Case report

Polyostotic fibrous dysplasia (McCune-Albright) with rare multiple epiphyseal lesions in association with aneurysmal bone cyst and pathologic fracture [☆],[☆☆]

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ABSTRACT

Fibrous dysplasia, including McCune-Albright syndrome, is a genetic, non-inheritable benign bone disorder that may involve a single or multiple bone, typically occurring in the diaphysis or the metaphysis of long bones. In very rare instances polyostotic fibrous dysplasia present involvement of the epiphysis in long bones. Aneurysmal bone cysts are benign, expansile, lytic bone lesions formed by cystic cavities containing blood, that may occur de novo or secondary to other lesions of bone, including fibrous dysplasia. We report a case of an 18-year-old female with polyostotic fibrous dysplasia (McCune-Albright syndrome) with diaphyseal and unusual multiple foci of epiphyseal involvement of long bones as well as in the patella, and a simultaneous aneurysmal bone cyst of the left femoral neck with pathologic fracture. This is the first report of a simultaneous aneurysmal bone cyst in a patient with polyostotic fibrous dysplasia (McCune-Albright syndrome) with involvement of diaphysis and epiphysis of long bones, highlighting that fibrous dysplasia should be included in the differential diagnosis of polyostotic tumors involving the diaphysis as well as the epiphysis. In patients with polyostotic fibrous dysplasia there should be an active search for lesions in the epiphysis.

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Introduction

Fibrous dysplasia (FD) is a developmental benign bone disorder, with fibroblasts proliferation resulting in excessive fibrous tissue replacing normal calcium hydroxyapatite of the osteoid matrix [1], with distortion and overgrowth of the affected bone [2]. FD is a genetic, non-inheritable disorder caused by mutations occurring post-zygotically in the guanine nucleotide alpha stimulating gene - GNAS1 gene (chromosome 20q13.2-13) - of the osteoblastic lineage cells [1,3], with consequent mutation of the α-subunit of the G_s stimulatory protein leading to activation and inappropriate overproduction of cyclic adenosine monophosphate (cAMP) [4] and c-fos overexpression [5], causing defects in the osteoblastic differentiation. The fibroblasts-like cells at histology correspond to poorly differentiated osteoblasts, leading to extensive proliferation of fibrous tissue [5]. In the mutated cells the secretion of interleukin-6 is elevated, with consequent activation of osteoclasts, allowing osteolysis and expansion of the FD lesion [5]. The combination of these pathways leads to the known radiographic appearance of FD, as an expansile lesion, with endosteal scalloping, without periostal reaction, and a ground-glass density within the lesion. FD arises sporadically, and there are no confirmed cases of vertical transmission [4,6]. FD is a rare disorder representing 2.5% of osseous tumors overall [1], and 5-7% of all benign bone tumors (7,2), found equally in both sexes [8]. The disease process may be localized to a single bone (monostotic FD also known as Jaffe-Lichtenstein disease) or multiple bones (polyostotic FD) [9]. Polyostotic FD accounts for 30% of the cases [1], including McCune-Albright syndrome (MAS) with polyostotic FD associated with endocrine abnormalities and overproduction of melanin in the skin (2-3% of patients with FD), while in Mazabraud syndrome polyostotic FD is associated with intramuscular myxomas [4,10,11]. Both monostotic and polyostotic lesions of FD affecting long bones occur in the diaphysis or metaphysis, but very rarely present involvement of the epiphysis [9]. Cherubism has been considered a variant of FD, but it is a genetically distinct disease [4], and in most cases arises from heterozygous pathogenic variants in SH3BP2, with autosomal dominant inheritance [6].

Aneurysmal bone cysts (ABC) are benign, expansile, lytic bone lesions formed by thin-walled communicating cystic cavities containing blood [2], with fibroblasts and osteoclasts-like giant cells, of unknown etiology [10]. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) demonstrate the internal septations and fluid levels. Cytogenetic data reveals that ABC corresponds to a neoplastic pathology resulting from rearrangements of chromosome bands 16q22 and 17p13, which in turn results in the formation of CHD11-USP6 fusion transcripts, and through oncogenic mechanisms, ABC patients express deregulated USP6 genes [1]. Aneurysmal bone cyst may occur de novo or secondary to other lesions of bone [8], and approximately 30% of ABCs are considered secondary [12]. ABC occurring in the setting of a previously diagnosed fibrous dysplasia is uncommon, and the lesion may appear as an aggressive process that is difficult to diagnose properly [10].

