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REVIEWS

Myositis ossificans: a short review

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Abstract
Myositis ossificans (MO, heterotopic ossification) consists of lamellar bone formation in soft tissues, without ossification properties under physiological circumstances. MO can be primary (isolated or associated with various congenital disorders) or secondary in the site of a pre-existing lesion, such as inflammation, a neoplasm or a benign tumor. Primary forms are rare, present systemic symptoms and usually have a worse prognosis. MO is relatively frequent after sports lesions, hip arthroplasty or central nervous system injuries. Posttraumatic MO complicates about 20% of large hematomas after muscle contusions and strains. Diagnosis can be made through imaging or histopathological methods. Although characteristic features can be distinguished on simple radiographic images, magnetic resonance imaging, computed tomography and ultrasonography provide diagnosis in the earlier stages. Despite MO not having a universal prophylaxis or treatment, nonsteroidal anti-inflammatory drugs proved to be efficient in certain forms, while surgical excision and extracorporeal shock wave therapy might be useful therapeutic options.
Keywords: heterotopic ossification, physical activity, posttraumatic myositis, bone formation

Introduction

Myositis ossificans (MO), otherwise known as heterotopic ossification, consists of non-neoplastic formation of lamellar bone in the muscle or other soft tissues which do not have ossification properties under physiological circumstances, without any direct connection to underlying bone tissue or the periosteum. MO is always extra-articular, although sometimes attachment to the joint capsule can be observed, without its disruption. MO can appear in the skin, subcutaneous tissue and skeletal muscles, causing inflammation and restricted, painful motion, severely influencing the quality of life of the patient and interfering with the career of professional athletes (Maheswarappa et al., 2004; Orava et al., 2017).

Epidemiology

MO complicates about 20% of the large hematomas after muscle contusions and strains in contact sports; nevertheless, a similar percentage of MO occurs after total hip arthroplasties (Torrance et al., 2011). MO is responsible for significant morbidity, with pain, tenderness and stiffness lasting over 1 year (Torrance et al., 2011). It was estimated that in athletes 9-20% of quadriceps injuries or contusions resulted in MO (Devilbiss et al., 2018).

Pathogenesis

The pathogenesis of MO is not fully known, but several underlying biological pathways were identified, such as bone morphogenetic protein (BMP) receptor signaling, ALK1 pathway, insulin pathway, PDGFR-beta signaling pathway, EGF receptor (ErbB1) signaling pathway, growth differentiation factor 15 (GDF15), etc. (Ruschke et al., 2012; Strelau et al., 2003; Schindowski et al., 2011).

In MO, a differentiation of primitive mesenchymal cells from soft tissues such as muscle, fascia, periosteum and bone marrow into osteoprogenitor cells is triggered which will produce osteoblastic tissue. In non-hereditary forms, histologically we can distinguish six different stages: perivascular infiltration of lymphocytes, migration of lymphocytes into the soft tissues, fibroproliferation, neovascularization, cartilage formation and ossification (Ohlmeier et al., 2019; Foley et al., 2018; Cholok et al., 2018).

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Table I
Types of heterotopic ossification (Huang et al., 2020; Bastepe, 2018).

Types	Etiology	Mechanism	Process of new bone formation
Inherited	Mutations in FOP gene (fibrodysplasia ossificans progressiva)	Gain of function of ACVR1 (activin receptor A type1) gene	Endochondral ossification
	Mutations in PHO gene (progressive osseous heteroplasia)	Loss of function of the GNAS gene [encoding the alpha-subunit of the stimulatory heterotrimeric G protein (Gsα)]	Intramembranous ossification
Acquired	Injuries	Injury to the nervous system	Distal to injury endochondral and intramembranous ossification
		Injury to the musculoskeletal system	Near the injury

