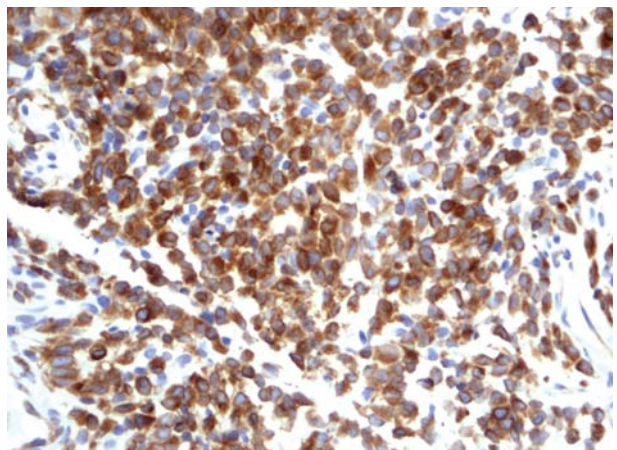
Fig. 6. Extraskeletal chondrosarcoma showing diffuse expression of BCL-2 in the tumour cells (BCL-2, magnification 200×)

showed focal positive expression in the tumour cells. Vimentin and BCL2 (Fig. 6) were diffusely positive in the tumour cells. Based on the morphological and immunohistochemical features, the case was diagnosed as high-grade sarcoma, comprising small undifferentiated cells. The differential diagnosis included synovial sarcoma, extraskeletal myxoid chondrosarcoma, and PNET/Ewing's sarcoma. The

latter diagnosis was the most favoured. The patient received preoperative 50 Gy radiation followed by wide local surgical excision of the tumour. Gross examination showed an oriented compartmental excision mass that measured 11 cm × 8.5 cm × 7.5 cm, with solid and cystic areas on cut sections. The closest margin was deep, with the mass being at 0.2 cm. Microscopic examination showed islands of tumour set within a fibrous background. In part, the tumour had the appearance of a small epithelioid malignancy with cytoplasmic clearance showing Ewing's sarcoma-like appearance (Fig. 4). Focal areas of cells arranged in linear cords in a myxoid stroma were noted. Occasional pleomorphic cells were seen. The tumour was widely necrotic with viable cells representing 1-5% of the tumour. The case was diagnosed as poorly differentiated/cellular variant of extraskeletal myxoid chondrosarcoma. Molecular testing excluded Ewing's sarcoma.

Discussion

Extraskeletal myxoid chondrosarcoma (EMC) was first recognized and described in a series of chondrosarcomas occurring in extraskeletal soft tissues by Stout and Verner in 1953 [1]. Extraskeletal myxoid chondrosarcoma is a rare and unique neoplasm, accounting for less than 3% of soft tissue sarcomas [2]. Myxoid chondrosarcoma is primarily a soft tissue tumour, with very occasional reports of sole skeletal involvement [2]. Extraskeletal myxoid chondrosarcoma most commonly develops in deep parts of the proximal extremities and limb girdles in middle-aged adults [4-6] and it tends to show a predilection for male patients [5, 6]. According to findings reported by the largest series described by six independent groups, the 254 recorded patients were composed of 154 male (61%) and 100 female patients (39%) with ages ranging from 6 to 89 years and a peak incidence during the fifth and sixth decades (48%) of life [7, 8-12].

The majority of cases of EMC present as a large mass, with reported size ranging from 6 to 13 cm [8-12].

