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CASE REPORT

Mutational analysis of high-grade spindle cell sarcoma of the femur in Mazabraud's syndrome

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Abstract

Mazabraud's syndrome is a rare disorder characterised by the association of fibrous dysplasia with intramuscular myxomas. We present a 36-year-old woman with right anterior knee pain and a buttock mass. Imaging showed aggressive bone destruction within an area of fibrous dysplasia in the right femur and a mass with myxoid signal characteristics in the right adductor region. Biopsy of the femur revealed both fibrous dysplasia and a high-grade spindle cell sarcoma. Biopsy of the adductor mass confirmed a soft-tissue myxoma. Molecular genetic analysis revealed an identical R201H substitution in the *GNAS1* gene in the sarcoma, the myxoma, and also the conventional fibrous dysplasia.

Keywords Fibrous dysplasia · Mazabraud's syndrome · Myxoma · High-grade spindle cell sarcoma · *GNAS1* gene

Introduction

Mazabraud's syndrome is a rare disorder characterised by the association of single or (more frequently) multiple benign intramuscular myxomata and fibrous dysplasia (FD), the latter affecting a single (monostotic) or multiple (polyostotic) bones.

Malignancy can develop in bones affected by monostotic or polyostotic FD, with or without associated syndromes (McCune–Albright and Mazabraud's), but is very rare. We report the case of a high-grade sarcoma arising on a background of FD in the femur in a 36-year-old female with Mazabraud's syndrome, in which the same point mutation in the *GNAS1* gene was identified in all three sampled areas of disease.

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Case presentation

A 36-year-old woman with no significant past medical history presented to a sports injury clinic with knee pain of insidious onset. During the course of the consultation, she mentioned that she had noticed a painless mass in the right buttock approximately 2 weeks previously.

Clinical examination showed a firm right buttock swelling, inferior to the ischial tuberosity. She walked with a normal gait and hip and knee movements were normal and symmetrical. An initial ultrasound of the right buttock mass showed a heterogeneous, predominantly solid mass measuring approximately 4 cm in diameter, with what appeared to be a small cystic area.

Magnetic resonance imaging showed a well-defined mass in the right adductor region (Fig. 1) that returned uniformly high signal on T2 and fluid-sensitive sequences and low signal on T1-weighted images (Fig. 2). Given the solid nature of the mass on ultrasound, the appearances were felt to be those of a myxoid tumour and consistent with a myxoma in view of the adjacent oedema-like signal superiorly and inferiorly. The MRI study also revealed extensive abnormality of the marrow signal throughout the right femur (Figs. 2 and 3): there was well-defined marrow replacement by heterogeneous tissue that showed intermediate to hyperintense signal on short tau inversion recovery (STIR) and fat-saturated fluid-sensitive sequences, was isointense to muscle on T1 weighted images, within which were focal areas of fat.

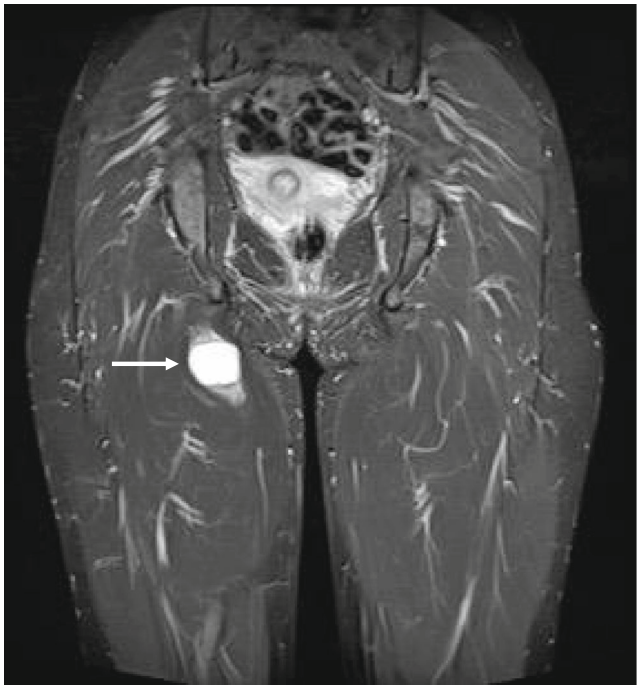

Fig. 1 Coronal short tau inversion recovery (STIR) MR image through the pelvis shows a hyperintense rounded mass lying in the posterior aspect of the adductor magnus (*arrow*). Oedema-like signal can be seen at the superior and inferior aspects of the mass

