EWSR1-PATZ1 gene fusion.^{11,12} No *EWSR1* gene rearrangement could be demonstrated using FISH, whereby this differential diagnosis could also be excluded.

In conclusion, we present a case of an unusual small cell variant of a PDSS, which is a histological mimic of other 'small blue round cell tumours'. The 'unforeseen' positivity for desmin made this case even more challenging. The morphology and the immunohistochemical profile (membranous staining for CD99, diffuse nuclear TLE1 positivity and patchy expression of cytokeratin AE1/AE3 and EMA) raised awareness for the diagnosis of a PDSS in this case. Molecular testing, confirming *SS18* (*SYT*) gene rearrangement, remains the gold standard for the diagnosis of this rare morphological subtype of synovial sarcoma.

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1. Suurmeijer AJH, Ladanyi M, Nielsen TO. Synovial sarcoma. In: *WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: soft Tissue and Bone Tumours*. Lyon: IARC Press, 2020.
2. Hung YP, Fletcher CDM, Hornick JL. Evaluation of NKX2-2 expression in round cell sarcomas and other tumors with *EWSR1* rearrangement: imperfect specificity for Ewing sarcoma. *Mod Pathol* 2016; 29: 370–80.
3. Li WS, Liao IC, Wen MC, Lan HH, Yu SC, Huang HY. BCOR-CNB3-positive soft tissue sarcoma with round-cell and spindle-cell histology: a series of four cases highlighting the pitfall of mimicking poorly differentiated synovial sarcoma. *Histopathology* 2016; 69: 792–801.
4. Kao YC, Owosho AA, Sung YS, et al. BCOR-CCNB3-fusion positive sarcomas: a clinicopathologic and molecular analysis of 36 cases with comparison to morphologic spectrum and clinical behavior of other round cell sarcomas. *Am J Surg Pathol* 2018; 42: 604–15.
5. Antonescu CR, Owosho AA, Zhang L, et al. Sarcomas with CIC-rearrangements are a distinct pathologic entity with aggressive outcome: a clinicopathologic and molecular study of 115 cases. *Am J Surg Pathol* 2017; 41: 941–9.
6. Hung YP, Fletcher CD, Hornick JL. Evaluation of ET4 and WT1 expression in CIC-rearranged sarcomas and histologic mimics. *Mod Pathol* 2016; 29: 1324–34.
7. Alholle A, Karanian M, Brini AT, et al. Genetic analyses of undifferentiated small round cell sarcoma identifies a novel sarcoma subtype with a recurrent CRTC1-SS18 gene fusion. *J Pathol* 2018; 245: 186–96.
8. Antonescu CR, Agaram NP, Sung YS, Zhang L, Dickson BC. Undifferentiated round cell sarcomas with novel SS18-POU5F1 fusions. *Genes Chromosomes Cancer* 2020; 59: 620–6.
9. Pelmus M, Guillou L, Hostein I, Sierankowski G, Lussan C, Coindre JM. Monophasic fibrous and poorly differentiated synovial sarcoma: immunohistochemical reassessment of 60 t(X;18) (*SYT*-*SSX*)-positive cases. *Am J Surg Pathol* 2002; 26: 1434–40.
10. Changchien YC, Katalin U, Filingier J, et al. Case report: a challenging case of metastatic intra-abdominal synovial sarcoma with unusual immunophenotype and its differential diagnosis. *Case Rep Pathol* 2012; 2012: 78683.

11. Chougule A, Taylor M, Nardi V, et al. Spindle and round cell sarcoma with *EWSR1-PATZ1* gene fusion: a sarcoma with polyphenotypic differentiation. *Am J Surg Pathol* 2019; 43: 220–8.
12. Bridge JA, Sumegi J, Druta M, et al. Clinical, pathological and genomic features of *EWSR1-PATZ1* fusion sarcoma. *Mod Pathol* 2019; 32: 1593–604.

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Malignant transformation of liposclerosing myxofibrous tumour

Sir,

Liposclerosing myxofibrous tumour (LSMFT) is a benign fibro-osseous bone lesion that was first described by Ragsdale and Sweet in 1986.¹ LSMFT is a comparatively rare bone lesion, and it is thought to be related to fibrous dysplasia (FD) because of similarities in their histological and radiographic features. A recent molecular study provided additional evidence for the relationship between LSMFT and FD: an activating point mutation in the alpha subunit of a G protein (GNAS) was identified in some LSMFT samples, and the same mutation is present in nearly all cases of polyostotic and monostotic FD.^{2–5} Only a few cases of spontaneous 'malignant transformation' (MT) of LSMFT have been reported.^{1,2,6,7} To the best of our knowledge, this is the first reported case of MT in LSMFT in association with presumed polyostotic FD.