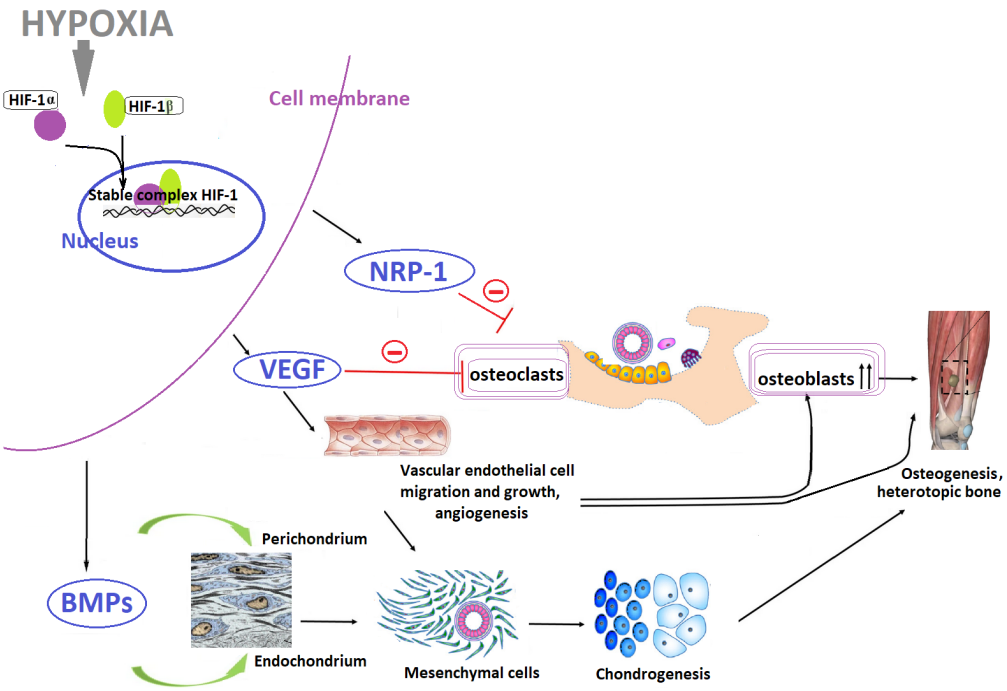

Fig 1 – The molecular mechanisms involved in the formation of heterotopic bone (adapted after Huang et al., 2020, Cholok et al., 2018).

Hypoxic microenvironment enhances the stability of HIF - hypoxia-inducible factors (HIF-1α and HIF-1β) which up-regulate a complex network including bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1). These promote angiogenesis, the proliferation and differentiation of cartilage and osteoblasts and inhibit the proliferation and differentiation of osteoclasts, thus being implicated in ossification (Fig. 1).

Two useful mnemonics were created by Bell et al. to help the memorizing of the causes of soft tissue calcification: My GHOSTS: Myositis ossificans, Gout, Hyperparathyroidism, Ochronosis, Scleroderma and other connective tissue diseases, Tumoral calcinosis, Sarcoma, and TIC MTV: Tumor, Inflammation/infection (dermatomyositis, scleroderma, parasitic infestation, leprosy, pancreatitis, calcific myonecrosis, bursitis/tendinitis), Congenital (Ehlers-Danlos syndrome, myositis ossificans progressiva), Metabolic (primary/secondary hyperparathyroidism, metastatic calcification, calcium pyrophosphate deposition disease, calcium hydroxyapatite deposition), Trauma (myositis ossificans, burn injury, hematoma) and Vascular calcification (Bell & Niknejad, 2021).

Regarding the types of heterotopic ossification (Table I), MO can be primary (isolated or associated with various congenital disorders, such as Albright's hereditary osteodystrophy (given by inactivating mutations in Gsα-coding GNAS exons), progressive osseous heteroplasia and fibrodysplasia ossificans progressiva) or secondary in the site of a pre-existing muscular or connective tissue lesion, such as inflammation, a neoplasm or a benign tumor (Hoda et al., 2014).

Secondary MO usually occurs after trauma (e.g. injuries suffered during sport activities), surgical intervention (e.g.: total hip or knee arthroplasty or hip arthroscopy) or neurological injury (Iorio et al., 2002; Lespasio et al., 2020). In sports medicine, MO is known to be a troublesome sequela of muscle lesions including voluminous haematomas, contusions, strains or repeated injuries causing an important setback in the athletes' career, in certain cases even permanent joint impairment. Brachialis, quadriceps and adductor muscle groups are most commonly affected in MO (Orava et al., 2017; Simon et al., 2016; Devilbiss et al., 2018).

