Mazabraud Syndrome

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Abstract

Mazabraud syndrome is defined by an association between fibrous dysplasia and intramuscular myxomas, and is thought to fall within the spectrum of protean disorders of syndromic fibrous dysplasia that includes McCune-Albright syndrome. In this article, we briefly discuss the history and evolution of the term *Mazabraud syndrome,* then detail the spectrum of imaging findings as they relate to the variable pathology and clinical presentations that may be encountered. Differential diagnostic considerations and potential diagnostic pitfalls are also considered.

The term *fibrous dysplasia* was coined in 1938 by Lichtenstein[1] to describe a nonheritable, aberrant development of fibro-osseous tissue replacing normal cancellous bone. The word *myxoma,* which describes a benign mesenchymal tumor of stellate and spindle cells within a polysaccharide rich avascular stroma, is derived from the Greek word *myxo,* meaning mucus or slime, first used by Virchow[2] to characterize the tissue comprising Wharton's Jelly in the umbilical cord. Myxomas were recognized as distinct lesions by Stout[3] in 1948. While a link was first observed in the German literature by Henschen[4] in 1926, it was not until 1967 that Mazabraud,[5] a French physician, re-examined the association between these 2 entities in their presently defined forms. In 1971, Wirth and colleagues,[6] subsequently described 11 cases of intramuscular myxoma and fibrous dysplasia for the first time in the English literature. Since then, more than 68 cases of what has come to be known as Mazabraud syndrome have been reported.[7]

Pathophysiology

Within the past decade, an activating post-zygotic mutation in the *GNAS1* gene encoding a G-protein involved in cell proliferation has been identified as causative of fibrous dysplasia, with the resulting mosaic distribution of the mutation accounting for the widely variable anatomic distribution of the disorder. The same mutation is also responsible for the manifestations of McCune-Albright syndrome,[8] in which fibrous dysplasia is classically accompanied by endocrine abnormalities (eg, precocious puberty, thyroid dysfunction) and café au lait spots.

Wirth and colleagues[6] described 5 cases of McCune-Albright syndrome among 11 patients with Mazabraud syndrome in 1971. However, evidence linking fibrous dysplasia and myxomas remains observational to this day. There are a number of distinct features that support the association. Mazabraud syndrome appears to lie on the severe end of the spectrum of fibrous dysplasia expression; nonsyndromic fibrous dysplasia is monostotic 75% of the time,[9] but myxomas are seen with the polyostotic form in the great majority of cases[10] and are themselves multiple in approximately 70%.[7]

While there have been no reported instances of malignant degeneration of myxoma, 4 cases of sarcomatous transformation of fibrous dysplasia in patients with Mazabraud syndrome have been reported in the literature.[7] This constitutes a significantly higher incidence of malignant transformation than that reported in the non-syndromic form of fibrous dysplasia, which is estimated at 0.5%. Although fibrous dysplasia is rare, representing only 7% of benign bone lesions,[11] Ireland and colleagues[12] identified fibrous dysplasia in 3 out of a series of 58 patients with myxomas. This may be a small proportion, but it is clearly much more than would be expected in the general population.

Curiously, whereas myxomas may occur in any number of locations including the heart and genitourinary tract, and are intramuscular in only 17% of cases,[13] the majority of those described in Mazabraud syndrome originated within muscle, typically occurring in close proximity to the most severely affected bones.[14] Finally, while fibrous dysplasia in isolation more commonly afflicts males, for unclear reasons, approximately 70% of Mazabraud patients are women.[10]

Clinical And Imaging Presentation

The natural history of Mazabraud syndrome is quite variable. Myxoma may be diagnosed in adolescents or young adults with symptomatic polyostotic fibrous dysplasia.[15] More commonly though, myxomas present as enlarging, either painful or painless masses in older patients (mean age of diagnosis, 46 years), in whom fibrous dysplasia is incidentally found at imaging.[10] Mazabraud syndrome is a rare but probably underreported entity; given the late presentation, it is likely that many cases go unrecognized. An appreciation of the varying radiographic appearances of both fibrous

