Myositis Ossificans Mimicking Osteosarcoma: Case Report

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Miosite Ossificante Mimetizando Osteossarcoma: Relato de Caso

Miositis Osificante que Simula un Osteosarcoma: Informe de Caso

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ABSTRACT

Introduction: Myositis ossificans is a benign, self-limiting condition characterized by heterotopic bone formation in skeletal muscles or other extra-skeletal soft tissue sites. It is most common in physically active adolescents and young adults. Its incidence is related to trauma, but it can be triggered by systemic diseases or be idiopathic**. Case report:** A 48-year-old female patient was investigated due to a 2.5-cm soft tissue lesion on the right thigh after tomography, with ill-defined edges, described as suspicious for neoplasia, submitted to biopsy and sent to the pathology laboratory. The sample was included for microscopic analysis, consisting of a spindle cell component showing atypia, without mitoses, and arranged in bundles. The presence of smaller quantities of osteoclasts surrounding the osteoid-like material was described. The material was also subjected to immunohistochemistry. The findings favored the diagnosis of osteosarcoma. In a later anatomopathological review, including a molecular study of the USP6 gene, it was concluded that it was myositis ossificans mimicking osteosarcoma. **Conclusion**: The differential diagnosis between osteosarcoma and myositis ossificans can be challenging due to the radiological and clinical similarities between these conditions. In the case reported, a 48-year-old female patient was diagnosed with osteosarcoma, but after re-evaluation, the diagnosis was myositis ossificans. This finding highlights the importance of correlating clinical and morphological findings with molecular biology analyses for accurate characterization of the lesion, ensuring appropriate management and avoiding unnecessary treatments for the patients.

Key words: Myositis Ossificans/diagnosis; Osteosarcoma/diagnosis; Diagnosis, Differential; Case Reports.

RESUMO

Introdução: A miosite ossificante é uma condição benigna e autolimitada caracterizada pela formação óssea heterotópica nos músculos esqueléticos ou em outros locais de tecidos moles extraesqueléticos. É mais comum em adolescentes e adultos jovens fisicamente ativos. Sua incidência está relacionada com o trauma, mas pode ser desencadeada por doenças sistêmicas ou ser idiopática. **Relato do caso:** Paciente do sexo feminino, 48 anos, em investigação de lesão de partes moles da coxa direita, medindo 2,5 cm ao exame tomográfico, bordas mal definidas, descrita como suspeita para neoplasia, que foi submetida à biopsia e enviada a um laboratório de patologia. A amostra foi incluída para análise microscópica, sendo constituída por componente celular fusiforme exibindo atipia, sem mitoses, e com disposição em feixes. Foi descrita a presença de osteoclastos em menor quantidade, circundando o material semelhante ao osteoide. Além disso, o material foi submetido à técnica de imuno-histoquímica. Os achados favoreceram o diagnóstico de osteossarcoma. Em revisão anatomopatológica, realizada posteriormente, e incluindo estudo molecular do gene USP6, concluiu-se que se tratava de miosite ossificante mimetizando osteossarcoma. **Conclusão:** O diagnóstico diferencial entre osteossarcoma e miosite ossificante pode ser desafiador em virtude das semelhanças radiológicas e clínicas entre essas condições. No caso relatado, uma paciente feminina de 48 anos foi diagnosticada com osteossarcoma, porém, após reavaliação, o diagnóstico foi de miosite ossificante. Esse achado ressalta a importância da correlação entre achados clínicos, morfológicos e análises de biologia molecular para uma caracterização precisa da lesão, garantindo manejo adequado e evitando tratamentos desnecessários aos pacientes.

Palavras-chave: Miosite Ossificante/diagnóstico; Osteossarcoma/diagnóstico; Diagnóstico Diferencial; Relatos de Casos.

