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Post-traumatic myositis ossificans: a benign lesion that simulates malignant bone and soft tissue tumours

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- Myositis ossificans (MO) is a benign bone formation in an extra-skeletal location. The most common subtype of MO, the post-traumatic, usually develops in young males after a traumatic event or sports injury.
- MO may simulate malignant bone lesions such as extra-skeletal or surface osteosarcomas, or soft tissue sarcomas such as synovial sarcoma or undifferentiated pleomorphic sarcoma. In the early phase the diagnosis of MO is challenging because imaging and histopathological findings may be non-characteristic.
- Detailed medical history as well as clinical examination, follow-up imaging studies and histological assessment are crucial for a proper diagnosis. Early and accurate differential diagnosis between MO and malignant soft tissue and bone tumours is important to maximize.

Keywords: bone sarcomas; extra-skeletal sarcoma; myositis ossificans; soft tissue sarcomas; surface sarcomas

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Introduction

Myositis ossificans (MO) is a benign, self-limiting, mature lamellar bone formation within skeletal muscles or other extra-skeletal soft tissue locations. MO subtypes include: (a) post-traumatic, which is the most common (up to 75% of cases), which is also known as focal or proliferative myositis; (b) non-traumatic, which is associated with burns, poliomyelitis, paraplegia, or infections; and (c) progressive MO, also known as fibrodysplasia ossificans progressive, a hereditary, autosomal dominant condition due to an activating mutation of bone-morphogenetic protein signalling.[1,2] The counterpart of MO for subcutaneous fat is panniculitis ossificans and for tendon and fasciae 46 fasciitis ossificans; the later ones represent also calcified lesions but without 'zonal' calcification.[3] Post-traumatic MO presents clinically with symptoms that simulate bone or soft tissue malignancies. The opposite is also true, because bone or soft tissue sarcomas, especially when there is a history of traumatic event, may be misdiagnosed as post-traumatic MO. Both entities often affect young patients who are physically active, with the lower extremities being the most frequent location. Adding to the diagnostic dilemma, in the early phase of MO imaging studies may be non-specific. To obtain a definitive diagnosis a biopsy may be essential.[4] Without adequate follow-up imaging studies or proper histopathological evaluation, there may be a significant delay in diagnosis or inappropriate patient handling may ensue.

There is extensive literature in case reports of MO that mimic musculoskeletal tumours. However, to the best of our knowledge, there have been limited reports addressing the clinicopathological and imaging findings of MO in comparison to other bone or soft tissue malignant tumours that emerge in the differential diagnosis of a rapid-growing muscular mass. Awareness that MO may simulate bone and soft tissue tumours can help orthopaedic surgeons in a prompt diagnosis and clinical decision making.

Pathophysiology

Pathophysiology of MO is poorly understood. Numerous theories have been proposed in an attempt to elucidate this issue. Recently the process of endothelial mesenchymal transition of vascular endothelial cells has been

suggested to explain the extra-skeletal bone formation. Prior injury causes an inflammatory cascade within skeletal muscles that leads to cytokine release. Cytokines act on vascular endothelial cells and cause endothelial-mesenchymal transition. The endothelial-derived mesenchymal stem cells differentiate into chondrocytes or osteoblasts, which at the end stage form extra-skeletal bone.[5]

Natural history

Natural history of post-traumatic MO can be divided in three phases: (a) the early phase, within the first four weeks after injury, which is characterized by an inflammatory cascade and cytokine release, without evidence of calcifications radiographically; (b) the intermediate phase, between the fourth and eighth week, with calcifications apparent in radiographs; and (c) the mature phase, after eight weeks and possibly lasting for several months, characterized by pronounced bone formation with radiographical 'zonation pattern'.[6,7] After several months the radiographically evident calcifications usually consolidate and finally dissolve.

Physical examination

Patients usually report a history of trauma or repeated minor injuries due to overuse in athletic activities; however, 25% of cases are of unknown aetiology without relevant history. MO usually affects young patients, usually males, in the second and third decades, probably related to increased athletic activity of young males. However, it has been also reported in younger patients.[8] It occurs in the extra-skeletal soft tissues of the upper and lower extremities, most commonly in the brachialis, deltoid, quadriceps and adductors, although atypical locations including intercostal or abdominal muscles, head, hands, feet and neck have been reported.[9] Clinical symptoms may differ based on location and phase of MO. Patients usually present with pain, swelling, oedema in superficial lesions and joint stiffness (up to 20% of patients). Pain generally persists longer than would be expected in a simple injury. Neurovascular structures close to the lesion may be compressed, resulting in weakness, paraesthesia, lymphoedema or even venous thrombosis.[10] The lesion typically presents as a rapidly growing mass. After approximately 2 to 3 months it reaches consolidation, with no significant symptomatology before undergoing partial or complete resolution.[7,11–13] Laboratory studies are not specific to the lesion or the progression of the lesion. The C-reactive protein, erythrocyte sedimentation rate and prostagandin-E2 serum level may be elevated during the initial phase. The serum alkaline phosphatase may be raised after the initial phase, while the creatine phosphokinase level is usually elevated and may be predictive of the severity of the lesion.[14]

Imaging characteristics

Plain radiographs usually show nothing during the early phase,[15,16] or may show a soft tissue opacity displacing fat planes. A mild periosteal reaction of the adjacent bone may be occasionally seen even before the typical egg-shell calcification of MO and may relate to periosteal haematoma[10] or irritation of the outer periosteum by the inflammatory process. In the intermediate phase, some fluffy calcifications develop, which consolidate over time to a peripheral rim. In the intermediate–mature phase the peripheral rim becomes thicker and denser[15] representing lamellar bone, typically surrounding a more radiolucent centre.[14] In the mature phase, after several weeks, the calcified rim is further thickened, the lesion can be completely mineralized, or, occasionally, trabeculae can be seen from the periphery to the centre of the lesion. A thin bony stalk may be seen between the mineralized shell of myositis ossificans and the adjacent bone cortex.[15] Occasionally in this phase, continuation with adjacent bone cannot be confidently excluded based only on plain radiographs.[16] After several months the lesion shrinks, is more oblique and parallel to the long axis of the muscle and, eventually, it may disappear.