Radiographs were advised for further characterisation and showed the typical appearance of FD in the femur (Fig. 4). In addition, there was an area of ill-defined lucency distally, in an area that had not been covered by the MRI, with destruction of the adjacent posterior cortex (Fig. 5). There was no adjacent aggressive periosteal reaction. The appearances in the distal femur were suggestive of a malignant bone lesion and were further assessed by CT and MRI. CT of the thorax was also performed at this stage to exclude metastatic disease in view of presumed malignancy: the patient was still largely asymptomatic with regard to the distal femur.

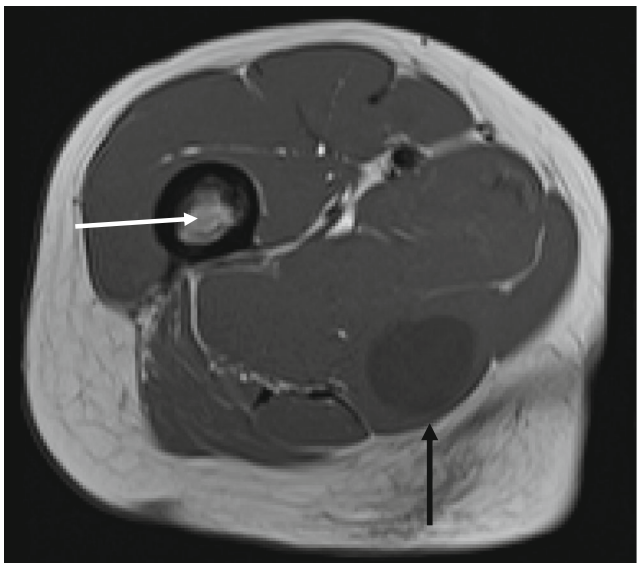

Fig. 2 Axial T1-weighted MR image through the upper right thigh showing the low signal mass in the right adductor magnus (*black arrow*). Note is also made of subtle intramedullary signal abnormality in the right proximal femoral diaphysis (*arrows*)

Magnetic resonance imaging of the distal femur showed an area of diffuse marrow replacement measuring approximately 10 cm craniocaudally, returning intermediate signal on T2-weighted FSE images and containing areas of fluid signal (Fig. 6). There was circumferential thinning and infiltration of the cortex, with concentric periosteal hyperintensity. The posterior cortex was focally destroyed with a small adjacent extra-osseous mass in continuity with the medullary lesion (Fig. 7). CT of the proximal femur showed changes consistent with extensive FD: there was diffusely heterogeneous density within the medulla, areas of "ground-glass" increased density, focal areas of relative lucency and diffuse cortical abnormality (thickening and endosteal scalloping). Distally, homogeneous soft-tissue density was seen within the medulla consistent with tumour, adjacent to an area of cortical thinning, irregular cortical destruction, a localised posterior cortical breach and a small adjacent extra-osseous mass (Fig. 8).

Computed tomography-guided biopsies of both the proximal and the more aggressive distal diaphyseal abnormalities were performed, and the adductor mass was biopsied under ultrasound control.

Biopsy of the proximal femur showed a fibro-osseous tumour composed of irregular ("C-shaped") trabeculae of woven bone with inconspicuous osteoblastic rimming, set in a moderately cellular fibrous stroma, consistent with FD. Biopsy of the aggressive distal femoral lesion showed a predominantly necrotic tumour entrapping numerous fragments of the lamellar bone. The scant viable areas showed spindle cells with marked pleomorphism and nuclear hyperchromasia, consistent with a high-grade spindle cell sarcoma. Neither area showed *MDM2* gene amplification by interphase fluorescence in situ hybridisation analysis.

Total femoral excision and endoprosthetic replacement was performed and the buttock mass was also excised. Analysis of the femur showed a fracture through the tumour in the distal shaft. The tumour was highly necrotic and composed of fascicles of atypical spindle cells with brisk mitotic activity (Fig. 9d). The FD component extended from the femoral head throughout the diaphysis and was seen merging with the proximal aspect of the high-grade component (Fig. 9a). Smaller areas of FD were also seen in the femur distal to the sarcoma (Fig. 9b).

Cells from the high-grade component showed scattered expression of pan-cytokeratin antibody (MNF-116). S100, smooth muscle actin and desmin were completely negative.