RESUMEN

Introducción: La miositis osificante es una enfermedad benigna y autolimitada que se caracteriza por la formación de hueso heterotópico en los músculos esqueléticos u otros sitios de tejido blando extraesquelético. Es más común en adolescentes y adultos jóvenes físicamente activos. Su incidencia está relacionada con traumatismos, pero puede desencadenarse por enfermedades sistémicas o ser idiopática. **Informe del caso:** Paciente femenina de 48 años de edad que fue investigada por una lesión de tejido blando en el muslo derecho, que medía 2,5 cm en el examen tomográfico, con bordes mal definidos, descrita como sospechosa de neoplasia, que se sometió a biopsia y se envió al laboratorio de patología. La muestra se incluyó para análisis microscópico, consistente en un componente de células fusiformes que mostraba atipia, sin mitosis y dispuestas en haces. Se describió la presencia de osteoclastos en cantidades menores, rodeando el material de aspecto osteoide. El material también fue sometido a inmunohistoquímica. Los hallazgos favorecieron el diagnóstico de osteosarcoma. En una revisión anatomopatológica posterior, que incluyó un estudio molecular del gen USP6, se concluyó que se trataba de una miositis osificante que imitaba un osteosarcoma. **Conclusión:** El diagnóstico diferencial entre osteosarcoma y miositis osificante puede ser complejo debido a las similitudes radiológicas y clínicas entre estas afecciones. En el caso reportado, una paciente de 48 años fue diagnosticada con osteosarcoma, pero tras una reevaluación, el diagnóstico fue miositis osificante. Este hallazgo resalta la importancia de correlacionar los hallazgos clínicos y morfológicos con los análisis de biología molecular para una caracterización precisa de la lesión, garantizar un manejo adecuado y evitar tratamientos innecesarios para los pacientes.

Palabras clave: Miositis Osificante/diagnóstico; Osteosarcoma/diagnóstico; Diagnóstico Diferencial; Informes de Casos.

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INTRODUCTION

Myositis ossificans is a benign and self-limiting condition characterized by heterotopic bone formation in skeletal muscles or in other sites with extraskeletal soft tissues. It is a condition that can develop at any age, however, it is most commonly seen in physically active men, adolescents and young adults. Its incidence is related to trauma, but can be triggered by systemic or idiopathic diseases, the most common are brachial, deltoid, quadriceps and adductor muscles although there are others reported in intercostal, and abdominal muscles, head, hand, feet and neck[1-3].

Patients complaining of pain, swelling, edema in superficial lesions, cough, and asymptomatic in addition to muscular rigidity in up to 20% of the cases are the common clinical conditions. Compression of neurologic structures leading to weakness, paresthesia, lymphedema or even venous thrombosis can occur as well. The typical lesion is a fast-growing mass, consolidated after two to three months, and reduced symptoms before a possible solution appears. Diagnostic imaging as magnetic resonance with angiography, computed tomography and ultrasound can be required, especially in intermediate and late stages of myositis ossificans. Whether typical zonal standard occurs, biopsy can be avoided, because it may be misleading, prompting differential diagnoses, particularly osteosarcoma[2,4].

The definitive diagnosis of myositis ossificans can only be determined after the exclusion of malignancies. Other diagnostic methods include biopsy, immunohistochemistry and clinical data of the patient. The final diagnosis, it must be said, is the sum of all these components. The treatment includes anti-inflammatory and physiotherapy for early lesions and surgical resection of advanced cases[2].

The objective of this article is to report a case of myositis ossificans initially diagnosed as extraskeletal osteosarcoma, highlighting histopathology, immunohistochemical and molecular characteristics that support this definition, in addition to underpinning the importance of the analysis of histopathological blades in situations of diagnostic discordance.

The Ethics Committee of "*Hospital Nossa Senhora das Graças*" approved the study, report number 7,538,343 (CAAE (submission for ethical review): 87465225.7.0000.0269) in compliance with Law 14,874[5] dated May 28, 2024.

CASE REPORT

Female, 48-old patient, healthy, submitted to hysterectomy in May 2020 due to uterine myomatosis, non-smoker or non-alcohol user, without family history of neoplasms of soft parts. In November 2024, noticed discreet and painless volume on the anterior side of the right thigh and reported sensation of local weight. Evolved with intermittent pain, no fever, weight loss or other systemic symptoms. At physical examination, presented approximately 3-cm palpable firm node, not-adhered to deep planes, discreet sensitiveness at palpation, no phlogistic signals. Preserved peripheral pulses and mobility maintained.