In the present article we describe an unusual case of an 18-year-old female with polyostotic FD (MAS) with multiple lesions involving not only the diaphysis but also the epiphysis of long bones, further complicated with a secondary ABC of the left femur with pathologic fracture. This is the first report of a simultaneous ABC in a patient with polyostotic FD with involvement of diaphysis and epiphysis, highlighting the concept that FD should be included in the differential diagnosis of polyostotic tumors involving the diaphysis as well as the epiphysis.

Case report

In the current report we present a case of an 18-year-old female patient who was diagnosed with polyostotic FD when she was 6-year-old and presented with a tibia fracture, "café-au-lait" spots in the abdominal wall and ovarian cysts. Bone scan at the age of 14 years, demonstrated metabolically active lesions in the pelvis, left femur, left tibia and left foot, with FD lesions in the femoral neck and trochanteric region, femoral and tibial diaphysis, as well as involvement of the distal femoral epiphysis, the proximal and the distal tibial epiphysis, as well as involvement of bones in the left foot (Fig. 1), consistent with hemimelic distribution. No evidence was present of facial bones or skull involvement. These constellations of findings were consistent with McCune-Albright syndrome (MAS).

In the current episode she refers a minor trauma in the left lower extremity hitting a garbage can, followed by functional impotence and progressive pain, leaving her in a wheelchair. On physical examination, antalgic restriction of the left hip mobilization, and absence of neurovascular deficit in the left lower limb were observed. The radiograph of the femur demonstrated an impacted fracture at the base of the left femoral neck in the context of an expansile lytic bone lesion, with partial ground-glass density and rind-sign suggestive of FD associated with an ABC (Fig. 2b), and multiple well-defined expansile lesions with ground-glass density, consistent with FD, in the left femur and tibia. Based on previous studies there was evidence that she developed the ABC secondary to a fibrous dysplasia lesion in the proximal left femur over a period of 36 months (Fig. 2a), manifested as progressive growth of the lesion and multiple low-density areas within the lesion.