The excised buttock mass comprised a 40x35x30-mm, well-circumscribed myxoid tumour covered by strands of skeletal muscle. The histological examination showed bland spindle cells embedded in a hypovascular myxoid stroma,

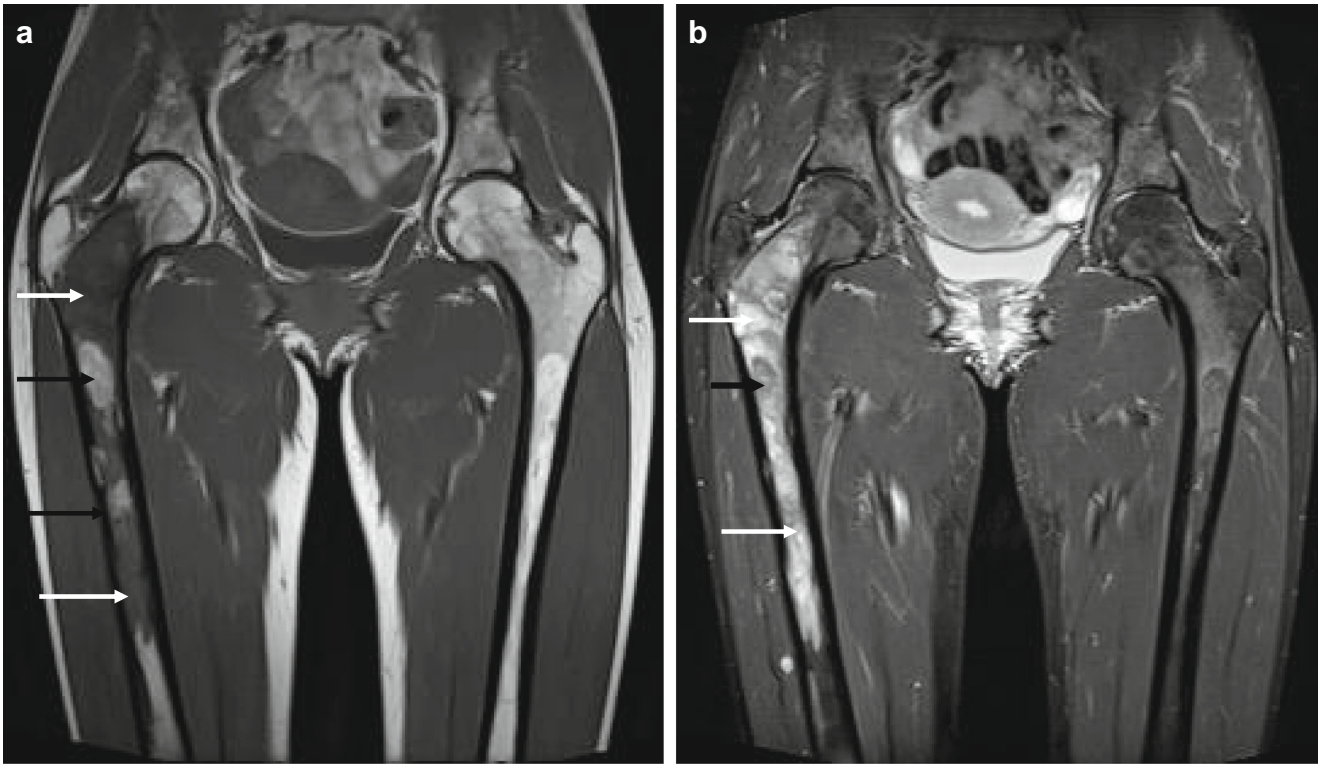

Fig. 3 **a** Coronal T1-weighted MR image through the proximal femora showing heterogeneous intermediate to low intramedullary signal (*arrow*), with interspersed areas of fatty signal (*black arrows*). **b** Coronal STIR MR image through the proximal femora showing heterogenous intramedullary hyperintensity (*white arrows*), interspersed with some foci of hypointense fat (*black arrow*)

consistent with an intramuscular myxoma. The histopathology is shown in Fig. 9c.

Samples from all three tumour types—FD in the proximal femur, high-grade spindle cell sarcoma in the distal femur and the intramuscular myxoma—were tested for *GNAS1* point mutation, and the same R201H substitution was detected in all samples.

