CASE REPORT

Mazabraud's Syndrome: Literature Review and Report of A Case Series.

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Abstract:

Mazabraud's syndrome is a condition that combines fibrous dysplasia with of single or multiple intramuscular myxomas, which etiology remains relatively unknown.

We present three cases of this uncommon disease. All patients received marginal resection of their symptomatic myxomas, with histopathological confirmation of the lesions after surgery and follow-ups of more than one year.

Mazabraud's syndrome corresponds to a very rare disease. The management of these patients should be focused on the treatment of symptoms and avoidance of complications. Fracture risk is to be studied and treated if necessary.

Conclusions:

This disease is probably underestimated. It's important to report cases in order to advance in the knowledge of this syndrome.

Keywords: Mazabraud; Oncology; Fibrous Dysplasia; Myxomas; Intramuscular Tumor;

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Introduction:

The first case of this disease was described in the literature in 1926[1], but it was Mazabraud in 1967 who recognized the association between intramuscular myxomas and fibrous dysplasia[2]. To our knowledge, only 106 cases have been reported in the literature, until 2019[3,4,5,6]. In this syndrome, polyostotic or monostotic fibrous dysplasia[2,3] is associated with single or multiple intramuscular myxomas[7], usually in large muscle groups[8]. It is a condition that is most commonly found in middle-aged women[6].

Case 1:

A 44-year-old woman with no significant medical history who consulted in 2016 for several soft tissue masses in the right thigh and crotch of one-year of evolution. Physical examination showed an indurated mass adhered to deeper planes in the distal and lateral area of the right thigh and in the inguinal fold, currently asymptomatic.

X-ray and MRI of the right lower extremity were performed, showing multiple soft tissue masses consistent with myxomas on the right thigh and fibrous dysplasia in the proximal femurs (Figures 1, 2, and 3).

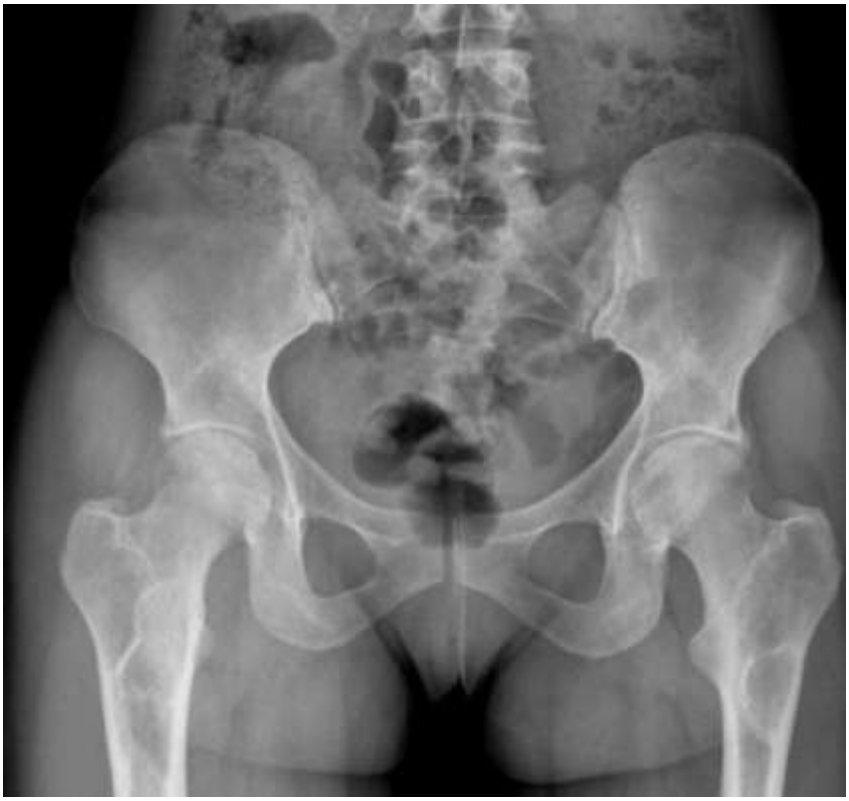

Figure 1: Simple X-Ray AP view showing bilateral fibrous dysplasia in both proximal femurs.