Posttraumatic MO can also frequently develop after significant injuries such as gunshot wounds, blast injury, burns, acetabular fractures and elbow injuries. Military injuries were first described in the literature in connection with the American civil war. Most cases of posttraumatic HO were reported during the Iraq and Afghanistan conflicts, which can be explained by the increased number of blast injuries due to frequent use of explosives (Eisenstein et al., 2017).

Para- or tetraplegic patients usually develop myositis ossificans circumscripta which only affects the motor level of the spinal cord lesion, explaining why this type of MO is more common in posttraumatic para- and tetraplegics with a more extensive spinal cord injury compared to spinal disc herniation or tumoral cases (Knudsen et al., 1982). Central nervous system complications of acquired immune deficiency syndrome (AIDS) can also be associated with MO (Drane et al., 1987).

Furthermore, MO can appear in autoimmune diseases as anti-NMDA receptor encephalitis, Guillain-Barre syndrome, dermatomyositis or inflammatory arthritis (Eckardt et al., 1981; Wang et al., 2016; Zeilig et al., 2016).

Symptoms

Patients with MO usually present pain aggravated by physical activity, persistent local edema, decreased range of motion and muscle strength, often accompanied by palpable firm protrusion within the muscle. Symptoms are increased after 2-3 weeks (Orava et al., 2017).

Diagnosis

Radiographically, MO has a phasic and dynamic image: in the early stages, ossification cannot be detected on radiographs. The typical appearance is a demarcated radiodense mass with a calcified outer shell, otherwise known as "eggshell calcification" (Kransdorf et al., 1993; O'Brien et al., 2012; Kaplan et al., 2000). Hereditary forms usually have a characteristic radiographic appearance: in FOP HO appears as a well-circumscripted area corresponding to a certain skeletal muscle, while in POH it is represented as a "cocoon-like web" connecting the connective tissues and the skeletal muscles (Kaplan & Shore, 2000).

Ultrasonography has been reported to be useful in the early diagnosis of MO, the signs occurring between the 3rd and the 5th week (Simon et al., 2015). Before the appearance of the classic radiological aspects, a unique "zone phenomenon" can be identified by ultrasonography, serving as an early, cost-efficient diagnostic method (Thomas et al., 1991). Power Doppler in muscles provides clues regarding neovascularization and thus healing, and its absence may suggest the possibility for the athlete to resume the sport (Simon et al., 2015).

Computed tomography (CT) can appreciate with precision the maturation of the lesion, although in the early stages only a hypoechogenic mass can be identified; therefore, if MO is suspected, follow-up CT scans are recommended. Cross sectional CT imaging is also important in preoperative planning (McCarthy & Sundaram, 2005).

By MRI, MO appears as a well-demarcated mass with heterogeneous signal, surrounded by perilesional edema (Kransdorf et al., 1991). MO signs appear 2 weeks earlier than ultrasonographic signs (Simon et al., 2015).

The histopathological aspect of early MO lesion is hypercellular, with little bone matrix, and it can be difficult to differentiate it from a soft tissue sarcoma. In later phases, prominent bone formation of a characteristic peripheral ossification can be observed (Hoda et al., 2014).

Differential diagnosis

Secondary MO must be differentiated from congenital forms of heterotopic ossification. Albright hereditary osteodystrophy is a genetic disorder associated with short stature, obesity and shortened fourth and fifth metacarpal and metatarsal bones. Progressive osseous heteroplasia presents with the progressive ossification of soft tissues, frequently resulting in deformity. Patients with fibrodysplasia ossificans progressiva (also known as myositis ossificans progressiva) exhibit bilateral hallux malformation at birth, progressively presenting disabling ectopic skeletogenesis with poor prognosis (Eichenfield et al., 2008).

Most importantly, MO must be distinguished from more aggressive tumoral processes, such as parosteal osteosarcoma, synovial sarcoma or malignant fibrous histiocytoma. In parosteal osteosarcoma, central calcification extends towards the periphery. The typical radiological appearance is the string sign - a thin, radiolucent line separating the tumor from the cortex that can also be seen in MO. A transition between woven bone and mature lamellar bone is found, which enables the distinction of MO from extraskeletal osteosarcoma (Hoda et al., 2014). Synovial sarcoma is a rare and aggressive periarticular soft tissue tumor with sharply demarcated and cystic or multi-lobulated MRI image. Malignant fibrous histiocytoma appears as a soft tissue mass on radiographs, near the diaphysis of a long bone with punctate calcification (Luczynska et al., 2014).