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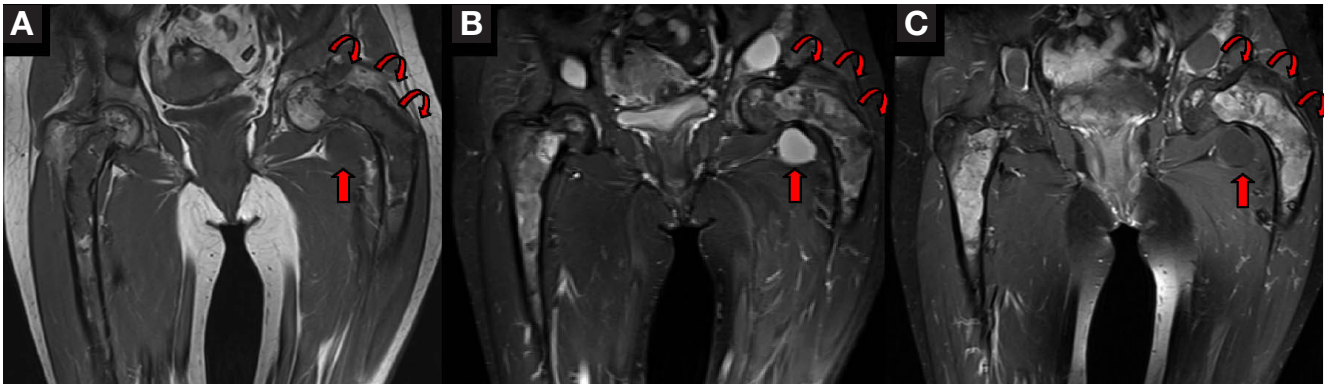

Figure 1. Large field of view coronal T1 (A), STIR (B), and postcontrast fat suppressed T1 weighted (C) MR images of bilateral thighs demonstrate typical findings of polyostotic fibrous dysplasia. The heterogeneous intramedullary signal intensity in the proximal femurs reflects a disorganized arrangement of low T1 signal intensity fibrovascular tissue and poorly formed osteoid, interspersed with cystic components, fat, and hemorrhage, which confer high signal intensity on T2. A typical rim-like enhancement pattern is also demonstrated. There is multifocal osseous scalloping and expansile remodeling, with characteristic Shepherd's crook deformity (curved arrows). Note the circumscribed soft tissues mass along the medial margin of the left femoral neck, which is isointense to skeletal muscle on T1, uniformly hyperintense to skeletal muscle on STIR, and demonstrates minimal peripheral enhancement, in keeping with myxoma (straight arrow) in this patient with Mazabraud syndrome.

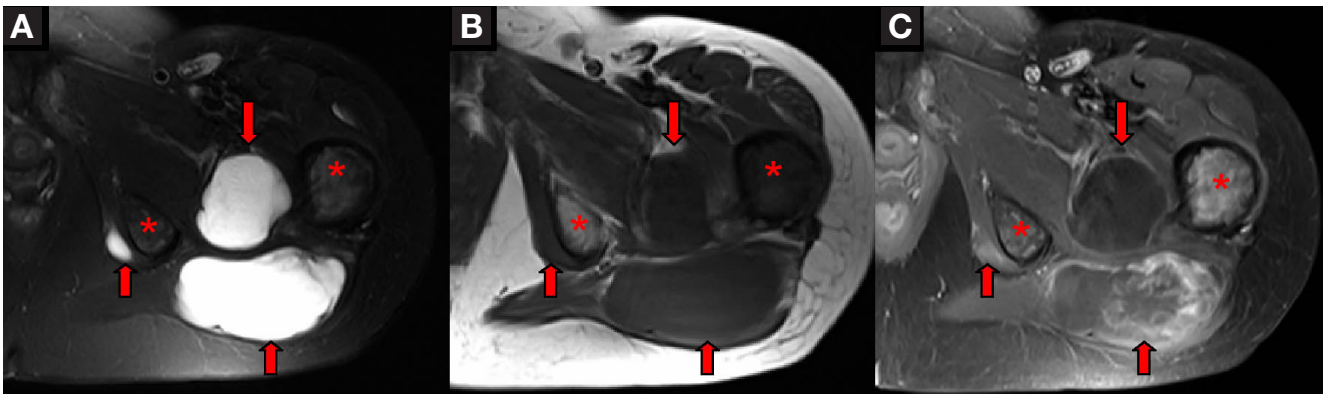

Figure 2. Axial fat suppressed T2 weighted (A), T1 weighted (B), and post contrast fat suppressed T1 weighted (C). There are 3 solid circumscribed soft tissues masses within the left hip adductor, short external rotator and gluteal muscles, reflecting myxomas (straight arrows). The tumors demonstrate uniform "fluid-like" signal, hyperintense to skeletal muscle on T2, isointense to skeletal muscle on T1, and with peripheral enhancement. Polyostotic fibrous dysplasia involving the ischium and proximal femur is denoted by asterisks.

dysplasia and myxomas is essential.