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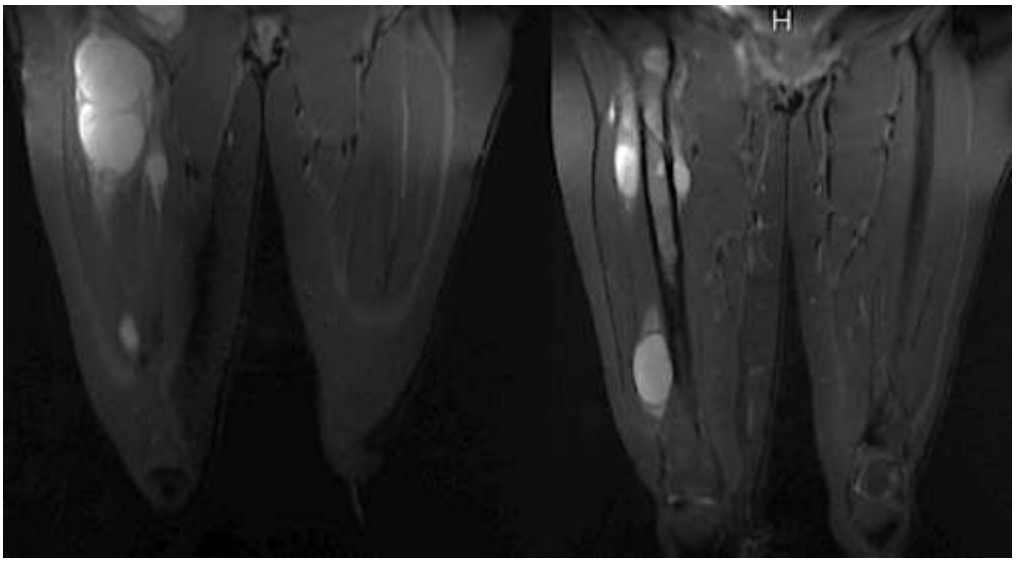

Figure 2: STIR sequence displaying the intramuscular myxomas of the right thigh. Coronal plane.

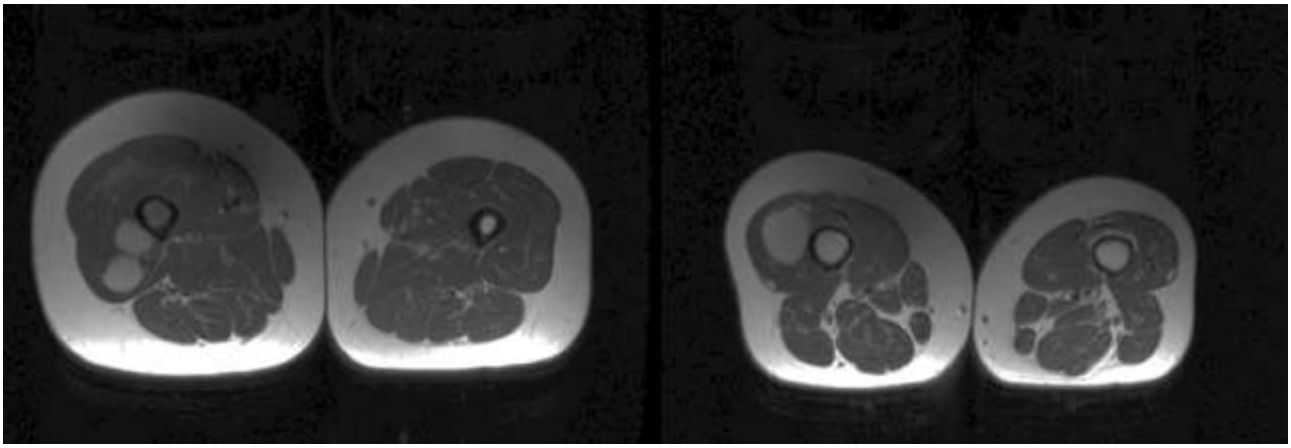

Figure 3: Axial view in T2 sequence of both thighs.

Whole body MRI and bone scintigraphy also showed polyostotic fibrous dysplasia (Figure 4) affecting the right ulna and the left femur. Multiple soft tissue lesions consistent with myxomas were found in the right iliac psoas measuring 7,3 centimeters in diameter, at its insertion in the iliac crest measuring 16,5 x 7,3 cm, in the vastus lateralis of the thigh measuring 11,5 x 6,5 cm, as well as multiple smaller lesions in the anterior, posterior, medial compartment of the thigh, posterior compartment of the leg and on the left biceps. A thoracic-abdominal CT scan showed no sign of widespread disease.

