Current Concepts Review

Bone Marrow Edema

Overview of Etiology and Treatment Strategies

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- Bone marrow edema (BME) is a nonspecific but relevant finding, usually indicating the presence of an underlying pathology.
- The gold standard technique for detecting BME is magnetic resonance imaging (MRI), as it allows for a correct diagnosis to be made, which is extremely important given the heterogeneity of BME-related diseases.
- Depending on the severity of painful symptomatology and the MRI evidence, different treatment strategies can be followed: physical modalities, pharmacological options, and surgical therapy.

The term *bone marrow edema* (BME) was first used, to our knowledge, by Wilson et al. in 1988[1]. The gold standard technique for detecting BME is magnetic resonance imaging (MRI) as it allows for a correct diagnosis to be made, which is extremely important given the heterogeneity of BME-related diseases. BME possesses an intermediate signal on T1-weighted MRI scans and a high signal on T2-weighted scans[2]. On fat-suppressed, contrast-enhanced MRI scans and short tau inversion recovery (STIR) MRI scans, BME appears hyperintense compared with normal marrow[3-5] (Fig. 1). It is a nonspecific but relevant finding, usually indicating the presence of an underlying pathological condition[6]. Currently, another term used to refer to this condition is *edema-like marrow signal intensity*, which indicates a histopathological diagnosis characterized by the presence of an eosinophilic bone marrow extracellular fluid and swollen fat cells[7]. When BME is found on MRI as an isolated finding without obvious cause, it is defined as *BME syndrome* (BMES)[2,5]. This term describes a clinical radiographic entity in which transient nonspecific subacute or chronic joint pain, predominantly of the hip and knee, is associated with characteristic MRI appearances in the absence of specific signs of osteonecrosis, antecedent trauma, or infection[5,8]. The triggering cause of pain perception in diseases characterized by the presence of BME is poorly understood and is thought to be multifactorial: the increased intraosseous pressure with irritation or disruption of sensory nerves within the bone marrow, venous hypertension, raised focal bone turnover with or without microfractures, and irritation of the periosteum and periarticular structures could all be possible mechanisms[4,9]. BME appearance includes homogeneity, lack of sharp margins, and no respect for anatomical boundaries such as physeal scars[1,3].

Etiologies of BME

Depending on the etiology, BME is classified as primary or secondary edema[10]. Primary BME presents as an isolated finding on MRI with no obvious cause[11]. The etiology of this kind of edema remains uncertain; it has been suggested that a local ischemic episode, due to a variety of possible triggers, may initiate a chain of events leading to BME[12-14]. Regarding secondary edema, 8 categories have been identified: trauma-induced lesions, degenerative lesions, inflammatory lesions, ischemic lesions, infectious lesions, metabolic or endocrine lesions, iatrogenic lesions, and neoplastic lesions[5] (Table I).

Trauma-induced lesions, which include 7 different known types, represent one of the most important and frequent mechanisms in determining the onset of BME[15]. Undoubtedly, the knee is one of the main sites subject to trauma, as it is the major weight-bearing joint that provides mobility and stability during physical activity, as well as balance while standing[16,17]. With respect to degenerative lesions, BME has been mainly related to osteoarthritis, generally characterized by pain, impaired joint function, synovitis, and joint effusion[18]. However, the progression of such

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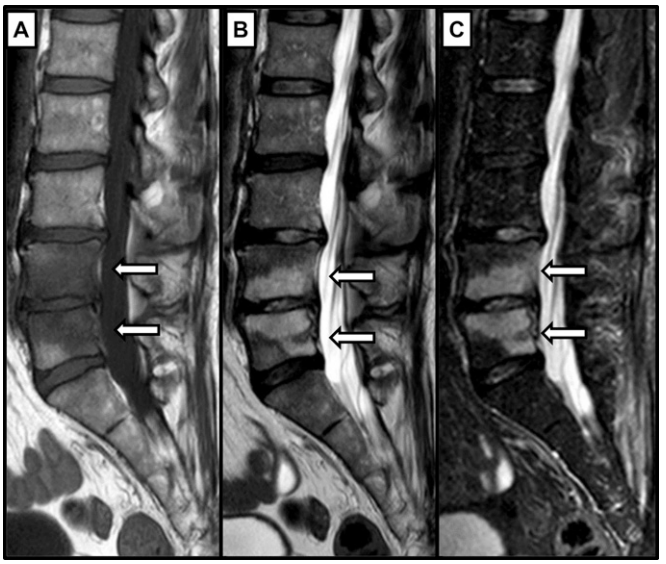