Discussion

This report illustrates a spindle cell sarcoma of bone secondary to Mazabraud's syndrome, in which the same mutation in the *GNAS1* gene was identified in the three components of the syndromic tumour tissue that were evaluated (the typical FD component, the soft-tissue myxoma and the high-grade spindle cell sarcoma). Identification of an identical mutation in the sarcoma is confirmation that the malignant neoplasm is a clone, originally genetically identical to the other components of Mazabraud's syndrome, implying malignant transformation of syndromic tissue, rather than an unrelated lesion (collision tumour).

Fibrous dysplasia is a benign, intramedullary fibro-osseous tumour that can affect one (monostotic) or multiple (polyostotic) bones. It is caused by an early embryonic post-zygotic activating missense mutation of the guanine nucleotide-binding protein/α-subunit (*GNAS1*) gene, frequently in codon 201 of exon 8, resulting in p.R201C or p.R201H substitutions or, less frequently, in codon 227 of exon 9, resulting in p.Q227R, p.Q227H or p.Q227K [1]. The various clinical forms of FD are determined by the level of mosaicism within the affected tissues. Bone disease develops in childhood, but can present in adults, as is often the case with monostotic FD.

Myxomas are rare, benign, usually intramuscular myxoid soft-tissue tumours composed of bland fibroblastic spindle cells embedded in an abundant hypovascular myxoid matrix. They generally present in adulthood, usually in the 5th to 7th decades, and the majority are sporadic, not associated with a systemic disease. Malignant change has not been reported in myxomas.

The association between FD and intramuscular myxomas was first described by Henschen in 1926 [2], but the existence of a syndrome was proposed by Mazabraud et al. in 1967 [3]. In this disorder, FD is often polyostotic, but can be monostotic. The intramuscular myxoma/myxomata are generally found in the vicinity of the affected bones [4], without any demonstrable continuity. A review of all the cases reported in the literature has revealed that in a majority, the diagnosis of the FD predates that of myxoma [5].

Mazabraud's is commoner in women. It is also caused by an activating mutation of *GNAS1*, occurring as a post-zygotic

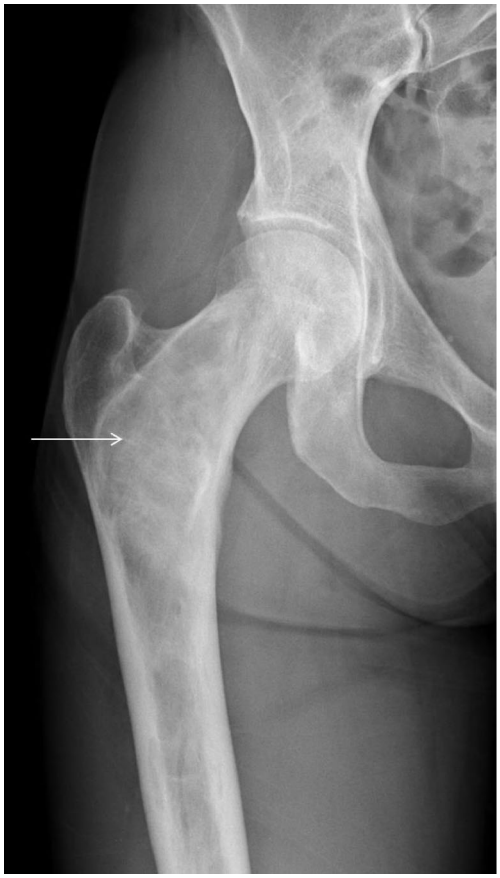

Fig. 4 Radiograph of the right proximal femur showing patchy mixed bone sclerosis and lucency and cortical thickening in the proximal shaft. Ground glass density is noted in the intertrochanteric region (*arrow*)