Subsequently an MRI study was preformed, showing a fibrous dysplasia lesion with well-defined margins, low T1WI signal intensity and intermediate to high signal intensity on T2WI, affecting the femoral neck, trochanteric and subtrochanteric region of the femur, surrounding a secondary ABC with a displaced fracture of the femoral neck, demonstrating multiple cystic spaces with fluid levels and well-defined margins, as well as foci of spontaneous T1WI hyperintensity. A complete transverse fracture of the left femoral neck was evident, with impaction of bone fragments, and varus angulation at the fracture site. In the MRI study there was also evidence of FD lesions in the femoral and tibial diaphysis, but importantly there was obvious involvement of the proximal and distal femoral epiphysis, the proximal and distal tibial epiphysis, as well as the patella, with smaller lesions with similar signal intensity compared to the lesions in the diaphysis (Fig. 3).
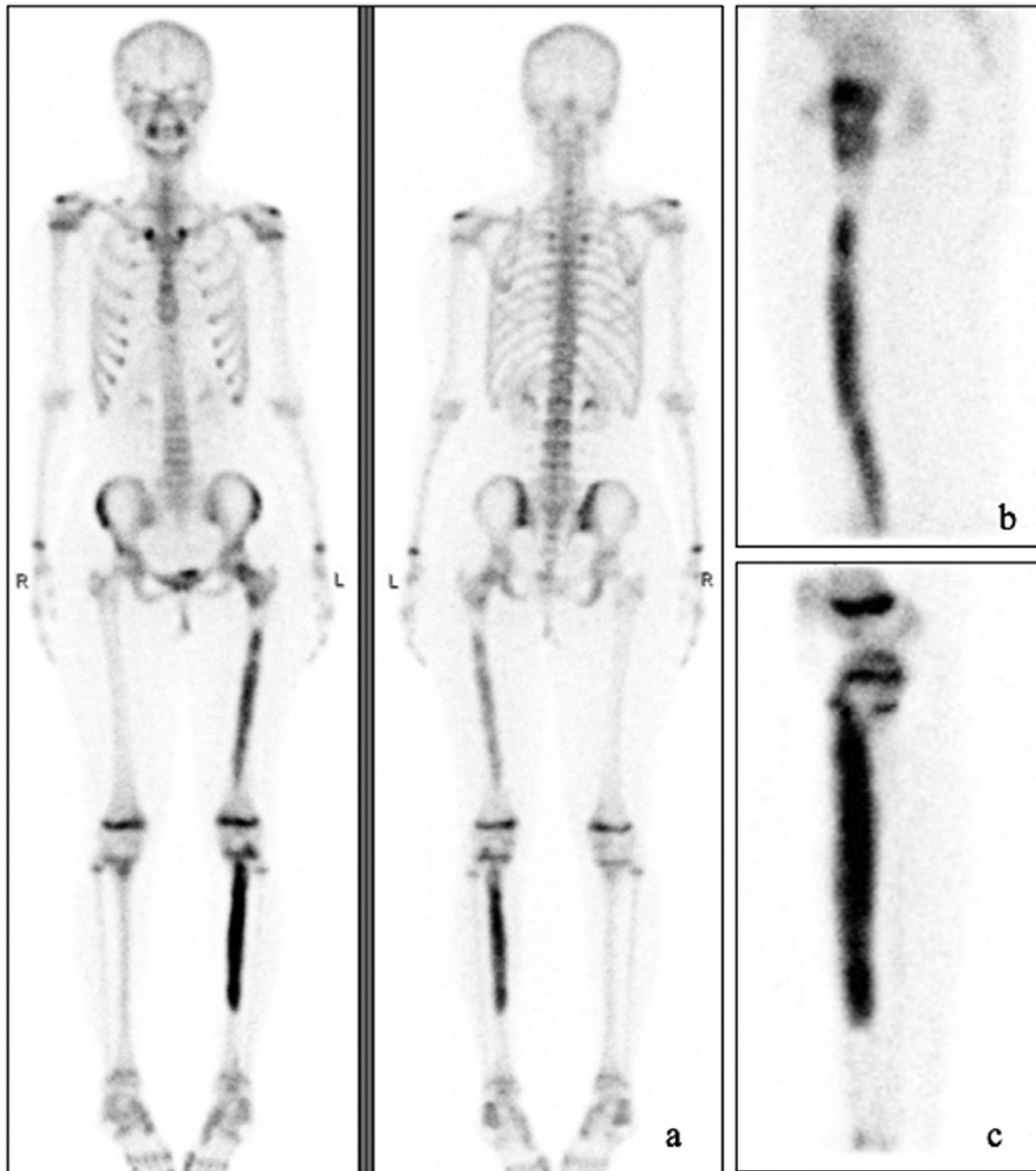
Fig. 1 – Bone scan at the age of 14 years. (a) Anteroposterior and Posteroanterior views. (b) Lateral view of the left femur. (c) Lateral view of the left tibia. Metabolically active lesions are depicted in the left lower extremity, involving the left femoral neck, trochanteric region, femoral diaphysis, distal femoral epiphysis, proximal and distal tibial epiphysis, proximal tibial metaphysis and tibial diaphysis. There is no evidence of skull or face involvement

Surgical management with curettage, bone grafting and internal fixation was performed with a dynamic hip screw (DHS) (Fig. 4). Tissue received in surgical pathology consisted of multiple bone fragments, and histopathology showed fibrous tissue consisting of spindle-cell fibroblasts and irregularly shaped bony trabeculae interspersed in between, with no osteoblastic rimming of the trabeculae, and areas of ABC degeneration characterized by aneurismatic cavities with no endothelial lining, fibrin, recent hemorrhage and granulation tissue (Fig. 5).

At the four-months follow-up the patient demonstrated mild residual pain in the left hip and left thigh.