After one month, computed tomography of lower limbs revealed lesion of soft parts at the anterior side of the right thigh, measuring 2.5 cm in its largest diameter, ill-defined margins, heterogeneous attenuation and slight and irregular enhancement after contrast and absence of calcifications or bone erosion. The aspect was suspicious for soft parts neoplasm, ultrasound-guided core needle biopsy was performed without complications. The fragments were histopathologically analyzed by external laboratory. The sample was fully included for microscopic analysis, consisting in spindle-cell cellular component, exhibiting discreet atypia, without mitosis and arranged in bundles. Small quantity of osteoclasts was described surrounding osteoid-like material.

Complementary immunohistochemistry exam revealed negativity for epithelial membrane antigen (EMA), S100, CD34, pancytokeratin (Pan CK), CD117, beta catenin and caldesmon. TLE-1 focal positive and diffuse STAB2. Still, reacted to CD68 in multinucleated giant cells and others fusiform. Ki-67 proliferation index was estimated in approximately 40%. The conclusive report indicated that the findings of immunohistochemistry together with clinical and anatomopathological characteristics favored the diagnosis of extraskeletal osteosarcoma, being recommended resection of the lesion with safety margins for better histopathological analysis and definitive evaluation.

The patient was submitted to staging exams – computed tomography of the thorax, abdomen and pelvis and bone scintigraphy –, all negative for secondary lesions. After the diagnosis, was referred to expert oncologic orthopedist at her hometown. Given the condition and the necessity of surgical treatment, expanded resection of the lesion at the right thigh with safety margins was indicated, a procedure that could entail local deformity and reduction of mobility. Prior to any further procedure, the orthopedist opted for reviewing the case, raising the hypothesis of differential diagnosis of myositis ossificans. Histologic, immunohistochemistry blades and paraffin blocks of biopsy were obtained and sent to another pathology laboratory to be reviewed by expert pathology physician specialized in soft parts.

A novel histopathological analysis described a tumor formed by fusocellular proliferation pattern of discreet polymorphism, containing multinucleated giant cells, foci of blood cells extravasation and areas of osteoid formation (Figure 1). There were no foci of necrosis, low mitosis index (1 mitosis/10 high power fields), not being identified atypical mitosis.

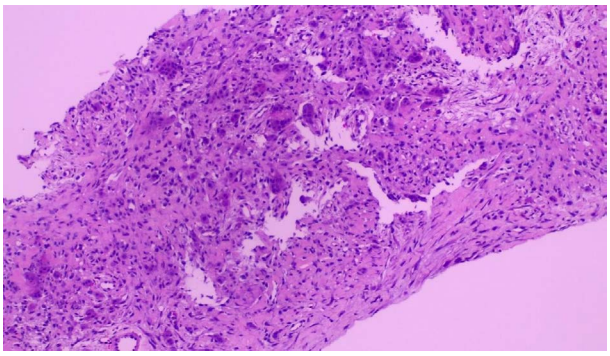

Figure 1. Fusocellular proliferation pattern containing multinucleated giant cells (optical microscopy, eosin-hematoxylin, 100x).

Cells of interest at complementary immunohistochemistry analysis were positive for SATB2 (Figure 2A), CD68 (Figure 2B), weak coloration and cytoplasmatic for beta catenin and TLE1 in rare cells and negative for EMA, S100, CD34, Pan CK, CD117 and caldesmon. Ki-67 proliferation index was estimated in approximately 12%.

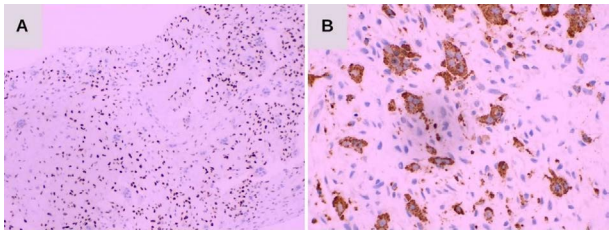

Figure 2. A: Positivity for STAB2 in fusocellular cells (optical microscopy, immunohistochemistry, 40X); B: Positivity for CD68 (optical microscopy, immunohistochemistry, 200X).