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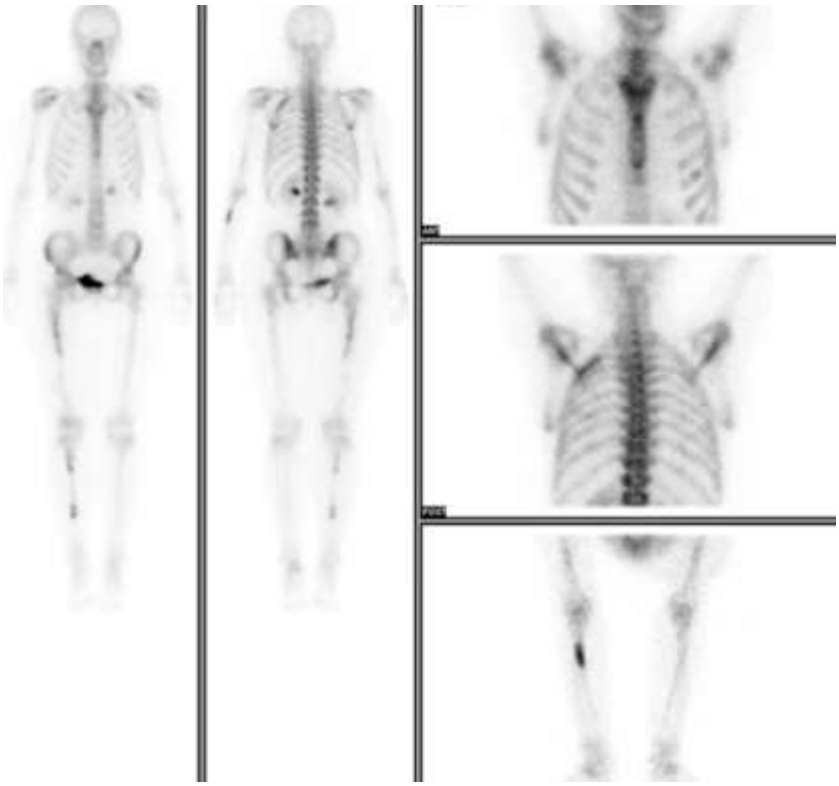

Figure 4: Total bone scintigraphy demonstrating caption in the delayed phase of the polyostotic fibrous dysplasia.

The follow-ups were realized carried out for 15 months from the diagnosis. The patient remained asymptomatic, and no significant increase in the lesion was observed.

Afterwards, the patient consulted for pain in the right thigh after volume increase. A Doppler ultrasound was performed which showed compression of the femoral vein. Consequently, a marginal resection of the multiple myxomas marginal.

(six) was performed in the anterolateral region of the right thigh. Pathological analysis showed a hypocellular and hypovascular mesenchymal tumor composed of uniform smooth spindle cells without atypia embedded in a myxoid stroma. There were no mitosis nor necrosis (Figure 5). Resection of the six intramuscular myxomas was marginal

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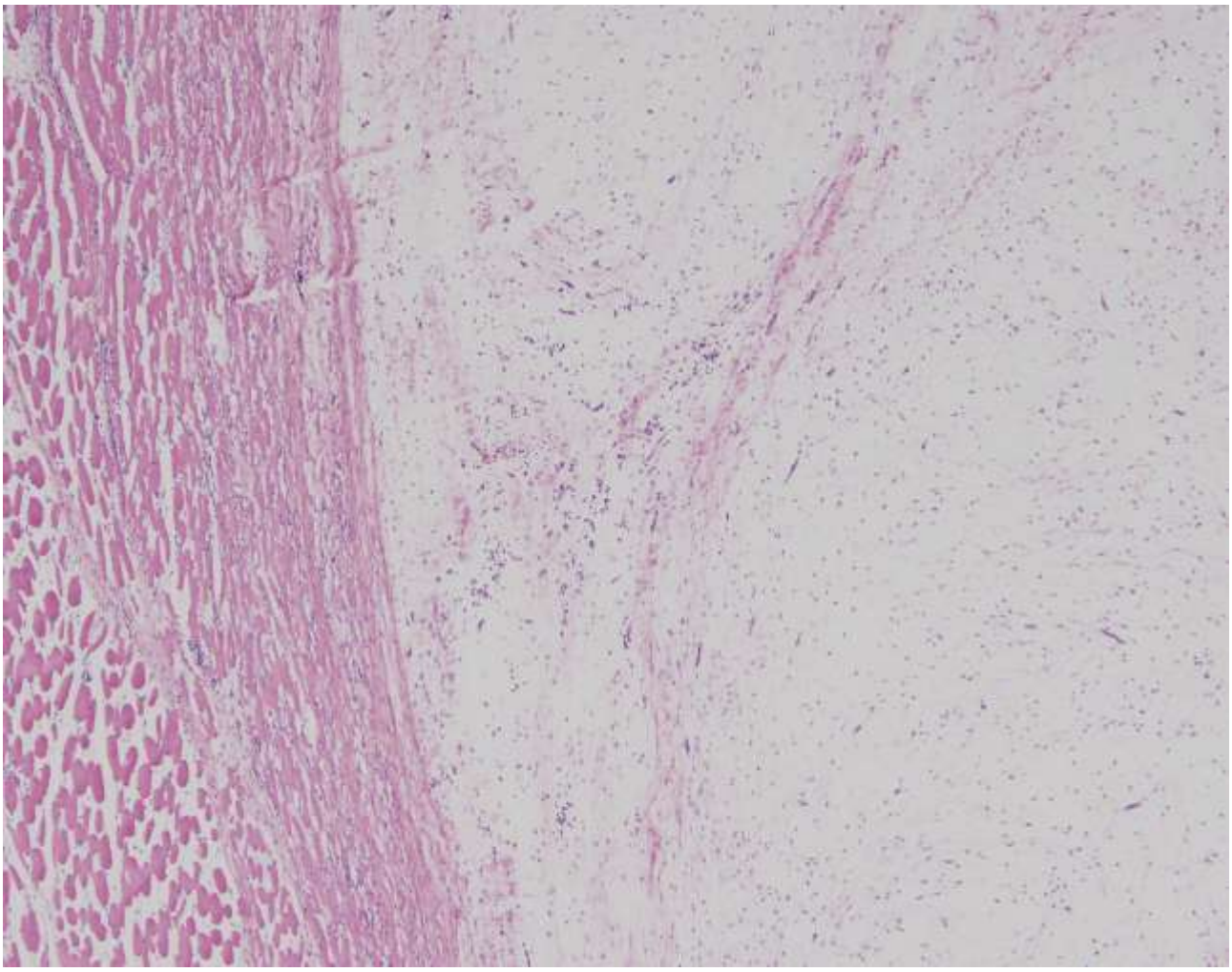