Ultrasound (US) has been established as a first-line modality for discrimination between cystic and solid soft tissue masses as it is a low-cost and easy to perform modality. It has been stated that US can be more sensitive and more specific than computed tomography (CT) and magnetic resonance imaging (MRI) in early detection – between three and four weeks – of MO. Ultrasound can disclose a typical 'zonal pattern' which consists, from periphery to centre, of a relative hypointense zone with Doppler signal that represents surrounding inflammation, a hyperechoic zone with calcifications which create acoustic shadowing, and an innermost hypoechoic centre.[15,17] As the lesion matures, the Doppler signal in the outer zone diminishes and the calcified rim becomes thicker.[14] However, ultrasound largely depends upon the operator's experience and, thus, should be interpreted with caution.[10,16] CT exhibits calcifications earlier than plain radiography but in the very initial phase it just shows a non-specific relative hypointense intramuscular lesion.[18] CT is very specific in the depiction of calcifications and can avoid superimpositions between MO and the nearby bone, revealing a thin cleft, the so-called 'string sign' which separates MO from bone (Fig. 1 and Fig. 2).[10,15,16,18]

MRI is the imaging technique of choice for detection of soft tissue masses but is considered generally non-specific in characterization of early MO when the mineralizations are not still apparent. In this early phase, MO can mimic sinister pathologies such as soft tissue sarcomas, all of them being isointense or mildly hyperintense on T1w and hyperintense on T2w images (Figs 1–4). Unlike sarcomas,

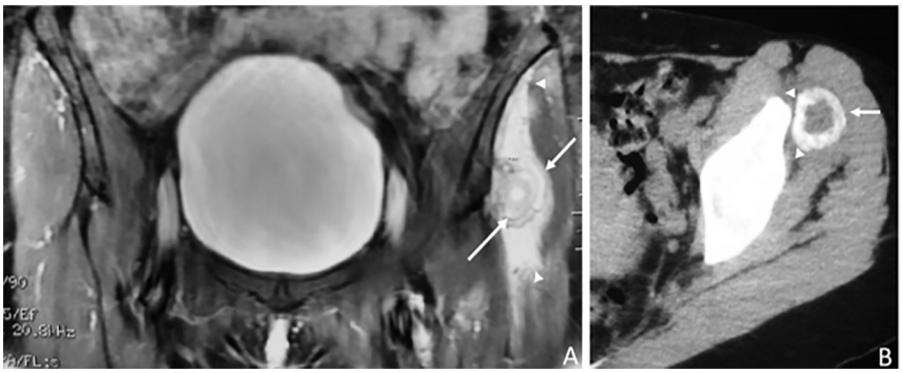

Fig. 1. A 42-year-old woman with a palpable mass in the left gluteal region. After questioning she recalled an injury at the gym about six weeks ago. The diagnosis of MO was confirmed by CT findings. (A) A coronal fat-suppressed contrast enhanced T1w MR image shows concentric hyperintense rings (arrows) within the mass and extensive oedema of the surrounding muscle (arrowheads). (B) An axial CT image shows a typical MO lesion with thick calcified rim (arrow) surrounding a mildly hypodense centre. A thin line separates the myositis ossificans lesion from ileac bone (arrowheads) the so-called 'string' sign.

Note. MO, myositis ossificans; CT, computed tomography; MR, magnetic resonance.

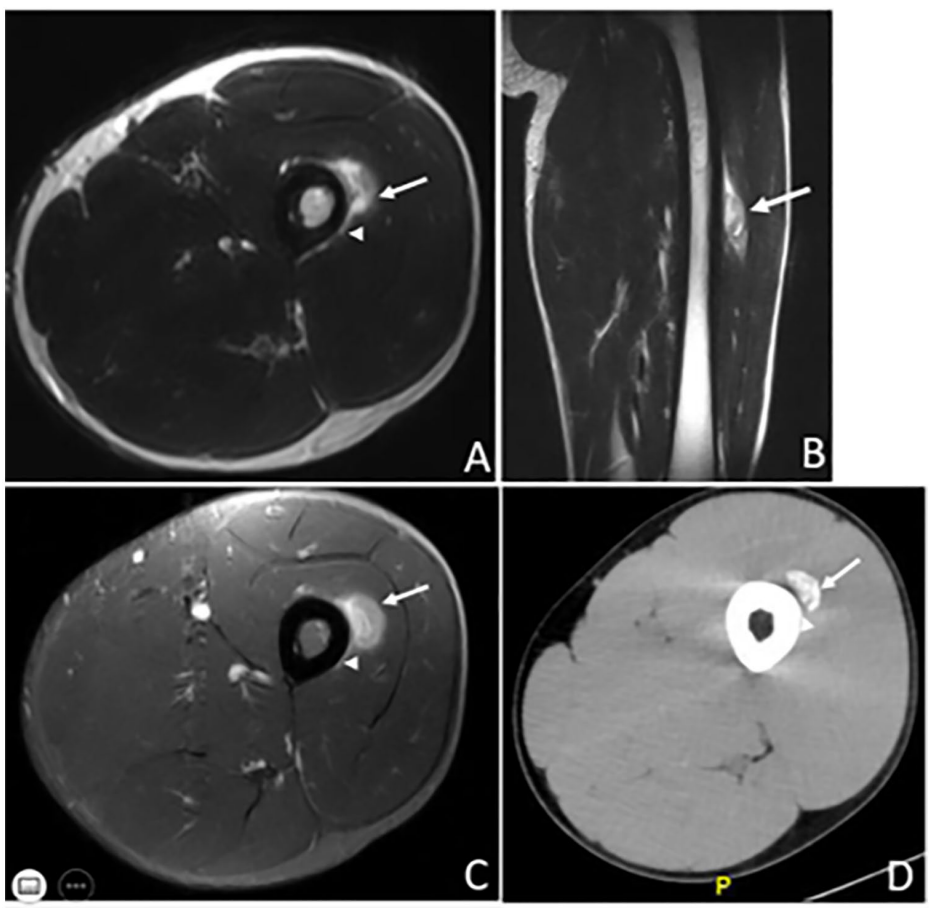

Fig. 2 A 15-year-old male soccer player with no history of trauma and mild pain on his right thigh. The diagnosis of MO was confirmed by follow-up CT findings. (A) An axial T2w MR image demonstrates a predominately hyperintense, well-defined lesion (arrow) with hypointense foci, within the vastus intermedius muscle and in contact with femoral cortex. The bone cortex exhibits mild periosteal reaction (arrowhead) but no disruption. (B) On a sagittal T2w MR image, the lesion is oblogue parallel to the muscle fibres of the vastus intermedius. (C) An axial fat-suppressed contrast-enhanced T1w MR image shows homogenous enhancement of the lesion (arrow) and mild periosteal enhancement (arrowhead). (D) Axial CT image. A diffusely calcified lesion is seen (arrow), separated from the adjacent bone cortex by a fine line (arrowhead).