After reviewing the case, the histology and immunohistochemical profile observed suggested the possibility of myositis ossificans, although it was not possible to evaluate the lesion zone due to the type of needle biopsy. The age of the patient, absence of pleomorphism, hyperchromasia and atypical mitosis reinforce this diagnostic hypothesis.

Based on this hypothesis, molecular investigation to detect USP6 gene rearrangement, commonly found in cases of myositis ossificans, was recommended. Additionally, a molecular study based on a fluorescence in situ hybridization (FISH) technique was performed to investigate the gene USP6 (ubiquitin protease 6), that codifies the protein of the family of deubiquitylation enzymes. After deparaffination, digestion and pre-treatment of the material, the tissue was incubated with separation probe ZytoLight SPEC USP6 Dual Color Break Apart Probe (Zytovision), that contains a mix of probes identified as ZyOrange and ZyGreen that hybridize in the proximal and distal locus of the gene USP6 (17p13.2), respectively. The test evaluated 869 cells in all and was positive for translocation of the gene USP6 (Figure 3).

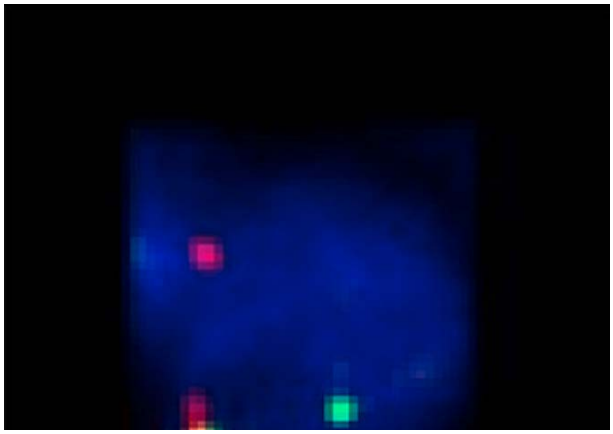

Figure 3. FISH positive (> 10% of the cells) for translocation of the gene USP6 (17p13.2).
Note: Quantitative morphometric analysis was performed by image analysis system Metasystems Metafer attached to a fluorescence microscopy Zeiss Axio Imager M1. Due to its capacity of analyzing tridimensional distances between signs, gene separations can be detected in areas of interest selected by the pathologist.

Due to the location (mobility of the right lower limb preserved yet), severity of the symptoms (the patient reported mild pain), conservative treatment was selected, including rest, elevation and immobilization to minimize additional trauma and promote spontaneous resolution of the ossification. Range of motion and resistance exercises were recommended for better recovery of the muscle and articular function.

The patient was in specialized follow-up for six months, with less pain but few changes on the right thigh lesion according to the imaging exams. In case of significant pain, muscle weakness or loss of movement, surgery can be indicated to remove the bone mass without safety surgical margins, circumventing extended exeresis.

DISCUSSION

Myositis ossificans is a benign, non-neoplastic, heterotopic ossifying process that is generally solitary,

well-encapsulated and circumscribed. It is commonly seen in the skeletal muscles but can also occur in tendons and subcutaneous fat. It is rare in infants and older adults, and most common in men[2,3].

The physiopathology of myositis ossificans is not fully understood. One of the hypothesis is that the initial trauma triggers an inflammatory cascade in skeletal muscles and cytokines release. These cytokines act on vascular endothelial cells causing the mesenchymal--endothelial transition. Endothelial-derived mesenchymal stem-cells differentiate in chondrocytes or osteoblasts which, in the final phase, form extraskeletal bone. Therefore, histological alterations occur on the affected tissue where a major non-ossified central core of proliferating fibroblasts and myofibroblasts accompanied by a minor component of osteoid and peripheral mature lamellar bone at the periphery can be seen in the early stage. In the intermediate stage, almost entirely osteoid component is rimmed by a shell of mature lamellar bone. The late stage is characterized by the typical zonal pattern with an innermost area made of proliferating fibroblasts and myofibroblasts, an intermediate zone which contains osteoblasts with immature osteoid formation and peripheral zone of mature bone[2,4].