This study was approved by the institutional review board (IRB) of our hospital (No. UC18SESI0111). Informed consent was obtained from the patient for publication of this case.

A 75-year-old female patient with left knee joint pain was referred to our hospital. Plain radiographs of both knees revealed osteoarthritis of the left knee joint (Fig. 1A). In addition, multiple osteolytic and sclerotic lesions were incidentally found in the right proximal tibia and distal femur (Fig. 1A,B, arrows). These lesions demonstrated sclerotic rims, internal septations, and calcifications. Plain radiograph of the pelvis showed lobular lesions with ground glass opacity in the bilateral femur necks to the proximal metaphysis (Fig. 1C, arrow). An osteolytic, sclerotic lesion was also detected in the skull occiput. Magnetic resonance images of the right proximal femur diaphysis and metaphysis revealed a 10×3 cm lesion without evidence of cortical breakage or expansion. This lesion showed heterogeneously low signal intensity on T1 weighted image (WI) and heterogeneously high signal on T2WI. Another lesion in the left femur neck showed high signal intensity on T2WI, indicative of avascular necrosis (AVN). Based on these imaging findings, the radiological diagnoses of the patient were the following: (1) presumed polyostotic FD involving right distal femur, right proximal tibia, and skull; (2) LSMFT of the intertrochanteric area of right femur; (3) osteoarthritis of the left knee joint; and (4) AVN of the left femur head. A total knee replacement arthroplasty was performed for the left knee joint osteoarthritis. Radiographic follow-up was recommended for the other lesions (presumed polyostotic FD, AVN, and LSMFT). After 2.3 years, the follow-up radiograph of the left femur neck lesion showed progression (Fig. 1D, black arrow). The patient

Fig. 1 (A) Plain radiograph of both knees reveals osteoarthritis of the left knee joint. Multiple osteolytic and sclerotic lesions were found in the right proximal tibia and distal femur (arrows). (B) Plain radiograph reveals multifocal osteolytic and sclerotic lesions in the right proximal tibia (arrows). (C) Plain radiograph of the pelvis shows a lobular lesion with ground glass opacity in the right femur neck to the proximal metaphysis (arrow). The image shows sclerotic rims, internal septations, and calcifications. (D) After 2.3 years, a follow-up radiograph shows progression of the left femur neck lesion (black arrow).

complained of aggravating pain in the right hip joint. Incisional biopsy was planned and performed to exclude cystic degeneration, secondary aneurysmal bone cyst (ABC) formation, or MT. The curettage specimen from the lesion consisted of many small fragments of tissue measuring up to 0.7 cm in diameter. Microscopic examination showed a few woven bone trabeculae with cement lines mimicking pagetoid bone, fibrous tissue, areas of lipomatous change, and pseudopagetoid bone spicules. Histopathologically, the curettage specimen was diagnosed as LSMFT.

On post-operative day 24, the right femur neck fractured and bipolar hemiarthroplasty with cementation was performed. Grossly, the resected femur head showed various cut surface appearances (Fig. 2A). Under low magnification, the intertrochanteric portion of the femur suggested various histological features (Fig. 2B): areas of xanthomatous and lipomatous change (Fig. 2C) and an area reminiscent of FD (Fig. 2D) were demonstrated. Furthermore, a hypercellular area composed of fascicles of mildly pleomorphic spindle cells is noted (Fig. 2E). This area displays a storiform cellular arrangement and destructive growth pattern. Malignant osteoids were not detected in the area. These findings represented characteristic fibrosarcomatous change and the area could be differentiated from an area of benign LSMFT (Fig. 2F). Immunohistochemical stains showed that both stromal cells of the benign area and the malignant spindle cells were positive for actin and negative for desmin and S-100. Ki-67 index was 7% in the malignant spindle cells of the

Fig. 2 (A) Gross photograph of the resected right femur head shows a variable cut surface appearance. (B) Under low magnification, the intertrochanteric portion of the femur (area labelled 3 in part A) shows the following various histological features: (C) areas of xanthomatous and lipomatous change; (D) an area reminiscent of fibrous dysplasia; (E) a hypercellular area composed of fascicles of mildly pleomorphic spindle cells, corresponding to fibrosarcomatous change; (F) note the transition from the benign liposclerosing myxofibrous tumour (LSMFT) area to the malignant transformation (MT).

fibrosarcomatous area. Based on these histopathological and immunohistochemical stain findings, a pathological diagnosis of 'MT of LSMFT into high grade sarcoma' was established. Unfortunately, 5 months after surgery the patient's pain worsened, destruction at the greater trochanter and shaft of the femur progressed, and she died of multiple distant metastases.