Note. MO, myositis ossificans; CT, computed tomography; MR, magnetic resonance.

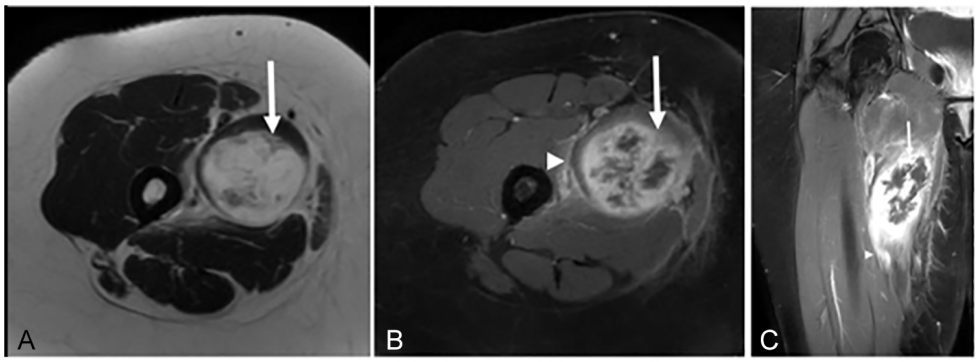

Fig. 3 Female patient aged 23 years, after Covid-19 lockdown. She presented with pain at the right thigh, increasing during daily activities, after long-distance walking during lockdown. (A) An axial T2w MR image shows a predominately hyperintense mass (arrow) within the adductor longus muscle. (B) Heterogenous enhancement of the mass (arrow) and mild enhancement of the adjacent fasciae at the medial aspect of the thigh are seen on a fat-suppressed contrast-enhanced T1w MR image (arrowhead). (C) A coronal fat-suppressed contrast-enhanced T1w MR image shows a hypointense thick incomplete rim (arrow) and marked oedema of the surrounding muscle (arrowhead). The differential diagnosis included soft tissue sarcoma.

Note. MR, magnetic resonance.

enhancement after administration of gadolinium is usually more pronounced peripherally (Fig. 1, Fig. 3) although diffuse enhancement may also be seen.[18] Periosteal reaction (Fig. 2) and bone marrow oedema of adjacent bone can be occasionally seen.[9] Wang et al recently described a striated or checkerboard pattern on T2w and contrast-enhanced MR images in all of their seven patients with early MO without calcifications.[19] The striated pattern can be also observed in proliferative myositis and other inflammatory myopathies.[20] Calcifications have low signal intensity both on T1 and T2-weighted images, but fibrosis and hemosiderin can produce the same signal intensities (Fig. 3 and Fig. 4). When mineralization is typically rim like and surrounded by diffuse oedema of the adjacent soft tissue the diagnosis of MO is straightforward (Fig. 1). On the other hand, scant calcifications in the early/intermediate stage can be seen also in extra-skeletal osteosarcomas, the rare extra-skeletal chondrosarcomas or synovial sarcomas. Intralesional haematomas are not uncommon both in sarcomas, especially synovial sarcomas, and early MO. In doubtful cases plain radiographs or CT can confirm or exclude the presence and reveal the pattern of calcifications (Fig. 1 and Fig. 2). Another differentiating feature between MO and sarcomas is the diffuse muscle oedema that surrounds the main lesion in the acute and intermediate stages (Fig. 1 and Fig. 3). Muscle oedema is uncommon in sarcomas.

With time, ossified lamellar bone develops in the periphery or even throughout the mass and bone marrow signal, that is high on T1w and low on water-sensitive MR images can be seen, whereas surrounding diffuse oedema subsides. Elimination of surrounding oedema signifies inactivity of MO and is considered favourable for resection of the lesion (Fig. 2 and Fig. 4).[15]

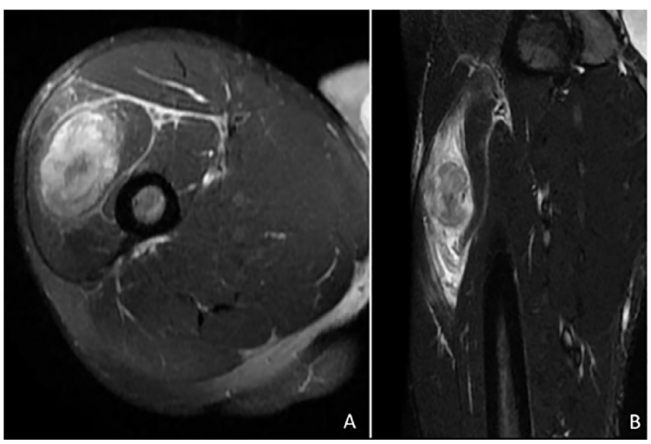

Fig. 4 Male patient aged 16 years, without prior history of injury. (A) An axial fat-suppressed MR image shows a predominately hyperintense mass within the vastus lateralis. A target-like configuration is seen created by alternating concentric hypointense rings, presumably representing calcifications and a hypointense centre that may represent fibrosis, blood products or calcifications. (B) A coronal STIR MR image displays a spindle-like inhomogenous region that follows the orientation of the vastus lateralis, with hyperintense apices, representing muscle oedema and predominately hypointense centre. The differential diagnosis included soft tissue sarcoma.

Note. MR, magnetic resonance; STIR, short tau inversion recovery.