Discussion

Fibrous Dysplasia

FD is a well-known developmental benign skeletal disorder, with fibroblasts proliferation resulting in excessive fibrous tissue replacing normal calcium hydroxyapatite of the osteoid matrix [1]. FD is a disorder caused by mutations in the GNAS1 gene of the osteoblastic lineage cells, and the mutation timing determines the extent of the disease and clinical manifestations, responsible for a somatic mosaic [5]. Mutations that occur at early stages of embryogenesis result in the widespread
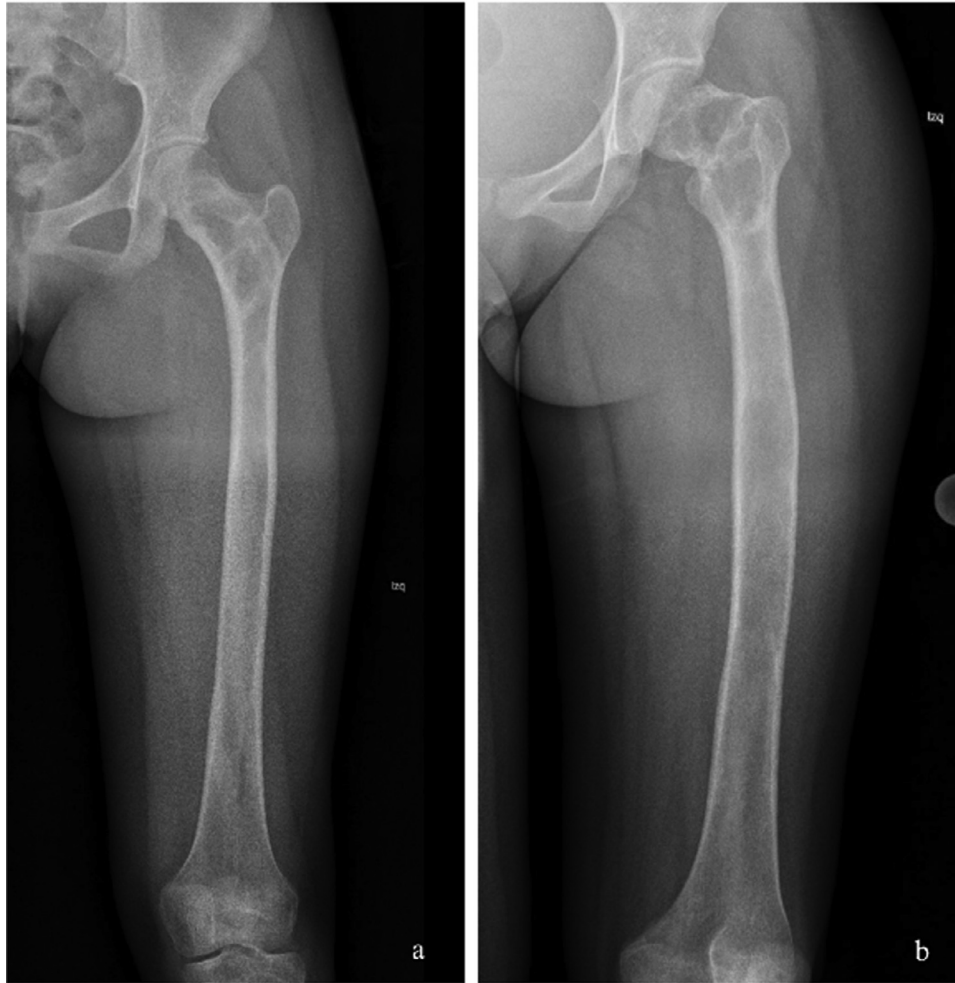
Fig. 2 – (a) AP radiograph approximately three years before the current episode. Multiple foci of FD are visible in the left femur, in the femoral neck, trochanteric region, and extensively involving the diaphysis. There is no evidence of fracture in the femoral neck. Fig. 2 (b) AP radiograph of the left femur in this episode, with an impacted fracture at the base of the femoral neck, in the context of an expansile lytic lesion involving the femoral neck and trochanteric region. Comparison with the previous study demonstrates further expansion of the femoral neck with a well-defined osteolytic lesion

distribution of the lesions or one of the FD-related syndromes. Conversely, mutations that occur at late stages of embryogenesis result in more focused distribution of the lesions [4]. This is the reason why the monostotic form of FD never progresses to a polyostotic form of FD, and spontaneous resolution of FD does not occur [4]. In adults FD lesions typically become less active, probably related to apoptosis of pathogenic variant-bearing cells [6]. In cases of MAS affected tissues commonly include skin, skeleton and endocrine organs, however, because Gs stimulatory protein signaling is present virtually in every tissue, additional sites may be affected [6].