Fibrous dysplasia occurs in a wide range of locations with no predilection for the appendicular or axial skeleton. The femur, humerus, tibia, phalanges, ribs, skull, and ischium may be involved.[11,15] On plain radiographs, diffusely increased ground glass density is typically seen and may be associated with scalloping or expansile remodeling. The findings reflect intramedullary conglomerations of fibrovascular tissue and poorly formed osteoid. Varying proportions of these histologies correspond to different signal intensities on magnetic resonance imaging (MRI).[16] A high degree of collagen or bony trabeculae confers hypointensity on both T1 and T2 weighted images, as do internal septations, and characteristic sclerotic rinds of reactive bone (Figure 1A).[15,16] Rests of cartilage occur within fibrous dysplasia with some frequency, with resulting calcifications that may appear hypointense on all sequences. Lesions are hyperintense to fat on T2WI in 60% of cases, with high signal seen in the presence of cystic components, fat, or hemorrhage, and inversely related to the degree of cellularity (Figure 1B).[15,16] On post-contrast images, enhancement is usually rim-like,[15] but may also be heterogeneous or solid (Figure 1C). Aneurysmal bone cysts may be seen in lesions of fibrous dysplasia and should be suspected when fluid-fluid levels are present.[15,16] MRI defines the extent of fibrous dysplasia more accurately than radiography, however, while cortical disruption and adjacent soft tissue involvement should raise the possibility of low grade osteosarcoma or sarcomatous degenration, soft tissue extension was described in nearly a third of cases of fibrous dysplasia in one series.[15] In rare cases, histopathologic correlation may be necessary to confidently exclude malignancy. Bone scan may demonstrate confluent asymmetric areas of high uptake,[10] and increased activity has also been described on fluorodeoxyglucose position emission tomography (FDG-PET).[11,17]

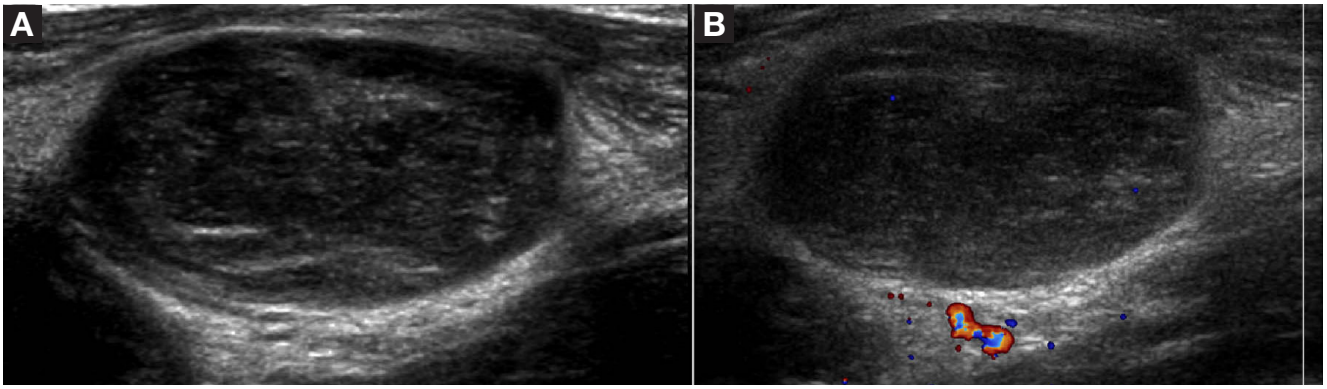

Figure 3: Short axis gray scale (A) and color doppler (B) ultrasound images show a solid circumscribed soft tissue mass within a left hip adductor muscle reflecting a myxoma. The lesion is heterogenously hypoechoic, and demonstrates a relative lack of internal vascularity on color doppler sampling (B).