Figure 5: Hematoxylin and eosin stain (10X). An intramuscular and hypoccellular tumor with abundant myxoid stroma is shown. No cytological atypia is witnessed.

The immediate postoperative period evolved satisfactorily. The pain diminished and a normal venous return was observed.

4-months after surgery, MRI showed no variation of the intraosseous lesions of both femurs plus persistence of four myxomas: one in the vastus lateralis measuring 2 x 5 cm, one in the vastus medialis measuring 7,6 x 3 cm, one in the rectus femoris of 0,8 cm and one in the posterior compartment of the leg of 2 cm.

At 10-months checkup, physical examination revealed a new indurated mass in the anterior compartment of the right thigh. MRI showed a slight increase in diameter of the myxomas located in the right thigh but no neurovascular compression. The other lesions remained unchanged, and no new lesions were discovered.

Case 2:

We present the case of a 47-year-old woman who presented cafe-au-lait spots on the neck and asymptomatic polyostotic fibrous dysplasia in the right tibia and humerus. The patient was diagnosed with probable McCune-Albright syndrome. The cafe-au-lait spots spontaneously disappeared in 2015. In the year 2016, the patient was referred for a deep indurated mass measuring 4 x 6 cm in the posterior and proximal area of the right arm. The patient was asymptomatic.

The whole body MRI and bone scintigraphy confirmed polyostotic fibrous dysplasia in the

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right tibia, right humerus, both iliac bones, both femurs and showed a soft tissue lesion in the posterior compartment measuring 5 x 6 cm, within the triceps muscle, with peritumoral edema plus a pseudocapsule, with a stroma of probably myxoid content (Figures 6 and 7). Although the x-rays of the humerus (Figure 8) could suggest an old pathological fracture.