LSMFT is a benign fibro-osseous bone lesion that was first described by Ragsdale and Sweet in 1986.¹ It is a rare lesion that is thought to be related to FD because of similarities in their histological and radiographic features. Histopathologically, this lesion is known to exhibit myxofibrous tissue, FD-like features, ischaemic-pattern ossification, lipomatous areas, and frequent cystic change.⁸ According to the report by Kransdorf *et al.* [29 patients from the Armed Forces Institute of Pathology (AFIP) 1999], pain was reported by 48% of patients with LSMFT.⁶ This occurrence was incidental in most cases (42%), but a pathological fracture was discovered in 10% of patients.⁶ LSMFT occurs most commonly in the fourth decade of life (range 15–80 years) and shows a strong predilection for the proximal femur. More than 90% of cases are detected in the intertrochanteric area. Non-hip sites include femur shaft, tibia, humerus, and ribs. Recently, Regado *et al.* studied the radiological, clinical and pathological features of nine cases of LSMFT.⁷ In their cases, the femur was the most affected bone (77.7%), with six cases (66.6%) in the proximal metaphysis and one case (11.1%) in the distal metaphysis. One case (11.1%) of LSMFT was reported in distal tibia and the other (11.1%) in the iliac bone. Radiologically, LSMFT presents as a well-defined, geographic lytic lesion with sclerotic margins and mineralised matrix, and it shows an indolent growth pattern.⁶

In terms of genetic pathogenesis, Matsuba *et al.* reported activating *GNAS* mutations at the Arg201 codon in two cases of LSMFT.⁵ They concluded that at least some cases of LSMFT are closely related to FD. Corsi *et al.* showed two confusing cases: one case with no *GNAS* mutation in an FD-like lesion (LSMFT) and the other case showing *GNAS* mutation in a histologically typical LSMFT.³ Unfortunately, we were unable to perform a molecular study in the present case due to degradation of DNA in the specimen during tissue decalcification.

Controversy still remains over the nature of LSMFT as a disease entity. Some authors argue that LSMFT is 'a genuine clinicopathologic entity',^{1,6,9} whereas others argue that it is 'not a distinct entity'.^{4,10} Dattilo *et al.* proposed discontinuation of the use of the term LSMFT.¹⁰ As Deel and Hassell pointed out in a review article, even if LSMFT is not a unique disease entity and only represents a reaction pattern imposed on a variety of precursor lesions, such as FD, in a fairly specific location, this lesion poses a distinct diagnostic challenge morphologically.⁸ We agree that LSMFT should be included in the differential diagnosis of fibro-osseous lesions, especially in specific locations, such as the femur neck. The proposed mechanisms of MT in LSMFT are as follows: (1) alterations in involution of a lipoma, (2) altered proliferative events in a lipogenic lesion, and (3) mechanical stress with associated ischaemic injury—a traumatised variant of FD.⁴

Some previous reports have stated that LSMFT shows a higher risk of MT (10–16%) than FD.^{1,2,6,7,11} It has been suggested that the increased MT of LSMFT than of FD is related to involutional and ischaemic changes from an area of

ischaemic ossification or progressive *in situ* atypism of altered lipomatous elements.¹¹ Reported entities of MT include osteosarcoma, undifferentiated pleomorphic sarcoma [UPS, previously called malignant fibrous histiocytoma (MFH)], malignant fibroxanthoma, and high-grade spindle cell tumour.^{1,6}

Campbell and Wodajo reported a unique case of two-step MT of LSMFT in which LSMFT evolved into a transitional lesion of a benign giant cell reactive lesion, followed later by transformation into a sarcomatous lesion with abundant giant cells.² Interestingly, the case demonstrated a wide discrepancy between the observed clinical behaviour and the benign histopathological appearance. Based on their findings, they recommend clinicians maintain a high level of suspicion for MT in patients with LSMFT whose lesions clinically behave aggressively. Furthermore, they especially recommended an increased level of suspicion for MT if a patient with a local recurrence reported pain out of proportion to clinical findings.²

The present case demonstrated two interesting points. First, this is the first reported case of MT in LSMFT in association with presumed polyostotic FD. The histological features of the present case were similar to those of previous malignancy cases arising in the underlying LSMFT. Second, both clinicians and pathologists should have an increased level of suspicion for MT, if a patient with a local recurrence reports pain out of proportion to clinical findings or progression of the lesion is suspected radiologically.

