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Extra-axial Skeletal Poorly Differentiated Chordoma. A Case Report.

Sir

Chordoma is a rare, malignant bone tumour showing notochordal differentiation and expressing brachyury on immunohistochemistry, occurring along the spinal axis, from the skull base to coccyx. Rare extra-axial cases have been described in literature[1].

The current 2013 WHO Classification subdivides chordomas into conventional, chondroid and dedifferentiated[2]. The diagnosis can generally be made on the classical histological features, namely the presence of epithelioid cells with abundant clear cytoplasm, arranged in cords and nests within a myxoid stroma and expression of cytokeratins in conjunction with brachyury expression. Less common features are also reported and in these, brachyury expression is particularly helpful[3]. Recently, a new subtype has emerged, mostly located at the skull base and upper spine, characterised by higher grade cytological features compared to the conventional subtype. However, its distinguishing criterion is immunoreactivity for brachyury with loss of SMARCB1/INI-1 expression[4]. This new subtype has been named poorly differentiated chordoma and it has a worse prognosis than for conventional chordoma[5].

Herein we present a case of a 67 year-old woman who experienced abrupt onset of left knee pain. Radiographs showed an area of bone destruction in the posteromedial aspect of the distal femur. A multilobular, heterogeneous lesion was seen on MRI, destroying the cortex and forming an extra-osseous mass (Fig.1). The biopsy showed a high grade tumour composed of epithelioid cells diffusely positive for MNF116 and CD10. Wide panel of antibodies, including

CK7, CK20, TTF-1, ER, S100, HMB45, CD45, ERG, CD31, CD34, desmin and TFE-3 were all negative. A diagnosis of metastatic carcinoma, possibly of renal origin, was favoured. No primary site was identified on staging and the tumour was considered a cancer of unknown primary (CUP).

The patient received a distal femoral replacement. Grossly, the tumour (45x25mm) involved the meta-diaphyseal region with cortical destruction and soft tissue extension. Histologically, the tumour was composed of relatively uniform epithelioid cells with amphophilic cytoplasm, arranged in solid sheets and lobules with a prominent lymphoid infiltrate at the periphery. Myxoid stroma was not a feature. Mitoses were frequent (11/10 HPF) and focal tumour necrosis was seen. Only after thorough study of the tumour, one could appreciated that part of the intramedullary component showed cells with clear/vacuolated cytoplasm and distinct cytoplasmic borders, whilst the rest showed features of a poorly differentiated tumour. In view of the diffuse cytokeratin expression with SMARCB-1/INI-1 (BD Bioscience, mouse monoclonal antibody, 1:400) loss, brachyury (Abcam, rabbit monoclonal antibody, 1:2000) was requested, that lastly defined the phenotype of the cells (Fig.2). The patient is alive and currently on surveillance after adjuvant radiotherapy, six months after surgery.

To the best of our knowledge, this is the first report of a poorly differentiated chordoma occurring in the extra-axial skeleton. Furthermore, the age of the patient is unusual for this subtype, as most occur in children and young adults[5]. The main entity that must be excluded is metastatic carcinoma which may share similar morphological and immunohistochemical features, including loss of INI-1 expression. However, brachyury positivity that is highly specific for chordoma confirms the former. Furthermore, a dedicated whole spine and skull MRI excluded metastatic chordoma. Other neoplasms included in the differential diagnosis are epithelioid sarcoma and myoepithelial carcinoma, either primary or metastatic. Epithelioid sarcoma is a rare high grade soft tissue tumour showing epithelial differentiation with histological features and immunoprofile that are not significantly dissimilar from a poorly differentiated chordoma. Both express cytokeratins and by definition are SMARCB1/INI-1-deficient tumours. Once again, the discriminating antibody is brachyury. Primary myoepithelial carcinoma of bone is rare but well documented[6]. Similar to their more common soft tissue counterpart, they are defined by S100 expression along with variable positivity for epithelial-lineage markers, such as cytokeratins, EMA and p63. In addition, SMARCB1/INI-1 expression may be lost. It had been long debated whether myoepithelial tumours, specifically parachordoma, represented an extra-axial localisation

of chordoma, until it was demonstrated that they are separate entities, as only chordomas express brachyury[1]. Another distinguishing feature of chordoma and myoepithelial tumours is that up to 70% of the latter harbours an *EWSR1* gene rearrangement, which is not seen in chordoma. Our case showed no abnormality of the *EWSR1* locus. Of note, a complex *EWSR1* gene pattern has been reported in poorly differentiated chordoma, explained on the basis that the *EWSR1* locus lies close to the *SMARCB1* locus on chromosome 22q and therefore co-deletion of *EWSR1* gene with *SMARCB1* represents a potential pitfall when interpreting FISH in such tumours[7]. In summary, we have described the first case of extra-axial skeletal poorly differentiated chordoma which was misdiagnosed as metastatic CUP on biopsy. Although this is an exceptional event, extra-axial notochordal tumours occur and they may be difficult to diagnose especially when presenting with poorly differentiated features. The diagnosis can be easily confirmed, and metastatic CUP excluded, if brachyury immunohistochemistry is performed.

