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MAZABRAUD SYNDROME: A NARRATIVE REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND ORTHOPEDIC IMPLICATIONS

Yesid Gabriel Castellano Posso MD. Universidad de Cartagena

ABSTRACT Mazabraud syndrome is a rare pathology characterized by the coexistence of fibrous dysplasia and intramuscular myxomas, driven by a somatic GNAS gene mutation. This narrative review provides a comprehensive overview of its pathophysiology, diagnosis, and orthopedic implications. We synthesize current literature on the genetic basis of the disease, the role of advanced imaging for accurate diagnosis, and the complexities of orthopedic management. The review highlights the importance of a multidisciplinary approach to address musculoskeletal manifestations, prevent pathological fractures, and guide both conservative and surgical strategies for this unique pathology.

KEYWORDS : Mazabraud Syndrome; Fibrous Dysplasia, Polyostotic; Myxoma.

INTRODUCTION

Mazabraud syndrome is a rare and complex condition characterized by the coexistence of fibrous dysplasia (FD) and intramuscular myxomas (1). First described in 1957, it presents a unique challenge for clinicians due to its variable clinical manifestations and potential for misdiagnosis. While FD is a well-understood benign bone disorder, the pathogenesis of the associated soft tissue myxomas and their relationship to FD remains a subject of ongoing research (2). This narrative review aims to provide a comprehensive overview of Mazabraud syndrome, focusing on its underlying pathophysiology, diagnostic strategies, and, most importantly, its significant orthopedic implications.

METHODS

A narrative review was conducted to synthesize the available literature on Mazabraud syndrome. The bibliographic search was performed across four main databases (PubMed, Scopus, Web of Science, and LILACS) using specific keywords such as "Mazabraud syndrome," "fibrous dysplasia," and "intramuscular myxoma" to maximize result relevance. Following a thorough review of titles and abstracts, selection criteria were applied to identify the most pertinent articles. Ultimately, 15 studies were included for a detailed qualitative analysis, providing a comprehensive and contextualized view of the pathology without statistical analysis.

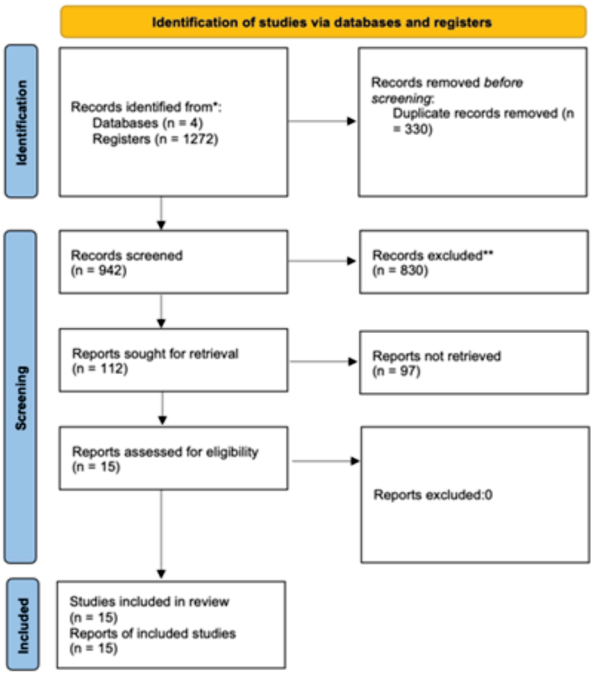

Figure. PRISMA.

Pathophysiology

The pathophysiology of Mazabraud syndrome is fundamentally rooted in a somatic activating mutation of the GNAS gene, located on chromosome 20q13.2 (3). This genetic defect results in the constitutive activation of the Gsα protein, leading to an overproduction of cyclic adenosine monophosphate (cAMP) within affected cells. This aberrant signaling pathway is the central mechanism driving both components of the syndrome: fibrous dysplasia (FD) and intramuscular myxomas.

In fibrous dysplasia, the GNAS mutation disrupts the normal differentiation and proliferation of osteoblasts (4). This leads to the replacement of normal bone marrow with disorganized fibro-osseous tissue, characterized histologically by woven bone trabeculae set in a fibrous stroma. This abnormal bone tissue is prone to expansion, causing skeletal deformities, pain, and an increased risk of pathological fractures. The clinical presentation of FD in Mazabraud syndrome can be monostotic or polyostotic, with the latter being more common and often more severe.

Simultaneously, the same GNAS mutation is believed to be responsible for the development of the intramuscular myxomas (5). While the exact mechanism is less understood than in FD, it is hypothesized that the sustained increase in cAMP levels drives the proliferation and differentiation of mesenchymal stem cells towards a myxoid phenotype. These lesions are typically benign, well-circumscribed, and located within the deep fascia and skeletal muscle. The synchronous or metachronous development of these distinct pathologies from a common genetic origin underscores the systemic nature of the syndrome and its unique pathological signature, distinguishing it from isolated FD or solitary myxomas.