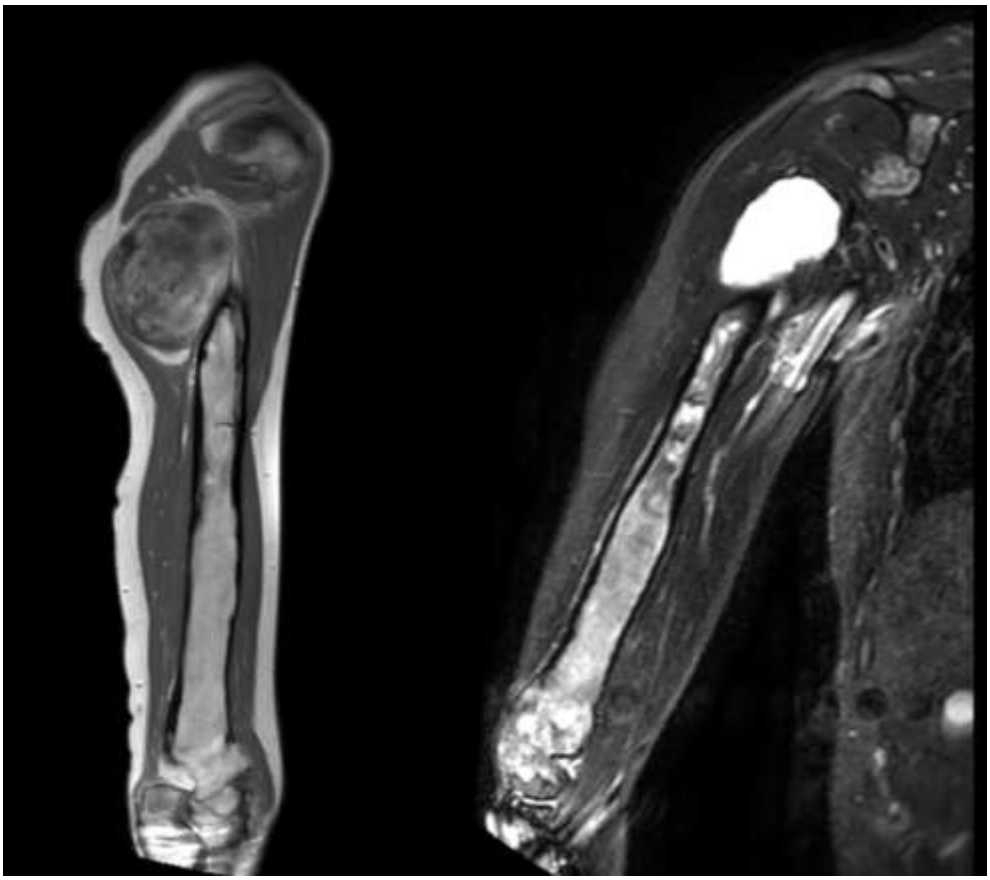

Figure 6: Sagittal T1 view and coronal STIR sequence of the intramuscular myxoma in the triceps muscle.

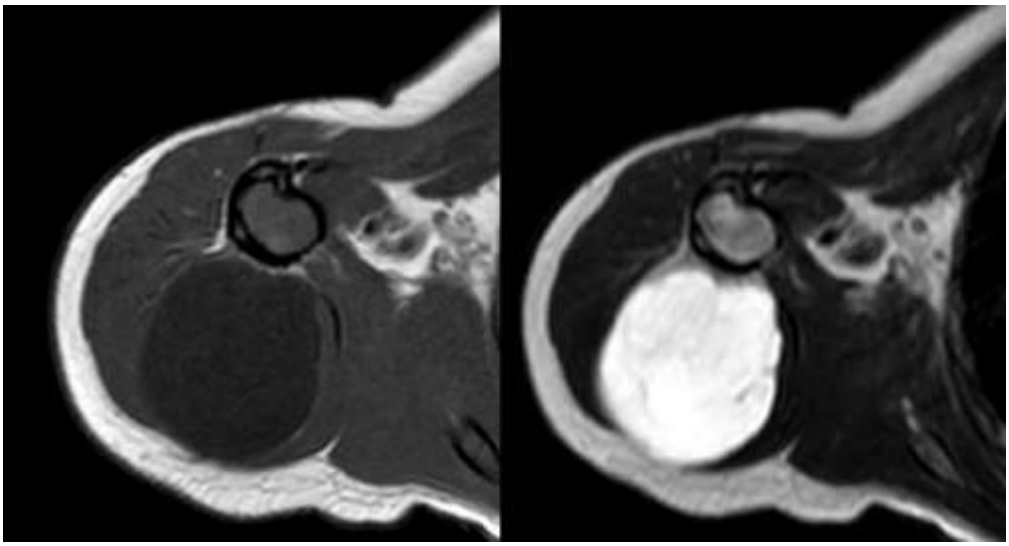

Figure 7: Axial view T1 and T2 sequence of the same lesion, showing peritumoral edema plus pseudocapsule with a high intensity stroma in T2 weighted image (WI) due to the myxoid content.

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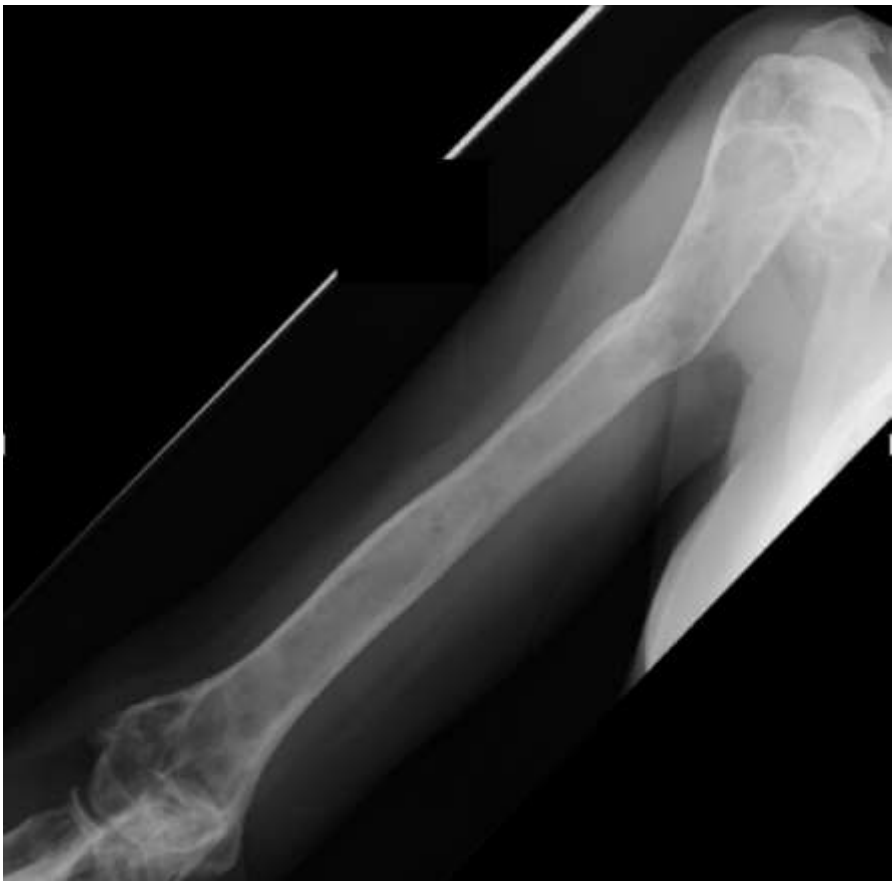

Figure 8: Simple X-Ray showing the typical lytic lesions of fibrous dysplasia in the humerus.