In MRI studies of FD the signal intensity and the degree of enhancement depend on the amount of bony trabeculae, cellularity, collagen, cystic and hemorrhagic changes, but typically with sharply defined margins [4]. The higher the number of bony trabeculae, the lower the T2 signal, and vice versa: cystic areas show high signal intensity on T2WI and low signal intensity on T1WI; active lesions show avid enhancement [4].

Polyostotic FD with lesions in the epiphysis

In patients with polyostotic-FD the skull, mandible, pelvic bones and the femur are the most frequently involved sites. The femur is the most common location of polyostotic FD (40%) [4], and the femoral neck is the most common site for both monostotic and polyostotic disease [10]. In the literature there are many reports of polyostotic FD, but only a few reports of cases of monostotic and polyostotic FD involving the epiphysis [9,13], and we found only one previous report of polyostotic FD with lesions in the epiphysis of the femur and the tibia [9], but no evidence of lesions in the face or skull. FD lesions in the long bones originate in the growth plate, and may extend into the epiphysis and the metaphysis [13], although the epiphyseal extension is very rare. Our patient presented with polyostotic compromise, including femoral and tibial diaphysis, proximal and distal femoral epiphysis, proximal and distal tibial epiphysis, as well lesions in the patella, but no involvement of skull or facial bones. Although other etiologies

Fig. 3 – Selected images from the MRI performed, displaying a focus of FD in the proximal left femur, affecting the femoral neck as well as the trochanteric and subtrochanteric regions, with low signal intensity on T1WI (a) and intermediate to high signal intensity on T2WI (b), with an expansile multicystic lesion with fluid levels and well-defined margins (c), associated with foci of spontaneous high signal intensity on T1WI. A transverse fracture is visible in the femoral neck, with impaction of the bone fragments, and varus angulation. Coronal images of the femur (d, e, f, g) and tibia (h, i) with T1WI and PDWI with fat-suppression, demonstrate multiple foci of FD in the proximal and distal femoral epiphysis, proximal and distal tibial epiphysis and extensive lesions in the femoral and tibial diaphysis. Axial PDWI with fat-suppression (j) shows lesions in the patella, as well as the distal femoral epiphysis

may potentially affect multiple epiphysis (e.g., osteomyelitis, geodes, avascular necrosis, eosinophilic granuloma), in the current case the morphology and signal intensity of the epiphyseal lesions was similar to the lesions in the diaphysis, and pathology proved the presence of fibrous dysplasia. Polyostotic FD is usually diagnosed during the first few years of life, with osseous lesions becoming non-silent and clinically significant by age 10 years, with almost no new lesions appearing after the age of 15 years [4]. Our patient was diagnosed with polyostotic FD when she was 6-year-old and presented with a tibia fracture. In the current episode she presents with a pathologic fracture in the proximal left femur, with FD and ABC in the fracture site. The FD lesions in the epiphysis were managed by observation only, but one should consider that these lesions may affect the articular surface depending on their size.

FD: risk of fracture and secondary ABC

FD lesions are characterized by age-related histological, radiographical and clinical transformations, demonstrating lesions metabolically active in early childhood, expanding during linear growth, with the lesions typically becoming static in size after puberty, and decreased metabolic activity throughout adulthood [4]. FD most commonly behaves as an indolent lesion, but occasionally the lesion may be symptomatic, with pain, paresthesia, pathologic fracture, ABC formation or malignant transformation [4], thus symptomatic or enlarging lesions should be closely followed clinically and radiographically. The risk of fracture in FD patients varies with age and are most prevalent between the age of 6 and 10 years, with a peak incidence of 0.4 fractures per patient per year [4]. Some factors may predispose patients to fracture, including the presence

Fig. 4 – Postoperative anteroposterior radiograph of the left hip, demonstrating changes of curettage, bone grafting and internal fixation with a dynamic hip screw

pected ABC in FD lesions [4,6], which proved useful in our clinical case, delineating the ABC area and the FD portion of the osseous lesion. Rapid expansion of FD lesions is concerning for possible malignant transformation or ABC development, and in the present case the patient presented with expansion of the lesion in the proximal left femur compared to previous radiographs, justifying the use of MRI in the morphologic assessment of the lesion.