Diagnosis

The diagnosis of Mazabraud syndrome is often challenging due to its rarity and variable presentation, requiring a multidisciplinary approach that integrates clinical evaluation, advanced imaging, and histopathological confirmation. The key to diagnosis is the synchronous or metachronous co-occurrence of fibrous dysplasia (FD) and at least one intramuscular myxoma.

Imaging Techniques

The diagnostic journey typically begins with imaging. Plain radiographs are the cornerstone for evaluating the bone lesions of fibrous dysplasia. These images classically reveal a "ground-glass" or "smoky" appearance within the affected bone, which is caused by the disorganized woven bone and fibrous tissue. Other radiographic findings include cortical thinning, endosteal scalloping, and a variable degree of bone expansion. While X-rays are excellent for identifying the bony component, they are limited in their ability to visualize soft-tissue masses.

Magnetic Resonance Imaging (MRI) is the gold standard for the comprehensive evaluation of both components of the syndrome. For the myxomas, MRI provides crucial details about their size, location, and relationship to surrounding neurovascular structures. On MRI, intramuscular myxomas typically appear as well-defined, lobulated masses that are isointense to muscle on T1-weighted images and markedly hyperintense on T2-weighted images (6). A characteristic finding is a T2-hyperintense peripheral rim or "rind" and sometimes a central cystic or low-signal area. Contrast-enhanced MRI may show a "lace-like" or heterogeneous pattern of enhancement. The simultaneous visualization of the classic FD bone lesions alongside the characteristic soft-tissue myxomas on the same MRI study is highly suggestive of Mazabraud syndrome. Computed Tomography (CT) scans can also be used, particularly for bony lesions, offering superior detail regarding cortical integrity and medullary involvement, which is essential for pre-operative planning.

Histopathological and Molecular Confirmation

A definitive diagnosis often requires a tissue biopsy of one or both lesions. Biopsy of the fibrous dysplasia lesion reveals a fibrous stroma containing irregularly shaped, spicule-like trabeculae of woven bone, often described as having a "Chinese character" morphology (7). It is crucial to rule out other bone tumors, such as osteosarcoma, which can rarely arise within FD. Biopsy of the intramuscular myxoma reveals a hypocellular tumor composed of bland, stellate-shaped fibroblasts within an abundant myxoid stroma, rich in hyaluronic acid (8). The low cellularity and lack of significant mitotic activity help differentiate it from malignant myxoid tumors. Given the established genetic link, molecular testing can be invaluable. The identification of a somatic GNAS gene mutation in either the fibrous dysplasia tissue or the myxoma confirms the diagnosis and distinguishes it from other similar conditions (9). This is particularly useful in cases with ambiguous clinical or histopathological findings. The differential diagnosis for Mazabraud syndrome includes isolated fibrous dysplasia, McCune-Albright syndrome, and other conditions presenting with myxoid soft tissue tumors.

Orthopedic Implications

The orthopedic implications of Mazabraud syndrome are the most significant clinical features of the condition, predominantly stemming from the presence of fibrous dysplasia (FD). The musculoskeletal manifestations, potential complications, and management strategies require a careful and often multidisciplinary approach, balancing conservative care with surgical intervention.

Musculoskeletal Manifestations and Complications

The most common orthopedic manifestation is pain, typically a dull, aching sensation at the site of the FD lesion. This pain can be a result of microfractures, bone expansion, or mechanical stress on the weakened bone. Skeletal deformities are also a hallmark of polyostotic FD. The abnormal, structurally compromised bone tissue is susceptible to stress, leading to bowing of long bones, particularly the "shepherd's crook" deformity of the proximal femur (10). Other common deformities include scoliosis, facial asymmetry, and leg length discrepancies, all of which can significantly impair function and mobility.

A major concern is the high risk of pathological fractures. The dysplastic bone's poor structural integrity makes it unable to withstand normal physiological stresses, leading to fractures with minimal or no trauma. The femur, tibia, and humerus are particularly vulnerable.

While rare, malignant transformation of fibrous dysplasia is a serious and potentially life-threatening complication. The incidence of this event is estimated to be less than 1%, but it is a critical consideration in long-term management (11). Any sudden increase in pain, rapid swelling, or radiographic changes suggesting cortical destruction or a soft tissue mass should raise suspicion of malignant transformation, prompting immediate investigation with biopsy. Osteosarcoma is the most frequent type of secondary malignancy, but fibrosarcoma and chondrosarcoma have also been reported.

Finally, while typically benign, the intramuscular myxomas can also contribute to orthopedic morbidity. Although they often remain asymptomatic, their growth can cause local pain, swelling, or mass effect, leading to nerve compression or compromised muscle function.