A core needle biopsy of the lesion was performed and the diagnosed of intramuscular myxoma was confirmed.
Surgery was performed in 2017 by marginal resection of the intramuscular myxoma without any complications. Currently, the patient is asymptomatic, and the lesions are unchanged.

Case 3:
An otherwise healthy 50-year-old female was diagnosed with fibrous dysplasia by X-Ray in 2009 as an incidental finding. The study was complemented with a bone scintigraphy and MRI showing the involvement of both proximal femurs. The patient consulted for various soft tissue masses located in the area of the right elbow and shoulder. The MRI of the right elbow performed in 2019 showed a pseudonodular soft tissue mass in the thickness of the supinator muscle of the right elbow measuring 2.6 x 1.8 x 1.9 cm, as well as a solid 2,1 x 1,6 x 3, 4 cm nodular soft tissue lesion in the right deltoid muscle. A core needle biopsy of both soft tissue masses was performed, and the histopathological diagnosis confirmed myxoma (Figures 9 and 10).

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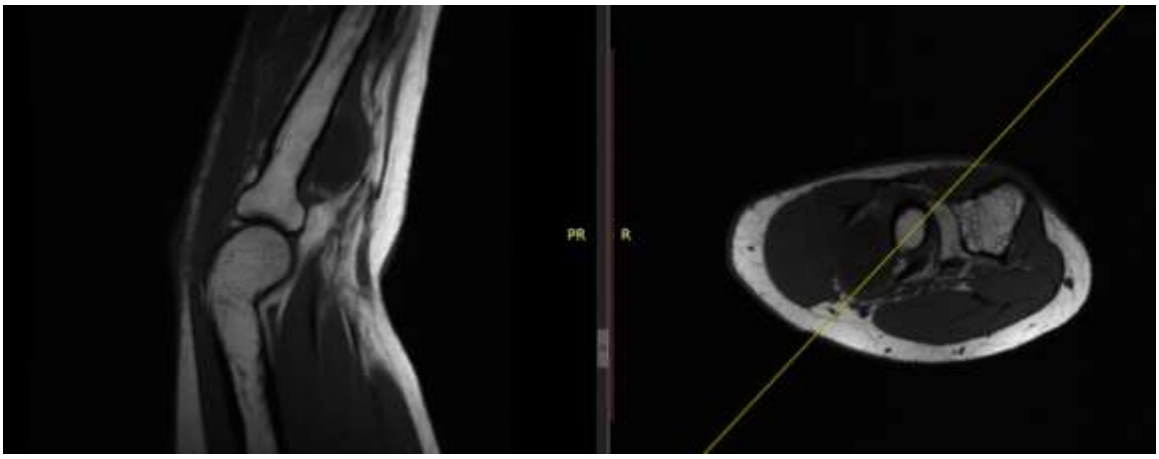

Figure 9: Sagittal and axial T1 sequence of the elbow showing an isointense mass in the supinator muscle.

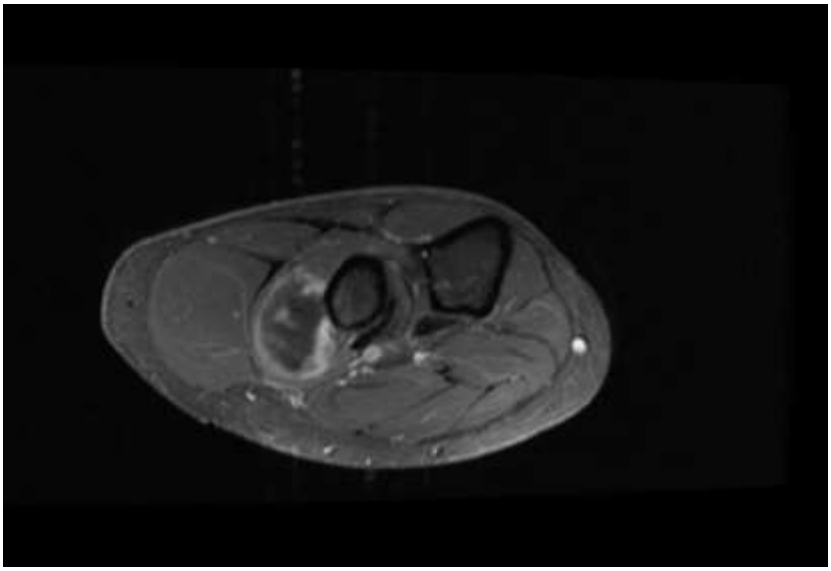

Figure 10: Axial Fat-suppressed gadolinium-enhanced T1 WI of the forearm showing patchy enhancement of the lesion after intravenous contrast (IVC).