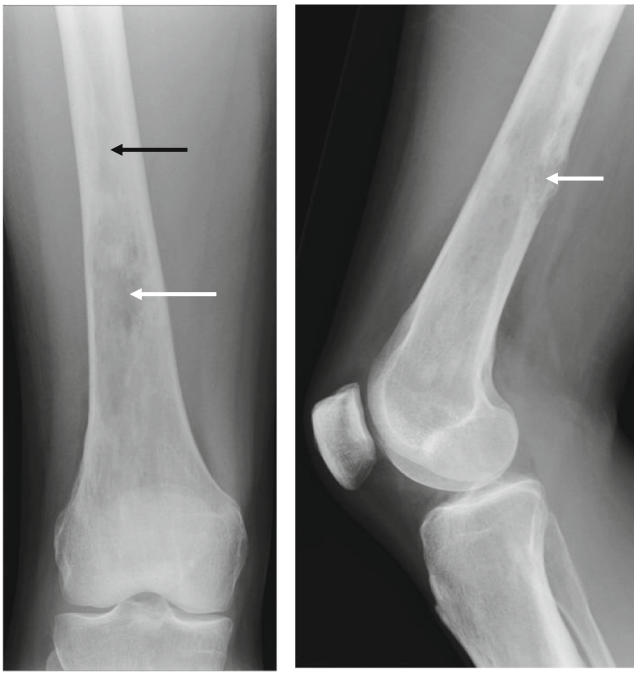

Fig. 5 Radiographs of the right distal femur showing aggressive bone lysis and posterior cortical destruction (*arrows*), inferior to an area of fibrous dysplasia (*black arrow*)

event and resulting in a mosaic distribution of the mutation-bearing cells [6]. A similar post-zygotic mutation is also responsible for McCune–Albright syndrome (FD, café-au-lait spots and endocrine tumours) [7, 8].

Malignant transformation in FD is very rare, occurring in less than 1% of monostotic and about 4% of polyostotic cases, further increased in the setting of Mazabraud's or McCune–Albright syndrome [9]. The most frequent sites of malignant transformation reported in the literature are the craniofacial bones (46%) and proximal femur (25%), with secondary tumours including osteosarcoma, high-grade spindle cell sarcoma, chondrosarcoma and pleomorphic undifferentiated sarcoma.

Imaging plays a vital role in the diagnosis of FD and the identification of clinically undetected intramuscular myxomas. Typical and unequivocal imaging appearances of FD and myxoma usually preclude the need for invasive biopsies.

The imaging appearances of conventional FD are well-known. It is vital to identify atypical, more aggressive regions within bone affected by FD: the permeative cortical irregularity seen on radiographs of the distal femur in our case suggests the possibility of malignant transformation, as do the MRI features of periostitis, cortical breach and extra-osseous

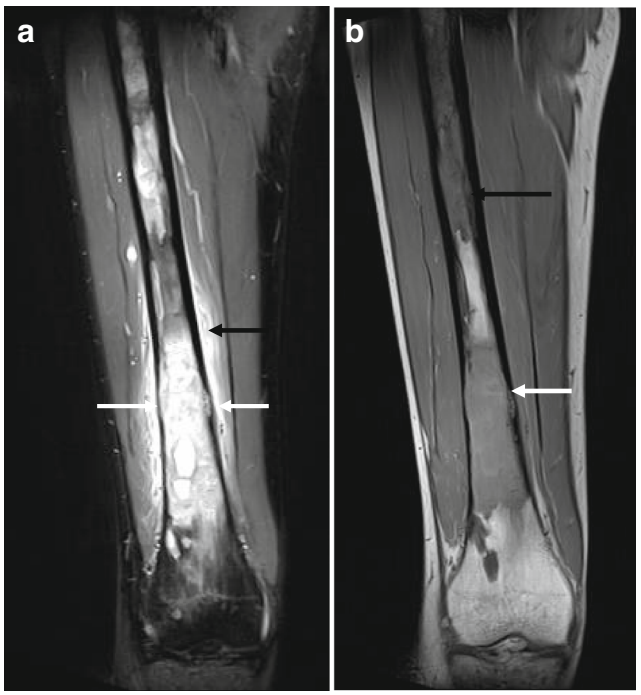

Fig. 6 **a** Coronal STIR MR image of the distal right femur showing hyperintense marrow replacement and cortical thinning at the site of bone destruction (*white arrows*), with surrounding hyperintense periostitis (*black arrow*). **b** Coronal T1-weighted MR image of the distal right femur showing hyperintense marrow replacement (*white arrow*), cortical thinning and adjacent areas of fibrous dysplasia (*black arrow*)