In conclusion, we report a case of MT with fibrosarcomatous features that arose from LSMFT associated with presumed polyostotic FD.

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1. Ragsdale BD. Polymorphic fibro-osseous lesions of bone: an almost site-specific diagnostic problem of the proximal femur. *Hum Pathol* 1993; 24: 505–12.
2. Campbell K, Wodajo F. Case report: two-step malignant transformation of a liposclerosing myxofibrous tumor of bone. *Clin Orthop Relat Res* 2008; 466: 2873–7.
3. Corsi A, De Maio F, Ippolito E, *et al.* Clinical vignette: monostotic fibrous dysplasia of the proximal femur and liposclerosing myxofibrous tumor: which one is which? *J Bone Mineral Res* 2006; 21: 1955–8.
4. Heim-Hall J, Williams R. Liposclerosing myxofibrous tumour: a traumatised variant of fibrous dysplasia? Report of four cases and review of the literature. *Histopathology* 2004; 45: 369–76.
5. Matsuba A, Ogoe A, Tokunaga K, *et al.* Activating Gs α mutation at the arg201 codon in liposclerosing myxofibrous tumor. *Hum Pathol* 2003; 34: 1204–9.

6. Kransdorf MJ, Murphey MD, Sweet DE. Liposclerosing myxofibrous tumor: a radiologic-pathologic-distinct fibro-osseous lesion of bone with a marked predilection for the intertrochanteric region of the femur. *Radiology* 1999; 212: 693–8.
7. Regado ER, Garcia PBL, Caruso AC, *et al.* Liposclerosing myxofibrous tumor: a series of 9 cases and review of the literature. *J Orthop* 2016; 13: 136–9.
8. Deel C, Hassell L. Liposclerosing myxofibrous tumor: a review. *Arch Pathol Lab Med* 2016; 140: 473–6.
9. Gilkey FW. Liposclerosing myxofibrous tumor of bone. *Hum Pathol* 1993; 24: 1264.
10. Dattilo J, McCarthy EF. Liposclerosing myxofibrous tumor (LSMFT), a study of 33 patients: should it be a distinct entity? *Iowa Orthop J* 2012; 32: 35.
11. Ragsdale BD, Sweet DE, Vinh TN. Radiology as gross pathology in evaluating chondroid lesions. *Hum Pathol* 1989; 20: 930–51.

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A NUT carcinoma lacking squamous differentiation and expressing TTF1

Sir,

NUT carcinoma (NC) is a rare highly aggressive malignancy refractory to most therapies, with a median overall survival of less than a year.¹ NC often shows keratinising foci and typically expresses high molecular weight cytokeratins, p63 and p40 (Δ Np63) by immunohistochemistry (IHC), and therefore is considered to be a poorly differentiated type of squamous cell carcinoma.²

Despite the near universal poor outcome, timely diagnosis of NC is important for appropriate clinical management and counselling. The presence of a fusion between the nuclear protein in testis (*NUT* or *NUTM1*) gene and bromodomain (BRD) and extra terminal domain protein family (BET) members *BRD4* or *BRD3* is considered pathognomonic, but in practice, expression of *NUTM1* protein by IHC is often regarded as diagnostic.² However, expression of *NUTM1* and/or *NUTM1* rearrangements can be present in tumours that are differential diagnoses for NC, including some germ cell tumours, lymphomas and sarcomas.³ Here we report an atypical TTF1/*NUTM1*-expressing malignancy that lacked evidence of squamous differentiation and required RNA sequencing in order to identify a *BRD4-NUTM1* fusion transcript to make a definitive diagnosis of NC.