The soft tissue mass in the elbow area presented symptoms such as constant pain and paresthesia, for which a marginal resection of the mass was performed with revision of the interosseous nerve and the branches of the radial nerve adjacent to the tumor. No nerve lesion was found at surgery, although the nerves were partially adhered to the mass. A careful resection was performed and the definitive pathological diagnosis confirmed the intramuscular myxoma.

Follow-ups were performed during the 12 months after surgery, during which the patient observed a substantial improvement in paresthesia and pain. The myxoma of the right shoulder was reviewed by an MRI performed in 2019 that shows an intramuscular myxoma measuring 2 x 1,6 x 2,2 cm inside the deltoid muscle (Figure 11).

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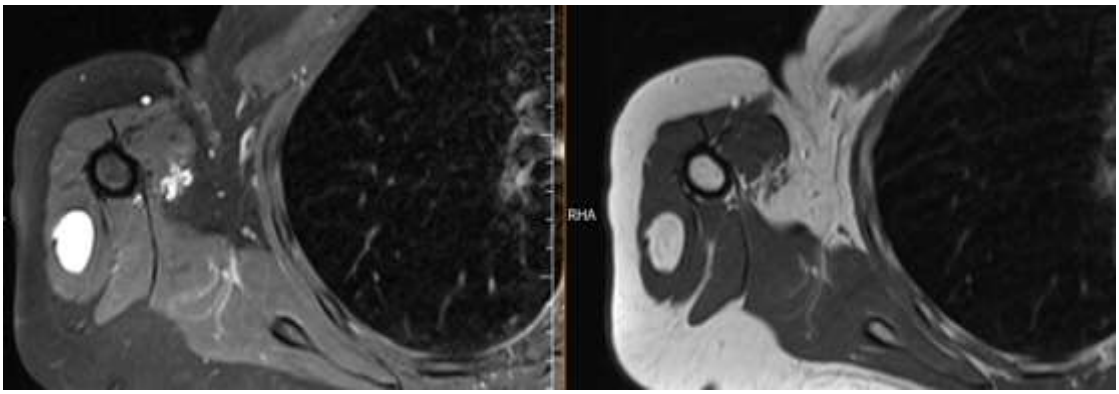

Figure 11: T2 and T1 axial view of the intramuscular myxoma in the deltoid muscle.

In 2020, the follow-up MRI showed an increase in the size of the intramuscular myxoma in the deltoid muscle (Figure 12), and marginal resection of the mass was done.

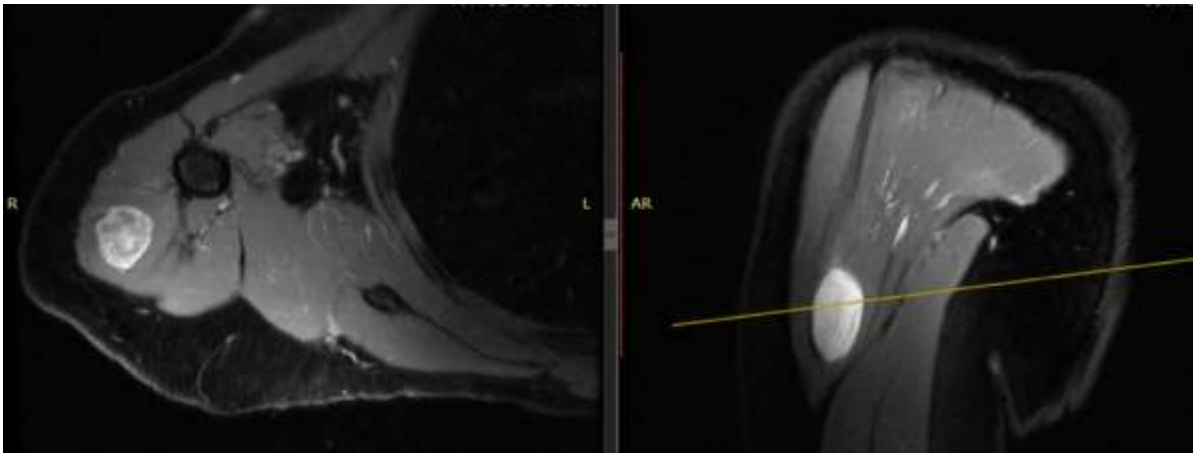

Figure 12: Increase of the diameter of the myxoma can be seen in this coronal and axial T2 sequence views.