Histopathological characteristics

MO is a well-circumscribed lesion comprising a central cellular spindle cell area with peripheral organized and mature lamellar bone formation. The central area consists of plump spindle cells (fibroblasts and myofibroblasts) with elongated nuclei arranged in short irregular fascicles sometimes with a vaguely storiform or cell culture-like

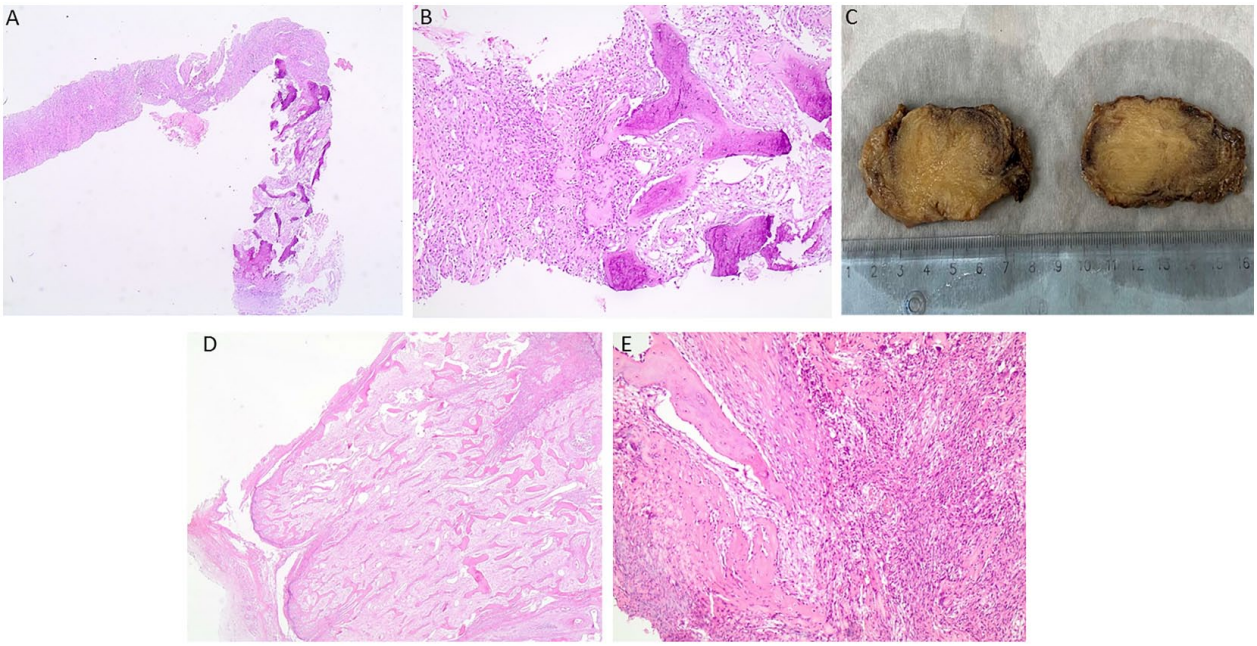

Fig. 5 The histopathological findings of the male patient shown in Fig. 4. (A) (H&EX20) Fine needle biopsy sample showing both spindle cells and woven bone. Calcifications are evident on MRI. (B) (H&EX100) Osteoid trabeculae rimmed by osteoblasts with adjacent proliferation of spindle cells. (C) Excision specimen. The lesion, located intramuscularly, measured 8 cm and was well circumscribed with gritty sensation in cutting. (D) (H&EX20) Organized mature lamellar bone formation at the periphery of the lesion. (E) (H&EX100) Spindle cells arranged in short irregular fascicles, embedded in loosely textured, mildly collagenized stroma, while osteoid and well-formed trabeculae are also noted.

Note. H&E, hematoxylin and eosin ; MRI, magnetic resonance imaging.

pattern, set in loosely textured myxoid or more collagenous stroma with scattered extravasated red blood cells. The spindle cells are mitotically active, with occasionally numerous mitoses that are almost always typical. The peripheral zone is formed by progressively maturing woven bone associated with osteoblasts and commonly foci of cartilage undergoing endochondral ossification are also noted. This typical architecture of the lesion (progressive maturation from the centre to the periphery) is called 'zoning' phenomenon or 'zonation' pattern and is essentially diagnostic of MO. Other features include cystic degeneration, foci of haemorrhage and presence of multinucleated osteoclast-like giant cells or chronic inflammatory cells. In typical cases, immunohistochemical studies are not necessary for the diagnosis. The spindle cells can be positive of muscle-specific actin of smooth muscle actin (SMA). Osteoblasts are positive for the marker SATB2. Molecular studies for USP6 rearrangement can assist the differential diagnosis in some cases (Fig. 5 and Fig. 6).[21,22]

Treatment

A conservative approach is the treatment of choice, because MO is a self-limiting condition. Immobilization for a short period and ice treatment are recommended, followed by physiotherapy to regain the range of motion.[10] However, if the lesion continues to be symptomatic with constant pain, decreased range of motion or signs of compression of important neurovascular structures, excision of the mass may be considered. It is preferable to delay the excision of the lesion until complete maturation and ossification has stopped (at least six to 18 months post-injury), to prevent recurrence.[23] However, conclusive data supporting a delayed approach is lacking.[24,25] Ogilvie-Harris and Fornasier studied 26 patients with non-traumatic MO and suggested that early excision has minimal risk of recurrence.[26] Therefore, decision making to proceed with surgery is personalized and based on radiographic findings and clinical evaluation.