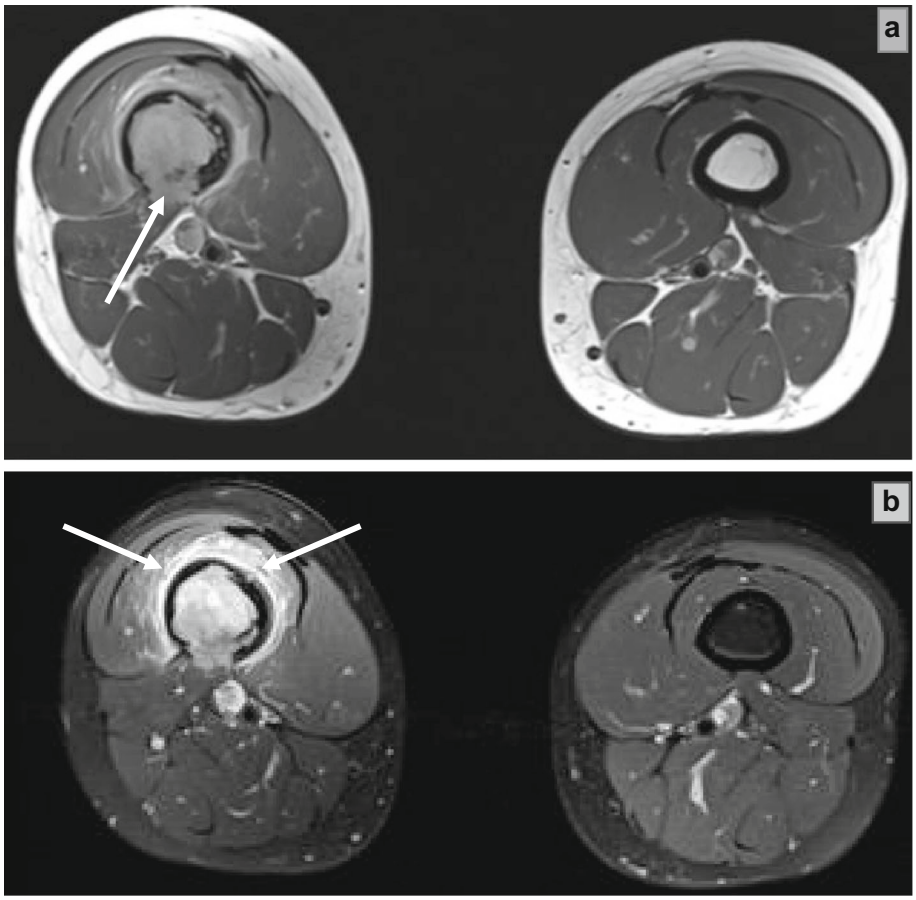

Fig. 7 **a** Axial proton-density (PD)-weighted and **b** PD fat-saturated MR images showing posterior cortical destruction of the right distal femoral diaphysis and a small extra-osseous mass (*arrow* in **a**). Concentric periostitis is also shown (*arrows* in **b**)