The diagnosis can be made my imaging exams, the main are plain films usually normal in initial phase, showing opacity of soft tissues displacing fat planes. In intermediate and mature stages, progressive peripheral calcifications develop. Ultrasound can detect the characteristic "zonal pattern" earlier but its interpretation depends on the experience of the operator. Computed tomography may identify early calcifications and distinguish myositis ossificans from other bone lesions. Magnetic resonance is the technique of choice to evaluate lesions of soft tissues. However, in initial phase, myositis ossificans can mimic soft tissue sarcoma[4].

Regarding histopathological findings in diagnostic biopsies, myositis ossificans presents a characteristic organization with a core zone formed by fusiform cells (fibroblasts and myofibroblasts) arranged in short fascicular patterns rounded by collagenous and loose stroma, an intermediate zone exhibiting immature bone trabeculae rimmed by active osteoblasts and a peripheral bone mature and lamellar zone, frequently associated with foci of cartilage in endochondral ossification. Therefore, the progressive "zonal pattern" from periphery to the core is the diagnosis for myositis ossificans[2,4,6].

The definitive diagnosis of the case reported was based on immunohistochemistry for EMA, S100, CD34, Pan CK, CD117, beta catenin, caldesmon, TLE-1 and STAB2, in addition to Ki-67, which indicates proliferation index. The major suspicion was of a differential diagnosis of myositis ossificans, the osteosarcoma, but after the complementary histochemistry evaluation for gene USP6[7], the clinical history of the patient and histopathological evaluation, the final diagnosis of myositis ossificans was obtained.

Traditionally considered a reactive lesion, usually associated with trauma, myositis ossificans is characterized by fibroblast proliferation and formation of immature bone. However, recent literature evidences show that myositis ossificans is part of a spectrum of benign alterations associated with USP6 gene rearrangements, sharing clinical, morphological and genetic characteristics with other entities as primary aneurysmal bone cyst, nodular fasciitis and fibro-osseous pseudotumor of digits[8,9].

There is diagnostic difficulty in cases of needle biopsy in this context, which fail to reveal all the details of the lesion; in addition, myositis ossificans can mimic bone and soft tissue tumors as extraskeletal osteosarcomas and synovial sarcomas. The differential diagnosis can be challenging, especially in initial phases when imaging and histopathological exams are unspecific. Biopsy samples can contain only core fusiform cells, leading to wrong diagnoses[4].

The patient reported mild pain and preserved mobility of the right lower limb. The symptoms varied according to the site and the phase of the myositis ossificans compared with the overall clinical condition of the disease. Typically, patients report pain, swelling and edema in superficial lesions, in addition to articular rigidity. Conservative treatment is the approach of choice because myositis ossificans is self-limiting. Brief immobilization, application of ice and physiotherapy are recommended to reclaim the range of motion[4].

Surgical resection can be considered in persistent symptomatic cases but should be postponed until the lesion is fully mature and ossified (at least, 6 to 18 months post-trauma) to minimize the risk of recurrence[10]. It was possible to avoid extended exeresis in the area of the patient's limb based on the search for differential diagnosis and the ensuing investigation[4].

CONCLUSION

The differential diagnosis between osteosarcoma and myositis ossificans can be challenging due to radiologic and clinical similarities among these conditions. A 48-year old patient was initially diagnosed with osteosarcoma, but after thorough reassessment and molecular study of the gene, the final diagnosis was myositis ossificans. This finding highlights the importance of the correlation among clinical and morphological findings and gene

analyzes for a precise characterization of the lesion, ensuring proper therapeutic management and avoiding unnecessary treatments for the patients.

CONTRIBUTIONS

All the authors contributed to the conception and design of the study, acquisition, analysis and interpretation of the data, writing and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

AVAILABILITY DATA STATEMENT

All content underlying the text is contained in the article.

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