MO simulates bone and soft tissue sarcomas

The ambiguous history with or without a traumatic event, the non-characteristic clinical symptoms of pain, swelling and limp and the imaging findings of MO in the early phase, may simulate those of malignant musculoskeletal tumours. Extra-skeletal or surface osteosarcomas or soft tissue sarcomas such as synovial sarcoma or undifferentiated pleomorphic sarcoma may affect active adults who

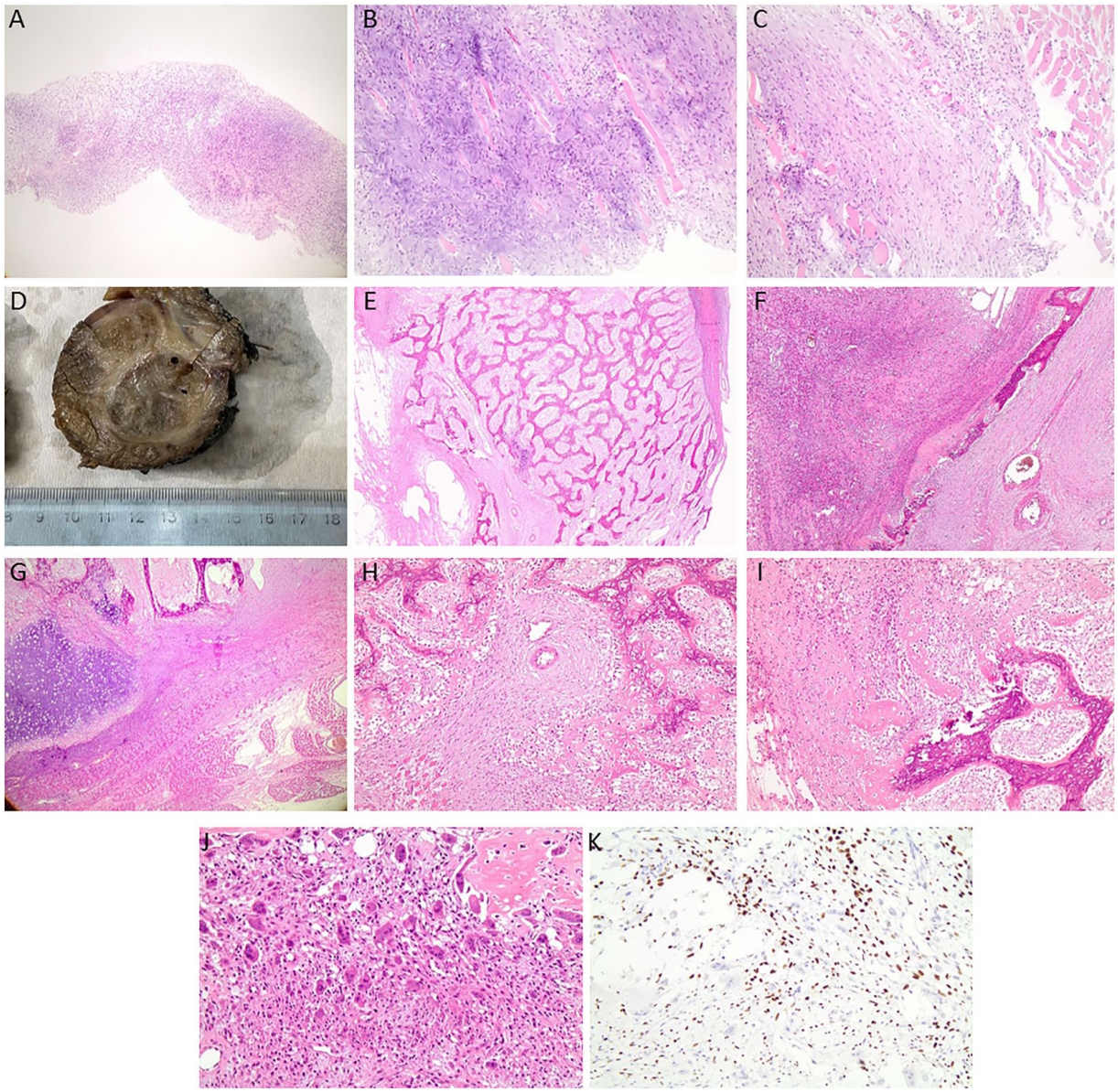

Fig. 6 The histopathological findings of female patient shown in Fig. 3. (A) (H&EX40) Fine needle biopsy sample showing proliferation of spindle and plump cells. Imaging studies were non-specific of MO. (B) (H&EX100) The cells are characterized by mild atypia and mitotic activity and set in loose myxoid stroma. Myxoid liposarcoma was proposed as probable diagnosis. (C) (H&EX100) The neoplastic population invades skeletal muscle. (D) Excision specimen. The lesion, located intramuscularly, measured 10 cm and was well circumscribed, with gelatinous and cystic areas centrally and gritty sensation in cutting peripherally. (E) (H&EX20) Organized mature lamellar bone formation at the periphery of the lesion. Cystic areas at the central portion, with evident 'zoning' phenomenon. (F) (H&EX40) Hypercellular spindle cell areas with ossification and bone trabeculae formation. (G) (H&EX40) Woven bone and foci of cartilage peripherally, adjacent to skeletal muscle. (H) (H&EX100) Bone trabeculae rimmed by osteoblasts, intermingled with plump fibroblasts which extend to skeletal muscle. (I) (H&EX100) Well-formed bone trabeculae, osteoid and plump fibroblasts in collagenized stroma. Cystic areas are noted at the lower left. (J) (H&EX200) Areas of multinucleated osteoclast-like giant cells adjacent to osteoid. (K) Immunohistochemical staining for SATB2, highlighting the large number of osteoblasts in this area.

Note. MO, myositis ossificans; H&E, hematoxylin and eosin.

are often involved in athletic activities and have a history of trauma. Even histopathological features may be misleading (Table 1). Inadequate biopsy sampling, especially when obtained from the central zone of the lesion with fine needle or very early in the physical history of the lesion, might be composed only of the spindle cell population component, lacking any osteochondroid elements. This may yield on morphological grounds differential

Table 1.