Fig. 1

Figs. 1-A, 1-B, and 1-C MRI features of BME in a patient with L4-L5 spondylodiscitis. The BME in these vertebral bodies (arrows) shows low signal intensity on T1-weighted sequences (**Fig. 1-A**) and high signal intensity on fluid-sensitive sequences, including a T2-weighted sequence (**Fig. 1-B**) and a short tau inversion recovery (STIR) sequence (**Fig. 1-C**).

pathology is also influenced by BME, represented by regions of high metabolic activity and increased expression of genes involved in neuronal development, pain, extracellular matrix turnover, cartilage and bone formation, and angiogenesis[19]. BME is also involved in the pathogenesis of many musculoskeletal inflammatory diseases, including rheumatoid arthritis, in which it is considered a predictor of rapid radiographic progression of this disease and may be a more sensitive indicator of the response to therapy than synovial appearance[20]. Among ischemic lesions, a typical example is osteonecrosis, a disease that causes a range of mild to severe osseous changes[21]. In osteonecrosis, the ischemia is of a prolonged duration, causing bone necrosis in addition to marrow necrosis[21]. In addition, complex regional pain syndrome (CRPS) is an ischemic injury, characterized by symptoms of continuous, diffuse burning pain; sensory-motor alterations; and trophic disturbances that initially occur at 1 joint and can, in chronic cases, spread to involve the entire limb[22,23]. Regarding infectious lesions, BME is frequently associated with primary osteomyelitis[24] and infectious arthritis[4]. BME has also been related to the occurrence of endocrine lesions, such as intraosseous tophi in patients with gout, or metabolic lesions, such as hydroxyapatite deposition disease (HADD), in which BME develops at the insertion site of a diseased tendon[25-27]. In relation to iatrogenic lesions, BME generally occurs after radiation therapy and manifests as a rapid change that is no longer detectable >21 days after treatment[28]. Finally, BME can be found in association with a variety of benign and malignant neoplasms, but is more often associated with benign lesions, such as osteoid osteoma, osteoblastoma, chondroblastoma, and Langerhans cell histiocytosis[29]. Each specific tumor has a particular pattern of edema, so it is possible to identify the histological type of the tumor even before performing the biopsy. In general, benign bone lesions often show a greater amount of surrounding BME than malignant lesions[30].

Reversible and Progressive BME

Depending on the differences in location (e.g., femoral head, femoral neck, or acetabulum), and the response of the lesion to conservative treatment, BME is classified as reversible or progressive[31-33]. The first category consists of transient BMES (TBMES) and regional migratory BMES (RMES), while the second category may include osteonecrosis of the femoral head (ONFH), subchondral insufficiency fracture (SIF), and hip osteoarthritis[34-37] (Table II). As these pathologies are very different in terms of medical therapies and clinical outcomes, a specific diagnosis is essential to avoid harmful or unnecessary treatments.

Transient BME Syndrome

Patients affected by TBMES have focal loss of radiodensity, positive bone scans, and evidence of BME on MRI[38]. The etiology of primary TBMES remains uncertain. It is believed that a local ischemic episode, which can caused by a variety of triggers, may initiate a chain of events resulting in BME; in fact, histological findings show abnormal vascularity, edema, and increased focal bone turnover[12,13]. Typically, patients without a history of major trauma are seen with an acute onset of hip pain accompanied by a decreased range of motion and a limping gait[32,39]. TBMES spontaneously resolves within several months to a year with conservative treatment focusing on decreased loading on the hip and hip-sparing activities and postures[37,40].