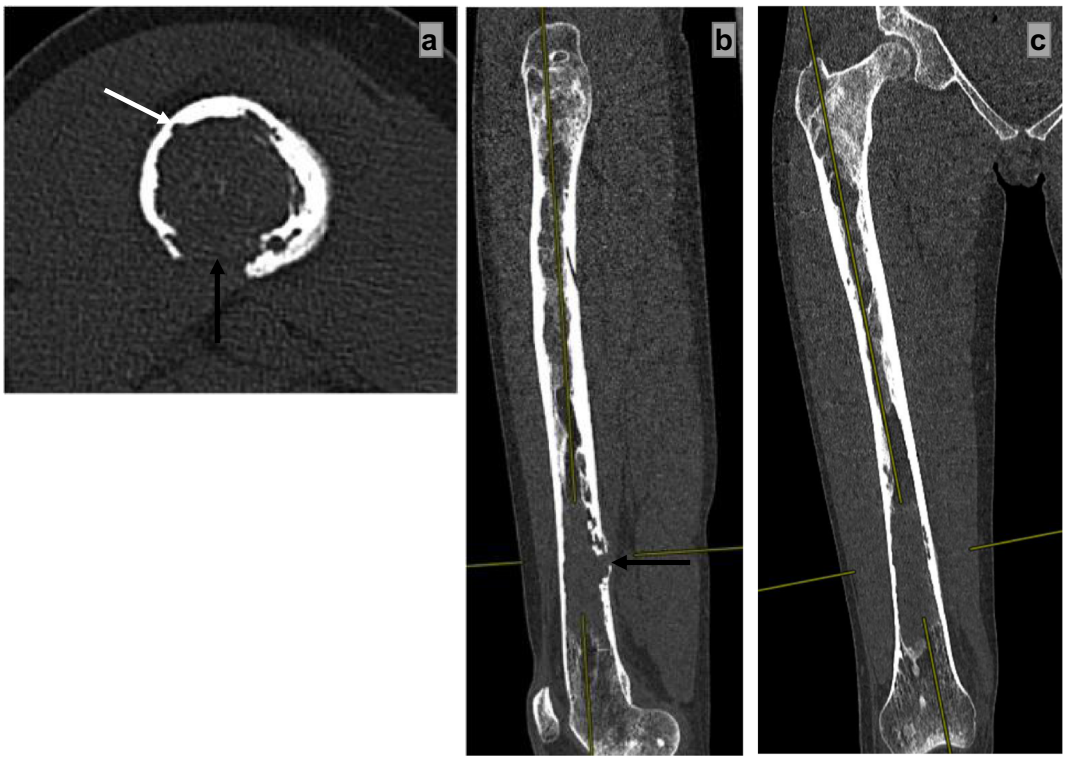

Fig. 8 **a** Axial, **b** sagittal and **c** coronal reformatted CT through the distal femoral diaphysis showing irregular cortical thinning (*arrow*), endosteal scalloping, and a large posterior cortical breach (*black arrow*)