	MO	EO	PAO	PEO	SS	UPS
Clinical features						
History	+/– History of trauma	+/– History of trauma, radiation	Long history (over a year)	Short duration (weeks–months)	History of minor trauma	History of radiation, Paget's disease
Demographics	Males > females, 2nd–3rd decade	Males > females older than 40 years	Females > males, 3rd decade	Males = females 2nd decade	Males = females adolescent, young adults > 50 yrs	Males > females 32–80 years
Clinical presentation	*Early*: rapidly growing painful soft tissue mass, swelling, oedema, joint stiffness After 2–3 months: no significant symptoms	Slowly growing painless bone tumour	Slowly growing bone tumour, occasionally painful	Swelling and/or pain, bone tumour	Slowly growing soft tissue tumour +/– painful, swelling, decreased ROM	Painless, enlarging palpable soft tissue tumour, decreased ROM,
Location (most common)	Extremities	Thigh, upper extremity	Long bones, metaphysis (distal femur)	Diaphysis (femur, tibia)	Lower extremities (knee joint), upper extremities (elbow joint)	Extremities, retroperitoneum
Imaging features						
X-rays **First-line Method*	*Early*: Nothing or STO Intermediate: Fluffy calcifications → Calcified rim Separated from bone Late: Thick calcified rim/complete mineralization	Nothing or STO + faint calcifications	Broad-based stuck attached to cortical surface Dense, central mineralization	Cortical thickening with saucerization ± perpendicular periosteal reaction	STO, ± amorphous calcifications, adjacent bone remodelling or invasion	Nothing or STO ± rarely calcification, erosion adj. bone
Ultrasound **Operator De-pend Method*	*Early*: NS STM Intermediate: Alternating hypo/hyperechoic zones + ↑ DS adjacent Late Hyperechoic lesion, thick acoustic shadow, ↓ DS adjacent	NS STM, calcifications	Skip (bone lesion)	Skip (bone lesion)	NS STM, calcifications	NS STM, calcifications
CT **Method of choice for calcifications*	*Early* NS hypointense STM Intermediate: Calcified rim Clear separation from bone (string sign) Late: Calcified STM	STM, discrete margins, calcifications centrally	STM Confirm broad -based stuck and central mineralization	Same as X-ray, ± STM, additional calcifications	STM, usually inhomogenous + same as X-ray	STM, usually inhomogenous + same as X-ray
MRI **Method of choice for soft tissue*	*Early*: NS STM, striated muscle oedema pattern *Intermediate*: Peripheral calcifications (↓SI T1/T2w) Oedema (↑T2w) adjacent muscle *Late*: Thick calcification/ossification Oedema-adjacent muscle subsides	STM, pseudocapsule, central calcifications (↓SI T1/T2w) NO oedema adj. tissues	Inhomogenous STM with mineralization ± Intramedullary extent, Inhomogenous cartilage cap NO oedema adj. tissues	STM, ↑↑SI on T2w, nodal/septal/peripheral enhancement (chondroid type) NO oedema adj. tissues	STM, pseudocapsule lobular contour, inhomogenous, ↑SI on T2w, ± Haemorrhage, calcifications NO oedema adj. tissues	STM, pseudocapsule, inhomogenous, ↑SI on T2w, ± less frequent haemorrhage, calcifications
Histopathologic features						
Architecture	Zonation pattern	Reverse zoning phenomenon	–	–	–	–
Localization	Intramuscular	Deep soft tissues	Juxtacortical	Juxtacortical	Deep soft tissues, juxta-articular	Not specific
Pattern	Fascicular, storiform, culture-like	Sheets of cells	Fascicular	Lobular, sheets of cells	Fascicular, sheets of cells, herringbone	Storiform, fascicular, nested, haphazard
Cellular composition	Spindle	Spindle, pleomorphic, epithelioid	Spindle	Chondroid, spindle	Uniform spindle, ovoid	Pleomorphic, bizarre, spindle, epithelioid, round
Mitotic activity	Yes, occasionally brisk (typical mitoses)	Yes (atypical mitoses)	Yes (low)	Yes (atypical mitoses)	Yes (atypical mitoses)	Yes (atypical mitoses)
Cellular atypia	0/+	++/+++	+/(+++ in case of dedifferentiation)	+++	+/++	+++
Stroma	Myxoid, collagenous	Osteoid matrix	Desmoplastic	Sparse	Hyalinized, collagenized, myxoid	Collagenous

(continued)

Table 1. (continued)

	MO	EO	PAO	PEO	SS	UPS
Bone/osteoid formation	Yes (periphery)	Yes (central area)	Yes	Yes	Yes	Yes
Cartilage formation	Yes (periphery)	No	50% of cases	Yes	rarely seen	No
Cystic areas	+/–	–	–	–	+	+
Necrosis	–	+	–	–	/+	+
IHC markers	SATB2	SATB2	SATB2, MDM2, CDK4	SATB2	TLE1, EMA, epithelial markers, antibodies towards SS18/SSX chimeric protein	Not specific
Helpful molecular findings	USP6 rearrangement (in the vast majority of cases)	Not relevant	MDM2 and CDK4 overexpression	Not relevant	Chromosomal translocation t(X;18)	Not relevant

Note. MO, myositis ossificans; EO, extra-skeletal osteosarcoma; PAO, parosteal osteosarcoma; PEO, periosteal sarcoma; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma; ROM, range of motion; CT, computed tomography; MRI, magnetic resonance imaging; NS, non-specific; STM, soft tissue mass; STO, soft tissue opacity; SI: signal intensity; T1w, T1-weighted MR images; T2w, T2-weighted MR images; DS, ; IHC, .

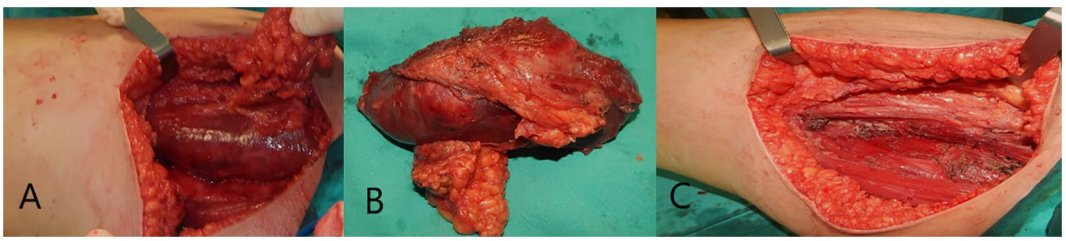

Fig. 7 The intraoperative images of female patient aged 23 years (Fig. 3 and Fig. 6). Imaging studies were non-specific of MO. (A) Intraoperative image showing the lateral approach of the thigh. (B) The excised mass measured 10 cm and was well circumscribed. (C) Intraoperative image showing the thigh after excision of the mass.