Management Strategies

The management of Mazabraud syndrome is highly individualized, depending on the extent of the disease, the patient's age, and the presence of symptoms or complications. Both non-surgical and surgical approaches are utilized.

Non-Surgical Management

For patients with mild pain and stable lesions, a conservative approach is often preferred. This includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain control and activity modification to avoid stress on affected bones. Bisphosphonates have emerged as a key pharmacological treatment for the bone pain associated with FD. These drugs inhibit osteoclast activity, reducing bone resorption and potentially decreasing pain and fracture rates (12). However, their effect on correcting existing deformities or preventing their progression is not well-established. Physical therapy is also a vital component of non-surgical care, helping to maintain range of motion, muscle strength, and functional independence, especially for patients with significant deformities.

Surgical Management

Surgical intervention is indicated for specific complications or to prevent them. The primary indications include:

- Prophylactic fixation of a bone at high risk of fracture (e.g., the femur with a "shepherd's crook" deformity).
- Surgical stabilization of a pathological fracture.
- Correction of a significant deformity that causes pain or functional impairment.
- Excision of a myxoma causing symptomatic mass effect or for diagnostic purposes.

For fibrous dysplasia, common surgical procedures include curettage and bone grafting (13). Due to the high recurrence rate of FD, curettage alone is often insufficient, and it is typically combined with bone grafting (using autograft, allograft, or bone graft substitutes) and internal fixation with plates, rods, or intramedullary nails to provide structural support. Osteotomies are performed to correct significant bowing or angular deformities.

For symptomatic intramuscular myxomas, complete surgical excision is the treatment of choice. These tumors are generally well-encapsulated and do not infiltrate surrounding tissue, making a marginal or wide local excision with clear margins a curative procedure with a very low risk of recurrence (14).

Surgical management, however, is not without its challenges. The dysplastic bone tissue has poor mechanical properties and can have impaired healing, increasing the risk of non-union or implant failure. Furthermore, the progressive nature of the underlying FD can lead to a recurrence of deformity or fracture despite surgical correction. Therefore, long-term radiographic and clinical follow-up is essential for all patients to monitor for disease progression, detect complications, and guide future management (15).

In conclusion, Mazabraud syndrome is a rare pathology

requiring a multidisciplinary approach. Its diagnosis relies on the coexistence of fibrous dysplasia and intramuscular myxomas. Management, which ranges from conservative options to complex surgical interventions, necessitates long-term follow-up for its diverse musculoskeletal manifestations.

REFERENCES

1. Gagliano A, Zoccali C, Calabrò G, Massari L. Mazabraud's syndrome: a systematic review and meta-analysis. Orthop Rev (Pavia). 2021;13(2):8918.
2. Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the Gs alpha-subunit gene in Mazabraud's syndrome. J Clin Endocrinol Metab. 1996;81(5):1848-1852.
3. DiCaprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am. 2005;87(8):1848-1864.
4. Chapurlat RD. Bisphosphonates in fibrous dysplasia. Bone. 2013;53(2):332-334.
5. Ozkan F, Dogan O, Sahin Z, et al. Mazabraud's syndrome: a case report and review of the literature. J Bone Joint Surg Am. 2006;88(1):162-166.
6. Chapurlat RD, Pinedo-Villanueva R, Gatti D, et al. Therapeutic options for fibrous dysplasia of bone. Bone. 2020;140:115502.
7. Wenz W, Scheil-Bertram S, Pfitzner D, et al. Intramuscular myxoma. A clinicoradiologic study. Orthopade. 1999;28(9):773-779.
8. Hoshi M, et al. Malignant transformation in fibrous dysplasia of bone: A report of two cases and a review of the literature. J Orthop Sci. 2005;10(1):108-111.
9. Li T, Gao J, Ma C, et al. Intramuscular myxoma and fibrous dysplasia (Mazabraud's syndrome). Arch Orthop Trauma Surg. 2019;139(2):169-176.
10. Unni KK, Inwards CY. Dahlin's Bone Tumors: General Aspects and Data on 10,165 Cases. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
11. Kumar R, Gupta A. Mazabraud's syndrome. Indian J Dermatol. 2012;57(5):400-401.
12. Vanhoenacker FM, Van der Woude H, De Praeter G, et al. Intramuscular myxoma: an imaging study of 36 patients. JBR-BTR. 2005;88(3):149-155.
13. Stanton RP. Fibrous Dysplasia of Bone: A Review. J Orthop Res. 2012;30(6):951-955.
14. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. World Health Organization Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC Press; 2013.
15. Manjila S, et al. Mazabraud's syndrome: a systematic review of the literature. Neurosurgery. 2012;71(5):989-1002.