Usually it has a multilobular or nodular configuration with a relatively well-defined margin and an incomplete fibrous capsule [8-12]. Its cut surface is grey to tan-brown and shows a gelatinous appearance, often accompanied by intralesional haemorrhage. On scanning magnification, the tumour is characterized by multilobular structures divided by fibrous septa of variable thickness, which is a consistent morphological configuration of EMC. Each lobule is typically composed of a proliferation of short spindle or oval cells arranged in clusters or short anastomosing cords or strands, often displaying a lacelike appearance and embedded in an abundant myxoid matrix. The tumour cells classically have a modest amount of deeply eosinophilic or vacuolated cytoplasm and uniform ovoid nuclei [8-12]. However, EMC tends to show several morphological patterns, its morphological spectrum is wide, and many times the differential diagnosis based on histology alone is problematic [4]. In some cases, the cells show rhabdoid, epithelioid and, on very rare occasions, small cell differentiation. The presence of the latter may raise the differential diagnosis of Ewing's sarcoma, which may pose a potential diagnostic pitfall particularly in core biopsies, as in our case. It has been noted that a subset of tumours have hypercellular solid areas with minimal or no myxoid matrix (a cellular–solid variant) [13, 14]. In addition to the low-grade, bland-looking characteristics noted in most cases, occasional cases may show high-grade features and are made up of larger and more atypical or pleomorphic cells displaying an epithelioid or rhabdoid or spindle cell appearance together with high mitotic activity and necrosis. Most such tumours contain areas of conventional EMC at least focally, especially with adequate sampling. In the current case the low-grade component was not appreciated in the core biopsy, but it was identified in the resected tumour.

As with all sarcomas, the most diagnostically consistent marker is vimentin. Expression of other immunohistochemical markers is limited. An almost consistent absence of cytokeratin positivity, with immunoreactivity for S-100 protein in some cases and in only a small percentage of cases positive expression for epithelial membrane antigen, muscle actins, and desmin were described. Frequent positivity for neural or neuroendocrine markers such as neuron-specific enolase, synaptophysin, and PGP9.5 and even chromogranin in a minor fraction of the tumours was reported. In our case, neuroendocrine markers were expressed; however, such expression was not of diagnostic utility as PNET shows similar immunophenotype.

Prognosis

Extraskeletal myxoid chondrosarcoma has a frequently prolonged course despite a high incidence of local recurrences and metastases [4]. Some authors have suggested that the cellular or high-grade EMC, such as the current case, is likely to have a worse prognosis than conventional EMC, although its prognostic significance has not yet been established [15]. Meis-Kindblom *et al*. emphasized that the prognosis of patients with EMC was not as good as originally assumed; they described an estimated survival rate of 70% at 10 years and high rates of local recurrence (48%) and metastasis (46%) [8].

Genetics

Recent cytogenetic and molecular genetic studies of EMC have specific fusion (or chimeric) genes involving three pathogenetically relevant chromosome translocations. The t(9;22)(q22;q12) translocation is found in 75% of cases. It results in a fusion of the 5' part of the EWS gene to the TEC gene [16-19].

The origin of EMC is controversial and this sarcoma is provisionally classified as a tumour of uncertain differentiation in the revised version of the World Health Organization classification of tumours of soft tissue and bone [20]. Although it is named as a chondrosarcoma, its histogenesis is uncertain and pilling evidence is against it being of cartilaginous origin. The immunophenotype of EMC may suggest a neural-neuroendocrine differentiation at least in a subset of EMC and has posed further questions regarding its histogenesis [21, 22].

The chondroblastic nature of EMC was originally suggested based on its histochemical and ultrastructural findings including abundant intracytoplasmic glycogen and extracellular, hyaluronidase-resistant sulfated mucopolysaccharides [7]. Chondroitin-4/-6 sulfate and keratan sulfate, which are major components of cartilaginous matrix, have been demonstrated to be present in the myxoid stroma of EMC using histochemical approaches with or without a critical electrolyte concentration technique [7, 23-25]. The divergent or bimodal differentiation in EMC may imply a neuroectodermal derivation of the tumour, because pluripotential precursor cells of the neural crest can give rise to many derivatives, including neurons and cranial skeletal components such as cartilage, bone and dermis [26].

As EMC has no characteristic immunophenotype and a wide morphological spectrum, the presence of a wide variety of differential diagnoses is not surprising. In the current case, the presence of the undifferentiated Ewing's sarcoma-like areas raised the possibility of PNET/Ewing's sarcoma. In this situation, only molecular studies are conclusive. Nevertheless, considering EMC during evaluation of a core needle biopsy as small cell sarcoma may avoid a potential diagnostic pitfall. Awareness of the small cellular variant of EMC, particularly during evaluation of a core needle biopsy, may avoid a potential diagnostic pitfall. Proper diagnosis of EMC and its differentiation from PNET/Ewing's sarcoma is crucial due to a difference in management protocols and prognostic outcome.

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