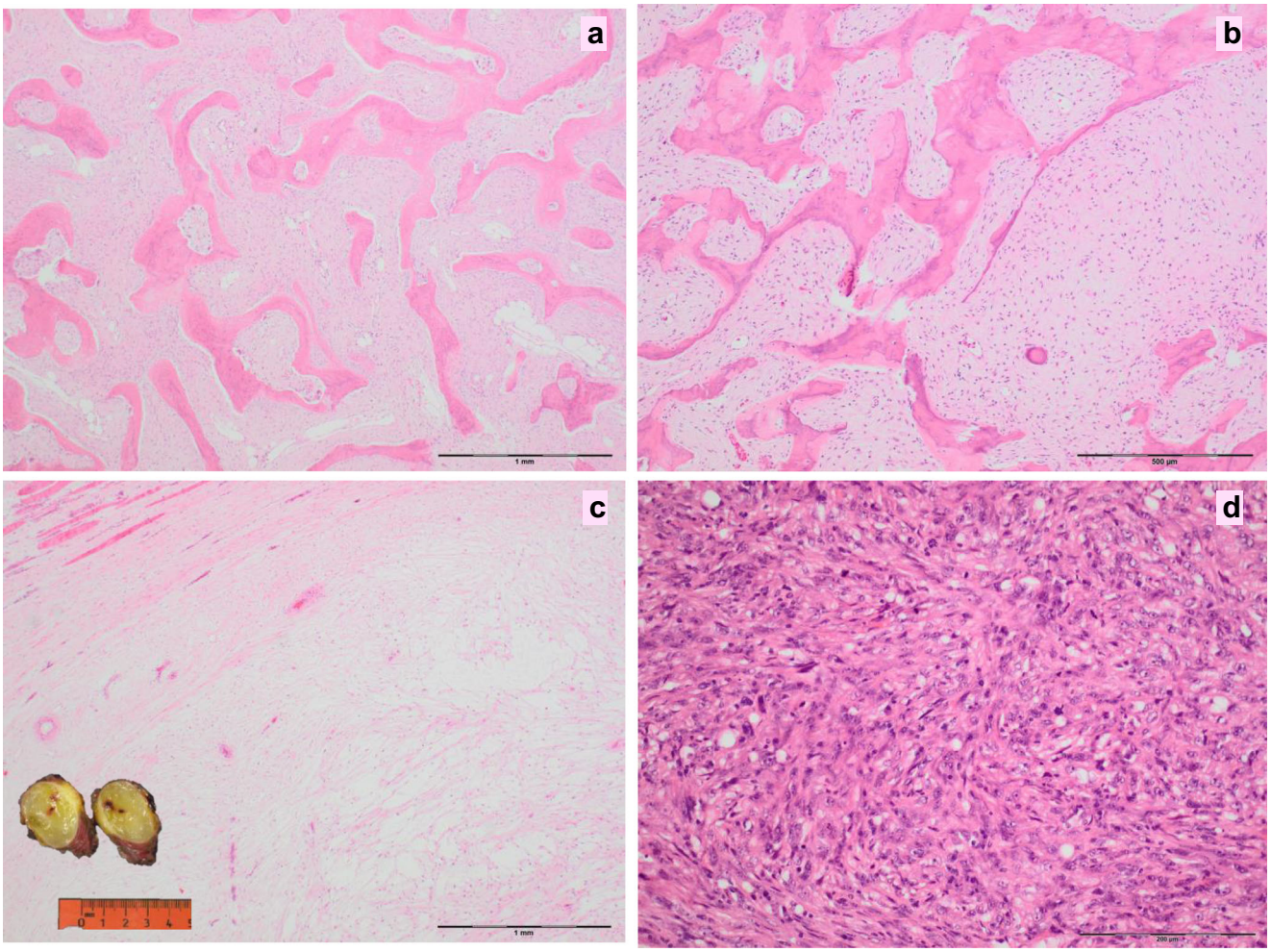

Fig. 9 Photomicrograph of the fibro-osseous tumour in **a** the proximal and **b** the distal femur, showing features consistent with fibrous-dysplasia. **c** Histological and macroscopic appearance of the intramuscular myxoma. **d** Microphotography of the high-grade sarcoma showing tumour necrosis, around the fracture in the distal femur

tumour. However, on rare occasions, uncomplicated FD may appear unusually aggressive—it can destroy bone cortex, especially in flat bones and ribs and extra-osseous tumour has been reported [10].

In this case, the diagnosis of Mazabraud's syndrome with malignant transformation was also confirmed by the identification of an identical point mutation in all three of the sampled sites: the area of classical FD, the myxoma and the secondary sarcoma. The R201H point mutation is the commonest, but several others have been described. To our knowledge, only one previous report of a genetically proven secondary sarcoma in FD has been published, and this also involved an R201H mutation in an osteosarcoma of the mandible developing in a pregnant patient with McCune–Albright syndrome [11].

In conclusion, we present the case of a female patient not previously known to have FD, with a high-grade spindle cell sarcoma of bone secondary to Mazabraud's syndrome. Molecular analysis showed the presence of an R201H substitution in the *GNAS1* gene in the sarcomatous component, the conventional FD and the intramuscular myxoma, confirming that the sarcoma is a clone and was initially genetically identical to the other neoplastic components of Mazabraud's, until further genetic events caused malignant transformation. The secondary sarcoma was discovered incidentally while the patient was asymptomatic. Careful scrutiny of all bones affected by FD, particularly when disease is extensive, is vital, to identify what may be subtle aggressive features, suggesting a rare secondary sarcoma.

References

1. Idowu BD, Al-Adnani M, O'Donnell P, et al. A sensitive mutation-specific screening technique for *GNAS1* mutations in cases of fibrous dysplasia: the first report of a codon 227 mutation in bone. Histopathology. 2007;50(6):691–704.

2. Henschen F. Fall von Ostitis fibrosa mit multiplen Tumoren in der umgebenden Muskulatur. Verh Dtsch Ges Pathol. 1926;21: 93–7.
3. Mazabraud A, Semat P, Roze A. A propos de l'association de fibromyxomes des tissus mous a la dysplasie fibreuse de l'os. Presse Med. 1967;75:2223–8.
4. Gaumetou E, Tomeno B, Anract P. Mazabraud's syndrome. A case with multiple myxomas. Orthop Traumatol Surg Res. 2012;98: 455–60.
5. Zoccali C, Teori G, Prencipe U, Erba F. Mazabraud's syndrome: a new case and review of the literature. Int Orthop. 2009;33:605–10.
6. Delaney D, Diss TC, Presneau N, et al. *GNAS1* mutations occur more commonly than previously thought in intramuscular myxoma. Mod Pathol. 2009;22(5):718–24.
7. Lumbroso S, Paris F, Sultan C. Activating Gsα mutations: analysis of 113 patients with signs of McCune-Albright syndrome—a European collaborative study. J Clin Endocrinol Metab. 2003;89(5):2107–13.
8. Schwindinger WF, Francoromano CA, Levine MA. Identification of a mutation in the gene encoding of the alpha subunit of the stimulatory G protein of the adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A. 1992;89:5152–6.
9. Riddle ND, Bui MM. Fibrous dysplasia. Arch Pathol Lab Med. 2013;137:134–8.
10. Muthusamy S, Subhawong T, Conway SA, Temple HT. Locally aggressive fibrous dysplasia mimicking malignancy: a report of four cases and review of literature. Clin Orthop Relat Res. 2015;473:742–50.
11. Kanazawa I, Yamauchi M, Yano S, et al. Osteosarcoma in a pregnant patient with McCune-Albright syndrome. Bone. 2009;45:603–8.