Histologically, hemorrhage and cystic changes may occasionally be seen in FD lesions [2], with secondary changes of ABC [4]. ABC occurring in the setting of a previously diagnosed fibrous dysplasia is uncommon, and has been reported in the facial bones, skull base, calvarium, and spine, as well as the radius and tibia [2,8,12,13]. Diercks reported a case of polyostotic FD with involvement of the right lower limb and hemipelvis, with a FD lesion in the right proximal femur with ABC development [14]. Montalti reported a case of FD with secondary ABC in the proximal femur [10]. To our knowledge our case is the first report of secondary ABC development and subsequent fracture in a patient with MAS and is the third report of FD with ABC development affecting the femur.

FD is able to degenerate into a high-grade sarcoma, with an incidence of 0.5% in monostotic disease and 4% in MAS [10,2], with osteosarcoma, fibrosarcoma and chondrosarcoma, in decreasing order of frequency, the most common forms of malignant degeneration [12,5]. Nonetheless, in the present case the MRI demonstrated evidence of ABC degeneration in a previously existing FD lesion, instead of a sarcomatous degeneration, although the differential diagnosis based on MRI may be challenging. Histopathology confirmed the diagnosis and excluded the presence of malignancy.

of hyperthyroidism, fibroblasts growth factor 23 (FGF 23) levels, and disease burden [4]. Our patient presented with a tibia fracture at the age of 6 years, and subsequently developed the ABC with pathologic fracture of the proximal femur at the age of 18 years. When ABC develops in a FD lesion, the cyst characteristically expands more rapidly than FD would, leading to increased bone pain, progressive deformity and pathologic fracture [4]. MRI is the modality of choice in patients with sus-

Conclusion

In summary we present an unusual case of polyostotic FD (MAS) with diaphyseal and epiphyseal involvement of long bones, as well as lesions in the patella, and a simultaneous ABC of the left femoral neck with pathologic fracture. This is the first report of a simultaneous ABC in a patient with polyostotic FD with involvement of diaphysis and epiphysis, high-
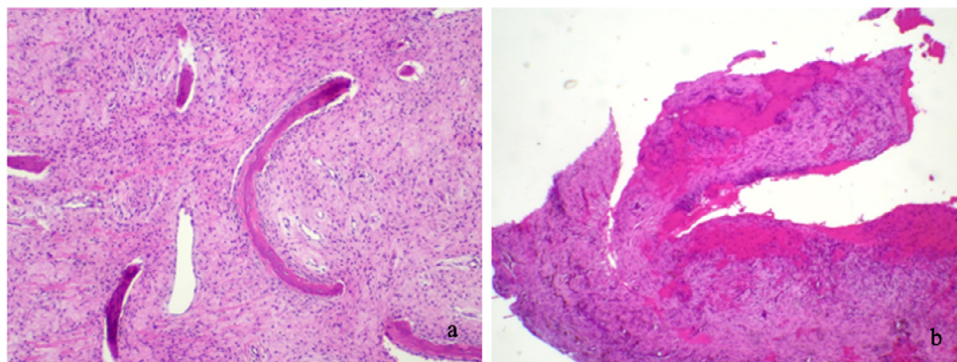
Fig. 5 – (a) 100× HE (hematoxylin and eosin stain) microphotograph, revealing characteristic C-shaped bony spicules with hipocellular spindle cell stroma. (b) 100× HE microphotograph, shows part of the wall of an aneurismatic cavity, with recent haemorrhage and granulation tissue

lighting the importance of the complete preoperative work-up to determine the presence and characteristics of multiple bone lesions. An important conclusion is that FD should be included in the differential diagnosis of polyostotic tumors involving the diaphysis as well as the epiphysis. On the other hand, in patients with polyostotic FD (MAS) there should be an active search for lesions in the epiphysis.

Secondary ABC on a previous FD includes a differential diagnosis of FD with sarcomatous degeneration, and radiologists are remarkably important in this differential, although this needs histopathologic confirmation.

Radiologists play a critical role at all steps of the management of patients with FD and MAS, from diagnosis, prognostic evaluation and identification of osseous complications associated with FD, to follow-up. Patients with FD and MAS may present with different extra-skeletal abnormalities, which require follow-up.

Ethics approval and consent to participate

Not applicable.

Consent for publication. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and materials. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contribution

All authors have made substantial contributions to all four categories:

Conception and design, or acquisition of data, or analysis and interpretation of data

Drafting the article or revising it critically for important intellectual content

Final approval of the version to be published

Agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

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