Treatment

MO may have a self-limiting course, when spontaneous resolution occurs, thus the "wait and see" approach is applied initially. Prophylaxis using the "RICE" (rest, ice, compression, elevation) method is important after every sports injury. There are several therapeutic approaches (Table II); conservative treatment including nonsteroidal anti-inflammatory drugs and physical therapy may be sufficient for recovery (Al-Qattan et al., 2017; Torrance & deGraauw, 2011; Simon et al., 2015).

For symptomatic patients with non-hereditary MO, surgical intervention is often the sole viable management option to mitigate the painful or restricted motion or discomfort caused by prominent bone structure. Optimally, the procedure is performed after the completion of maturation (approximately 6 months after initiation), using complete excision. Athletes can resume light physical activity by 1-3 months, full activity by 6 months, and reaching their preinjury level in 1 year postoperatively (Orava et al., 2017; Simon et al., 2016; Devilbiss et al., 2018). In certain cases incomplete excision remains the only option, as the intervention may result in the lesion of major neurovascular structures, causing neurovascular injuries (Winkler et al., 2015).

Table II
Classification, types of therapeutic approaches.

Pathogenesis	Types of therapy	Mechanisms	References
Addressing tissue hypoxia	Shock wave therapy	Microdisruption of avascular tissues, neovascular angiogenesis; mechanotransduction to myocytes, fibroblasts and ECM	Torrance & deGraauw, 2011; Hara et al., 2020
	Radiotherapy	Angiogenesis inhibition	Delos et al., 2013
	Moderate activity	Vasodilation; ECM remodeling	Vanden et al., 2005
	Vasoactive agent (phentolamine, safflower injection)	Promote vasodilatation, blood flow to the injury site	Huang et al., 2020; Wang et al., 2018; Joyner et al., 2014
	HIF-1α inhibitors (PX-478, Rapamycin)	Inhibition of *HIF-1α* gene expression	Liu et al., 2015; Wu et al., 2019; Koh et al., 2008; Qureshi et al., 2017; Kaplan et al., 2018
	Selective HIF-1α knockout (in animal studies)	Decrease target gene expression	Huang et al., 2020
Addressing inflammation	NSAID (Nonsteroidal anti-inflammatory drugs)	Inhibition of COX, reduce inflammatory response	Huang et al., 2020; Ma et al., 2018; Xue et al., 2011
Addressing ossification	Colchicine	Inhibits heterotopic ossification	Dudkievicz et al., 2005
	Bisphosphonates	Decrease mineralization of bone matrix; useful in post-trauma prophylaxis rather than therapy	Mavrogenis & Soucacos , 2011; Barra de Moraes et al., 2012; Hara et al., 2020
	Ascorbic acid	Modulation of procollagen III synthesis	Barra de Moraes et al., 2012
Surgical removal	Excision of ossified myositis	Surgical timing is critical (a year-long after injury to ensure full maturation and minimize recurrence)	Vanden Bossche & Vanderstraeten, 2009; Delos et al., 2013

NSAID: non-steroidal anti-inflammatory drugs; ECM: extracellular matrix; HIF-1α: hypoxia-inducible factor-1α; COX: cyclooxygenase

In elite and sub-elite athletes the use of extracorporeal shock wave therapy proved to be an efficient treatment alternative (Torrance & deGraauw, 2011). Colchicine has been found to reduce MO after total hip arthroplasty through its tissue mineralization and cell proliferation inhibitor properties (Salai et al., 2018). The absence of power Doppler hypervascularisation may be a useful method to monitor the response to therapy and return to sport, in athletes (Simon et al., 2015).

Conclusions

1. MO is a rare but serious, often misdiagnosed disorder.

2. While hereditary forms generally have poor prognosis, secondary MO may also present potentially disabling consequences.

3. Although there are no universal therapeutic or prophylactic measures, there are some possible options to prevent or mitigate the symptoms of this disease.

Conflict of interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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