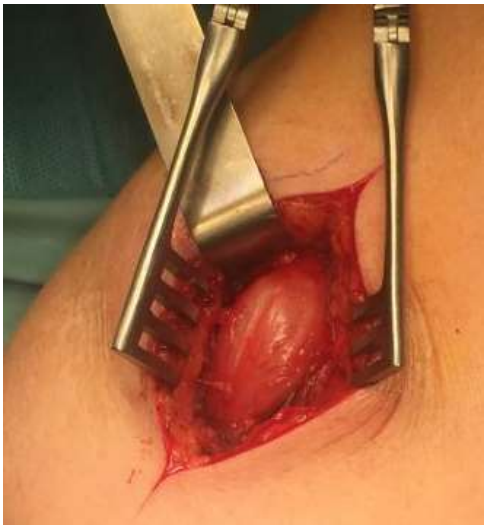

Figure 13: Marginal resection of intramuscular myxoma

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Discussion:

Although the etiology of the disease remains totally unknown, the hypothesis of a genetic origin seems the most likely[9]. Cox et al[10] found that mutations in the GNAS cell proliferation gene are expressed in patients with Mazabraud's syndrome. More precisely, missense mutations at position R201 and position Q221 disrupt the enzymatic activity of GSα, leading to constitutive activation of downstream signaling. Consequently, affected osteoprogenitors produce abnormal woven bone trabeculae within a fibrous stroma that is structurally inadequate and responsible for the characteristic lytic lesions[11,12]. Furthermore, sporadic intramuscular myxomas as well as those associated with fibrous dysplasia present to some degree mutations in *GNAS*[9].

Furthermore a mutation is detected in exons 8 and 9 of the GNAS gene in more than 90% of cases, both sporadic[9] and in those associated with Mazabraud syndrome[10]

Histologically, myxomas are relatively hypocellular with a myxoid matrix and loose reticular fibers. The cells are stellate in shape with small hyperchromatic pyknotic nuclei and scant cytoplasm. Vascular and collagen structures are rare[13].

The cases presented in our article illustrate some average characteristics of this syndrome, such as the clinical presentation: a slow growing painless soft tissue mass[13,14].

It has been reported in the literature that the right side is the most commonly affected[15].

Intramuscular myxomas are most often found on the lower extremities, especially the thighs, but they can also reside in the shoulder and buttock area. Moreover, myxomas are found on the same limb as fibrous dysplasia, as demonstrated by two of the cases presented.

In general, fibrous dysplasia precedes the appearance of intramuscular myxomas, which manifests itself many years later, usually in the fifth or sixth decade of life[15].

The imaging findings in our patients were consistent with previously reported cases. Radiographs showed the distinctive fibrous lesions with the geographic borders and a ground-glass appearance surrounded by condensed bone. MRI shows low signal intensity in T1 sequences but high or mixed intensity in T2-weighted images. On the other hand, myxomas have low signal intensity in T1 and high signal in STIR and T2 sequences. The CT scan can advantage of the degree of bone involvement.

Patients with Mazabraud's syndrome are at increased risk for malignant bone transformation, and rare cases of osteosarcoma and fibrosarcoma developed from fibrous dysplasia lesions have been reported[16, 17, 18, 19]. None of these situations has been detected in our patients.

No reported cases of malignant transformation in intramuscular myxomas have been identified, but high recurrence rate of the benign lesions has been observed in numerous cases[20, 21].

The treatment of Mazabraud's syndrome is variable and depends on the extent of the disease. Due to benign nature of the myxomas, conservative management is indicated, except when symptoms develop, in which case a marginal local excision is usually sufficient. A histopathological histopathological analysis of the lesions should always be carried out to rule out differential diagnoses such as primary malignancy, mainly low-grade myxofibrosarcomas or metastatic tumor[12]. Fibrous dysplasia has a favorable prognosis if the involvement is local and progresses slowly. Its treatment is also conservative and aims to prevent complications[20,21]. In case of severe skeletal deformity and/or high risk of pathological fracture, preventive osteosynthesis is indicated[22]. Bisphosphonate therapy can play an important role in this disease, since they relieve the pain caused by fibrous dysplasia[23]. In a case study, the use of zoledronic acid for 4 years provided a clear reduction of an intramuscular myxoma[24], but its use needs controlled clinical trials to determine if it can really control the progression of the disease.

Conclusion:

This disease is quite rare, but its frequency is probably underestimated. It is important to report these cases to improve our understanding of this

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syndrome. We consider a prolonged follow-up of these patients mandatory. Generally, the management of orthopedic surgeons should be directed to its different components; with regard to fibrous dysplasia, pain can be controlled with both oral analgesics and bisphosphonate. Risk fracture is a condition that must be diagnosed and treated to avoid unnecessary complications. For intramuscular myxomas, a resection should be performed if there are symptoms.

Abbreviations:

CT: Computed Tomography
MRI: Magnetic Resonance Imaging

Statement of informed consent:

All patients were informed and signed the consent concerning that the case would be submitted for publication.

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