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Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

P Balogh, P O`Donnell, D Lindsay, A Fernanda, AM Flanagan and R Tirabosco wrote and edited the manuscript.

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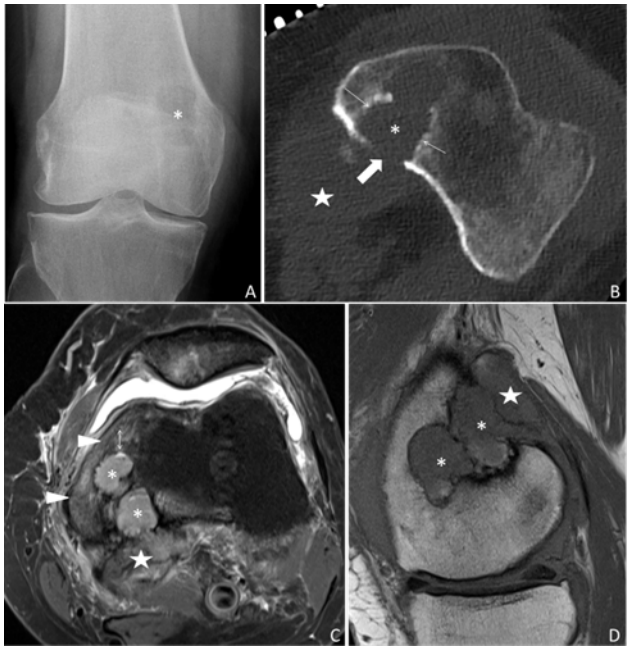
Figure legends

Figure 1. (A) AP radiograph. Lucency projected over medial femoral condyle (*). (B) CT. Lobular destruction of distal femur (*), with marginal sclerosis (arrows). The posterior cortex is destroyed (block arrow) and there is an extra-osseous mass (star). (C) Axial proton-density fat-saturated MRI. The tumour (*) shows intermediate and oedema-like signal (arrowheads). Fluid-fluid level is seen anteriorly (double arrow). There is also a posterior extra-osseous mass (star). (D) Sagittal T1 MRI. Lobular tumour (*) appears mildly hyperintense. It is marginated by a low signal rim. Posterior extra-osseous mass (star).

Figure 2. (A) Microphotograph showing a cellular tumour with lobular pattern (H&E, 4x). (B) The cells have vacuolated or clear cytoplasm. Mitoses are seen (H&E, 20x). (C) Immunohistochemistry for brachyury shows diffuse staining with (D) loss of SMARCB1/INI-1 that is retained in the inflammatory cells.



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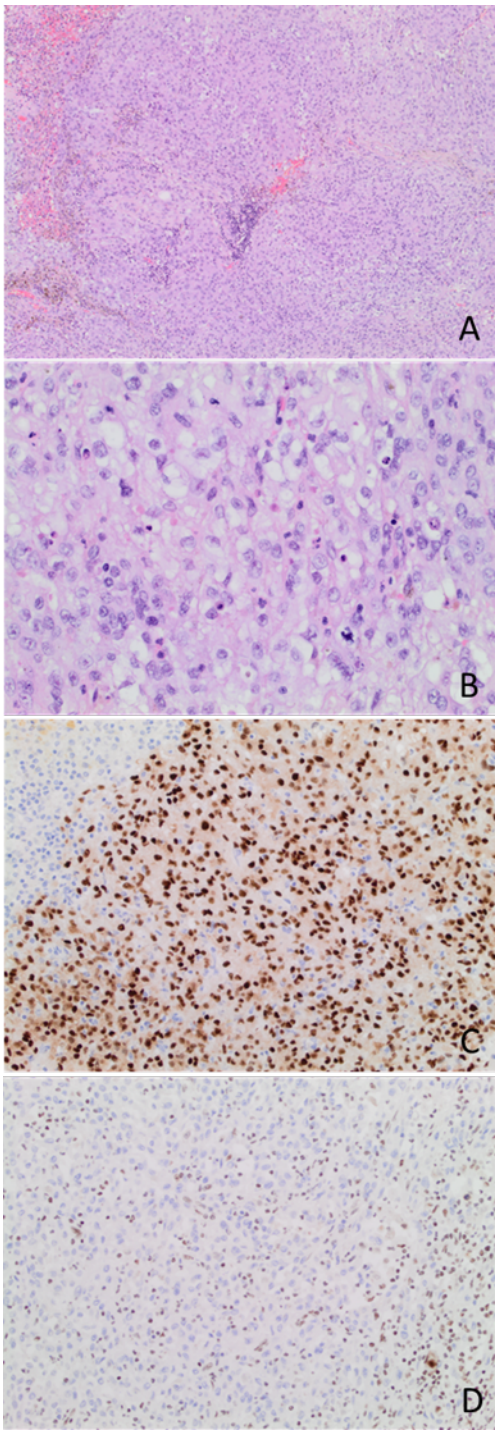

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