Note. MO, myositis ossificans.

diagnosis of any spindle cell tumour invading muscle, such as myxoid liposarcoma or desmoid-type fibromatosis (Fig. 7).[27] Moreover, fine needle biopsy samples often fail to depict the actual architecture of the lesion, as it is very difficult to identify the characteristic 'zonation' pattern. Misdiagnosis can lead to delayed and improper treatment in the case of a malignant tumour mistaken for MO, adversely affecting patient survival, or in cases of MO treated as malignant lesions, unnecessary diagnostic studies and treatment regime may be applied.

Bone sarcomas

Extra-skeletal osteosarcoma (EO)

Extra-skeletal osteosarcoma (EO) EO is a rare malignant osteoid producing sarcoma located in soft tissues, with or without minimal skeletal or periosteal attachment.[22,28,29] This extra-skeletal variant of osteosarcoma more commonly affects males older than 40 years old. Symptoms usually include a slowly growing painless mass in an extremity, most commonly the thigh (46%), followed by the upper extremity (20%), although it can occur in any part of the body.[30] History of prior trauma is present in 12.5% of patients[30] and renders differential diagnosis with MO more challenging. Previous radiation is considered a risk factor.[31] The tumour is well marginated on CT and MRI, separated from adjacent bones with a pseudocapsule, mineralizations in approximately half of cases, and, not infrequently, foci of haemorrhage. In contrast to MO, mineralizations develop from the centre to the periphery. Unlike early and intermediate MO there is no substantial oedema in adjacent muscles whereas the lesion lacks lamellar bone at any stage, as is seen in mature MO.[32]

Histologically, this tumour is characterized by the presence of osteoid produced by neoplastic cells that can be spindle, epithelioid or pleomorphic. The pattern of deposition is lace-like or trabecular. The neoplastic cells are mitotically active as in MO but in contrast with MO show cytological atypia. Moreover, osteoid formation in extra-skeletal osteosarcoma is more abundant in the central part of the lesion, which is the opposite of the zonation pattern typical of MO.[21,22]

Due to the rarity of EO, there is no universally accepted treatment algorithm. Amputation or wide surgical resection are common treatment practices with no difference in overall survival between patients treated with resection

and those treated by amputation.[33] After surgery, patients with localized disease followed by chemotherapy have shown encouraging results compared to surgery alone.[34] For patients treated with a combination of surgical resection and chemotherapy protocols suitable for high-grade conventional osteosarcoma, overall survival three years after diagnosis is 77%, and event-free survival is 56%.[33] Radiation therapy has been commonly applied in cases of marginal resection or as a palliative treatment.[33]

The prognosis of EO is poor, compared to conventional osteosarcoma, with a five-year survival rate of 28%. Tumour size is the best predictor of outcome.[35] More than 80–90% of patients develop local recurrences and metastasis to the lungs and bones.[22,30]

Surface osteosarcomas

Parosteal osteosarcoma (PAO)

PAO is a low-grade malignant bone-forming neoplasm that arises on the cortical surface of bone and is more frequent in young females with a peak incidence in the third decade. It is the most common type of surface osteosarcoma, and 65% of all the surface variety subtypes.[36] Patients usually present with a long history of a painless, slowly enlarging mass, occasionally painful.[22,37] Lesions are usually located at the metaphysis (80–90%) of long bones, most commonly of the distal femur (70%) tibia or proximal humerus and tend to wrap themselves around the bone with a lobulated 'cauliflower like' surface mass.[37,38] On X-rays the tumour displays a broad-based attachment to the bone surface[39] and is densely calcified centrally following a reverse pattern to MO.[16] As the tumour wraps around the bone, a cleft may be seen partially separating the exophytic part of the tumour from the cortex; the so-called 'cleft sign'.[40] The cortex appears thickened but without aggressive periosteal reaction.[39] CT and MRI can confirm the presence of a broad-based thick stalk and central mineralization allowing distinction from MO in doubtful cases. MRI can additionally show intramedullary extension of the tumour.[39]

Histopathological, PAO comprises well-formed bone trabeculae embedded in fascicles of spindle cells with minimal and more rarely moderate atypia and low mitotic activity. Half of the lesions show cartilaginous differentiation. At the periphery of the tumour the spindle cell component may invade skeletal muscle, which can cause confusion with MO, particularly in fine needle biopsy samples. However, the neoplastic cells in PAO are arranged in more intact fascicles lacking a cell-culture-like appearance or presence of myxoid stroma, and the zonation pattern is absent. Additionally, immunohistochemical studies for MDM2 and CDK4 can aid the differential diagnosis as PAO can be characterized by MDM2 and CDK4 overexpression.[21,22]

PAO is a low-grade tumour, and metastases occurs rarely. Wide excision is the treatment of choice. It has an excellent prognosis after wide excision, while incomplete resection can result in local recurrence.[22]

Periosteal osteosarcoma (PEO)

PEO is the second most common type of surface osteosarcoma after PAO, comprising 25% of the surface variety of osteosarcomas.[36,38] It is a malignant, predominantly chondroblastic, intermediate-grade bone-forming sarcoma arising on the surface of the bone, typically underneath the periosteum.[22] It is considered an intermediate-grade osteosarcoma (grade 2), affecting patients in the second decade of life. Lesions tend to be diaphyseal, with femur and tibia the most common locations. Swelling and/or pain of short duration (weeks to months) is characteristic. The tumour presents on radiographs with cortical thickening and cortical scalloping by a broad-based soft tissue mass which erodes the outward aspect of the cortex. Perpendicular periosteal reaction extending into the soft tissue mass is common,[39,41] unlike the circumferential calcification of MO. CT can reveal additional foci of calcifications within the soft tissue mass. MRI usually exhibits a very high signal intensity soft tissue mass on T2w images and a chondroid-type of enhancement that is nodular, septal and peripheral; the above features reflect the chondroid-rich content of the tumour.[41]

Histologically, the tumour is characterized by poorly delineated lobules of atypical cartilage with intervening aggregates of primitive sarcomatous cells and bone formation. The tumour typically does not infiltrate skeletal muscle, and has high-grade cytologic features that distinguish it from MO.[21,22] PEO is of intermediate grade with better prognosis in comparison to conventional osteosarcoma, but not as good as PAO, with wide excision being the treatment of choice.[22]