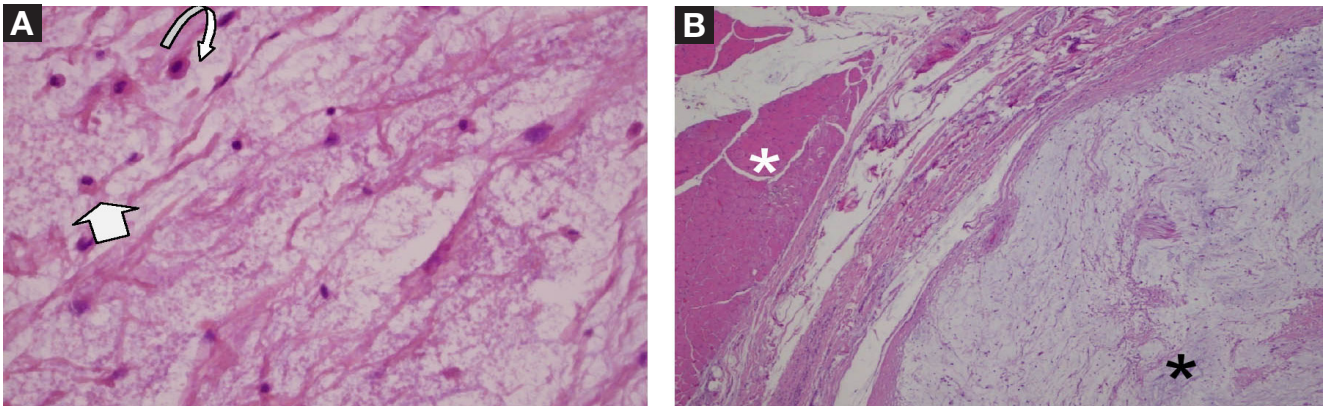

Figure 4. A 40x light microscopy image (A) of a hemotoxylin-eosin stained slide from a resected intramuscular mass in the same patient reveals hypocellular tissue with bland stellate cells (straight arrow) and spindle cells (curved arrow) within a polysaccharide rich myxoid stroma. The appearance is diagnostic of myxoma, confirming the diagnosis of Mazabraud syndrome. At 4x magnification (B), the hypovascular myxoma (black asterisk) has a well-defined border with the adjacent skeletal muscle (white asterisk), corresponding with the pseudocapsules seen on MR.

As fibrous dysplasia commonly affects the femur, it stands to reason that the thigh is the most common location of myxomas in Mazabraud syndrome.[7] On MRI, myxomas typically appear as well defined ovoid intramuscular masses that are low signal intensity on T1, with homogeneous fluid-like signal on T2WI (Figure 2). Myxomas may demonstrate avid heterogeneous enhancement in some cases, reflecting focal areas of hypervascularity, or may contain enhancing fibrous septa within a matrix of non–enhancing solid myxoid tissue.[9,18] Additional specific features of myxoma include a rind of adipose tissue, seen as high signal on T1 weighted images, and hyperintensity on fluid sensitive sequences involving the adjacent muscle, corresponding with reactive muscular atrophy and edema.[18] The masses have an average size of 5 cm and typically do not come into contact with adjacent bone.[18] The tumors are usually hypoattenuating on computed tomography and hypo-echoic on ultrasound (Figure 3). A rind of adipose tissue is often seen and is attributable to atrophy from a slowly expanding mass.[18] Myxomas are hypometabolic and demonstrate lack of activity on PET.[11]

Differential Diagnosis and Pitfalls

Differential diagnostic considerations of myxomatous masses includes sarcoma with myxoid degeneration, particularly liposarcoma.[9,18] Metastatic lesions, lymphoma, peripheral nerve sheath tumors, and degenerating desmoids are other possibilities. Intramuscular lymphoma is rarely focal and usually spans multiple muscle compartments.[19] Metastatic lesions are distinguished by a greater degree of peri-tumoral high signal.[14] The presence of fibrous dysplasia greatly narrows the differential and while biopsy of myxoma is nearly ubiquitous in the literature, Mazabraud syndrome should be a principal consideration in these cases pending histopathologic confirmation (Figure 4).

Due to the rarity of this syndrome, delayed diagnosis and unnecessary biopsy of additionally discovered myxomas is common. Misdiagnosis may lead to the initiation of inappropriate therapy for sarcoma.[9] Management involves continued radiographic and clinical follow-up of fibrous dysplastic lesions, particularly when involving weight-bearing bones. Pain and swelling suggests a complication such as pathologic fracture or

sarcomatous degeneration, the former treated with excision and curettage, as well as fixation in amenable cases. MRI may be particularly useful in the follow-up of treated lesions.[16] Myxomas may grow to enormous sizes and have a propensity to recur.[20] Painful or bothersome masses can be removed with wide excision.

Conclusion

In conclusion, knowledge of the association between fibrous dysplasia and myxomas known as Mazabraud syndrome and the individual radiographic appearances of these entities is important in guiding appropriate management and preventing incorrect or delayed diagnosis.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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