A 22-year-old male, a non-smoker, presented with a one month history of dyspnoea and nausea. Imaging showed extensive mediastinal, nodal and bone disease. A piecemeal biopsy from the mediastinal mass and a transbronchial needle aspirate (TBNA) from subcarinal lymph nodes showed sheets of malignant cuboidal cells with indistinct cytoplasmic borders, pale eosinophilic vacuolated cytoplasm, large irregular nuclei, vesicular chromatin and large nucleoli. No keratin or inter-cellular bridges or glandular differentiation were identified. Malignant cells were also present in a pleural fluid specimen.

IHC (Fig. 1) on all three specimens showed weak cytoplasmic expression of CAM5.2 and strong diffuse nuclear expression of TTF1. PAX8, MYC, SOX2 and PRAME (a melanocytic marker) were also positive in tumour cells.

Tumour cells in the mediastinal biopsy showed unusual granular cytoplasmic membrane pattern of expression of pan-cytokeratin AE1/AE3. AE1/AE3 immunostains were negative in tumour cells in the TBNA and pleural fluid specimens. IHC for the squamous cell markers p63, p40 and cytokeratins CK5/6, CK1/5/10/14 (clone 34 β E12) were negative in all specimens, as were CK7, CK19, CK20, napsin-A, CD56, synaptophysin, S100, SOX10, vimentin, germ cell (SALL4, OCT3/4, KIT, PLAP, CD30) and lymphoid markers (CD45, CD3, CD5, CD19, CD20, BCL6, TdT).

IHC for *NUTM1* showed speckled nuclear staining in tumour nuclei (Fig. 1) and *NUTM1* (chromosome 15q14) breakapart fluorescent *in situ* hybridisation (FISH) showed split signals in tumour cells (not shown). RNA was extracted from formalin fixed, paraffin embedded (FFPE) tumour from the mediastinal biopsy. Whole transcriptome sequencing was performed with the Illumina NextSeq 550 platform (Illumina, USA). An in-frame RNA fusion transcript involving exon 14 of *BRD4* and exon 3 of *NUTM1* (Fig. 2A) was identified by two fusion calling programs (Arriba⁴ and Pizzly⁵) that are based on unrelated algorithms. Based on the clinical, histological and molecular findings, a diagnosis of NC was made despite the lack of squamous differentiation.

The transcriptome of the tumour was investigated further by comparing it to a transcriptome obtained from RNA sequencing FFPE tissue from a NC with a *BRD3-NUTM1* fusion. Although this fusion is present in only ~10% of NC, this tumour showed typical histology and protein expression by IHC for a NC, i.e., strong expression of p40 and high molecular weight cytokeratins, consistent with squamous differentiation. It did not express TTF1. Normalised RNA expression profiles from both NCs showed similar levels of *NUTM1* (Fig. 2). Of the known *BRD-NUTM1* transcriptional targets, *MYC*, *TP63* and *SOX2*^{6,7} high expression of *MYC* was seen in both NC, *TP63* was only highly expressed in the typical NC and *SOX2* in the *BRD4-NUTM1* NC (Fig. 2B). There were high RNA levels for multiple cytokeratins including *KRT4*, *KRT5*, *KRT7*, *KRT14*, *KRT17* and *KRT19* in the typical NC, but not in the *BRD4-NUTM1* NC. Cytokeratins with detectable RNA in the *BRD4-NUTM1* NC were *KRT8* and *KRT18*. RNAs that were highly expressed in the *BRD4-NUTM1* NC included *NKX2-1* (the gene for TTF1), *PRAME* and *PAX6*. *BCL6* RNA was highly expressed in the typical NC but not *BRD4-NUTM1* NC.

Overall, the transcriptome findings were consistent with our IHC findings. There were high RNA and protein levels for TTF1/*NKX2-1* in the *BRD4-NUTM1* NC, and low RNA and protein expression levels for p63, p40, BCL6 and most cytokeratins, with the exception of CK8 and CK18 (notably CAM5.2 and AE1/AE3 both detect CK8; expression of CK18 was unable to be confirmed due to exhaustion of tumour tissue). *PAX6*, but not *PAX8*, RNA was expressed at high levels in the *BRD4-NUTM1* NC. However, *PAX8* was readily detectable by IHC in the *BRD4-NUTM1* NC. *PAX6* IHC was not performed, and it is possible that cross reaction of the *PAX8* clone that we used (MRQ-50) with *PAX6* may explain the discordance between the RNA and IHC results, although this was not investigated further.

The diagnosis of NC is often relatively straightforward, as the clinical presentation, morphology and immunophenotype in most cases is typical.² *NUTM1* IHC shows a near 100%