Soft tissue sarcomas

Synovial sarcoma (SS)

SS is a relatively rare soft tissue sarcoma, presenting in patients aged 15 to 40 years old.[41] Chromosomal translocation t(X;18) is observed in more than 90% of cases.[22] Approximately 70% of SSs occur in the deep soft tissues of the lower and upper extremities, often at a juxta-articular location, usually arising adjacent to a joint, especially the popliteal fossa of the knee.[42,43] Patients may present with a slow-growing mass, pain and swelling, whereas range of motion may might be compromised. Patients may have a history of minor trauma that perplexes differential diagnosis making MO a possible diagnosis. Regional lymph node metastases may be present.[44]

Radiographs are often normal. Calcifications are seen in 30% of cases, are peripheral in distribution and usually amorphous, not rim-like as in myositis ossificans. Periosteal reaction, adjacent bone remodelling or bone invasion may be seen and may have a misleading non-aggressive appearance. US and CT are usually non-specific, whereas MRI can reveal a large spectrum of imaging patterns ranging from a well delineated homogenous and relatively small lesion to a large, inhomogenous mass. Areas of low, intermediate and high signal intensity are intermixed, particularly on T2w images, creating the so-called 'triple sign'. The triple sign is not specific, can be also seen in other types of sarcomas but also, occasionally, in MO (Fig. 3 and Fig. 4) and represents the coexistence of haemorrhagic areas, cystic areas with central necrosis, fibrosis and viable tumour. High signal intensity areas predominate even in the presence of extensive calcifications.[41,45,46] Again, CT can be useful to discriminate between calcifications, fibrosis and blood degradation products. Serpentine vessels and lobular contour are also frequent MR features of SS.

Chromosomal translocation t(X;18) is observed in more than 90% of cases.[22] Recently, novel fusion-specific antibodies that aid the diagnosis have been developed.[47] Histologically, SS shows three main patterns: monophasic (spindle cell), biphasic and poorly differentiated. SS shows three main patterns: monophasic (spindle cell), biphasic and poorly differentiated. Other rare patterns include purely glandular monophasic SS, SS with prominent bone formation and calcification and myxoid SS. Of the aforementioned variants, monophasic SS and SS with prominent bone formation and calcification could overlap morphologically with MO. Cystic areas can occur. Monophasic SS is characterized by delicate spindle cells that are uniform in appearance, relatively small with scant cytoplasm that gives the impression of nuclei overlapping. The nuclei are ovoid and hyperchromatic with regular granular chromatin and inconspicuous nucleoli. Nuclear pleomorphism is generally not a feature of synovial sarcoma. The neoplastic cells form highly cellular solid sheets or fascicles with occasional herringbone pattern. Characteristically, there are discrete hyalinized or wiry collagen bundles with variable calcification and resemblance to osteoid. However, cartilage formation is not recognized. Furthermore, the uniform cellular features of monophasic SS with high N:C ratio and lack of zonation pattern distinguish it from MO. Immunohistochemically, the neoplastic cells of monophasic SS are typically positive for the marker TLE1, EMA and epithelial markers, providing further assistance in the differential diagnosis.[21,22]

Because early diagnosis is crucial, SS must be considered in the differential diagnosis of any mass arising near a joint. Treatment depends on the stage and grade of SS. Most patients are treated with limb salvage surgery. Wide resection of the tumour combined with radiation therapy is the preferred treatment, although chemotherapy may be considered in metastases. Overall, the prognosis is poor, with five-year survival rates reaching approximately 60% to 70%.[48]

Malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma (UPS)

UPS is the most common soft tissue sarcoma of adult life, usually affecting males between 32–80 years old.[49] Risk factors include prior radiation treatment for another malignancy.[50] It is believed to originate from primitive mesenchymal cells and is located in soft tissue or bone, usually in the extremities or retroperitoneum.[51] Common presentation is a painless, enlarging palpable mass[49] restricted movement of the limb and limping, which make the differential diagnosis with MO challenging. Radiographically, UPS usually presents as a deep-seated mass with large size, pseudocapsule and inhomogeneity on CT and MRI due to areas of necrosis, haemorrhage, myxoid elements, fibrosis and calcifications.[45,46] Calcifications are seen in 5–20% of cases can be curvilinear or punctuate and do not have a specific pattern. Bone erosion is common in large tumours but, unlike MO, there is no surrounding soft tissue oedema.

Histologically, the neoplastic population is composed of highly pleomorphic, bizarre, spindle, epithelioid or round cells, corresponding to the pleomorphic, spindle cell, epithelioid cell and round subsets. The cells are arranged haphazardly or in storiform, fascicular or nested pattern. The neoplastic cells are characterized by numerous mitoses including atypical ones and a variable amount of eosinophilic or amphophilic cytoplasm. The stroma is commonly collagenous, with or without presence of inflammatory cells. Bone or cartilage formation along with the typical zonal architecture characteristic of MO are absent, and the highly atypical appearance of the neoplastic cells with numerous atypical mitoses is in contrast with the neoplastic spindle cell population in MO which is relatively bland with typical mitoses. Additionally, younger patients, who are the main age group MO affects, present with UPS of round cell type, which morphologically bears no resemblance to MO.[21,22]

Patients usually present late with metastasis, most frequently to lungs or lymph nodes.[49] Treatment of choice is wide surgical excision combined with neoadjuvant/adjuvant radiotherapy and chemotherapy.[52,53] Prognosis varies depending upon size, grade, location and presence of inflammatory component. Tumours sized more than 10 cm have a five-year survival rate of 51%. Intermediate-grade tumours showed a five-year survival rate of 80%, and the five-year survival rate for high-grade tumours is about 60%.[21,54]

Conclusions

Although post-traumatic MO is a benign self-limiting lesion, it may simulate a number of malignant bone and soft tissue tumours both clinically, radiographically and histologically. Clinical history and physical examination may not be diagnostic in the early phase of the lesion and imaging features are not specific. For full-blown lesions, proper clinical and imaging correlation and adequate biopsy sampling are crucial in the differential diagnosis between MO and malignant soft tissue and bone tumours.

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