Regional Migratory BMES

RMES is an uncommon condition that develops spontaneously or may be triggered by minor trauma[32,41]. The clinical presentation is unspecific and similar to TBMES[42,43]. Typically, men between the third and fifth decade of life are 3 times more commonly affected[40,41,44]. MRI shows BME-related findings with possible involvement of the subchondral bone of the femoral head. The condition can also migrate to the contralateral hip or other joints after a few years[45]. It resolves spontaneously in each joint within 4 to 6 months.

ONFH

ONFH affects young subjects between 20 and 40 years old and may lead to permanent joint failure[46], resulting from an idiopathic process or secondary to an ischemic lesion caused by trauma, alcoholism, corticosteroid use, or hematological disorders[45,47]. It is caused by a decrease in blood flow to the femoral head, leading to cellular death, fracture, and collapse of the articular surface[48-50]. The collapse of the femoral head may occur within 2 years in 85% of hips with symptomatic ONFH, leading to disastrous consequences to the joint[51]. BME of the proximal femur in ONFH is most likely to be a secondary finding, representing increased intercellular fluid related to fracture[37]. Depending on the disease stage, the hip can have a wide range of radiographic appearances: normal, mottled radiodensity and a

TABLE I Etiological Classification of Secondary Bone Marrow Edema*

Clinical Condition According to Etiology	MRI Findings	References
Trauma-induced lesions		
Altered stress and/or biomechanical injury	Subchondral and wedge-shaped BME, with the base of the wedge located at the site of greatest stress or load, correlated to an area of extensive microfractures due to repeated altered stress on the bone	Starr et al.[4] (2008)
Plantar fasciitis	Thickening of the plantar fascia, T2-weighted high-signal-intensity area in the fascia, and BME around the plantar fascia and the calcaneus	Quaranta et al.[88] (2021)
Bone bruise, contusion, and/or microfracture	Areas of reticular stranding (decreased signal intensity on T1-weighted spin echo image surrounded by BME); STIR imaging demonstrates a heterogeneous distribution of BME	Fukui et al.[89] (2015)
Stress fracture	Irregular band of low signal intensity on all sequences with surrounding BME	Fabbriciani et al.[90] (2012)
Compression fracture	"Bone bruise" pattern of decreased T1-weighted signal and increased T2-weighted signal, with or without associated fracture line	Rolvien et al.[91] (2017)
Internal derangement with joint effusion	Fat-saturation proton-density MRI shows hyperintense effusion	Chien et al.[92] (2020)
Osteochondral injuries	BME manifests as a region of low signal intensity on Tl-weighted and high signal intensity on T2-weighted sequences	Starr et al.[4] (2008)
Degenerative lesions		
Osteoarthritis	BME pattern is typically associated with subchondral cysts, cartilage defects, meniscal degeneration, and subchondral insufficiency fractures	Xu et al.[19] (2012)
Inflammatory lesions		
Rheumatoid arthritis	Synovitis, osteitis, tenosynovitis, bone erosion, and cartilage damage	Østergaard and Boesen[20] (2019)
Ankylosing spondylitis	BME is visible as hyperintense signal in the STIR sequence and as hypointense signal in the T1-weighted sequence. Post-inflammatory changes, such as fat deposition, are visible as hyperintense signal in the T1-weighted sequence and hypointense signal in the STIR image. Structural changes (subchondral erosions) are seen in both sequences	Sudol-Szopinska and Urbanik[93] (2013)
Psoriatic arthritis	Enthesitis, multifocal BME, periostitis, cortical bone thickening, and extracapsular enhancement accompanying articular or tendon sheath synovitis	Spira et al.[94] (2010)
Ischemic lesions		
Osteonecrosis	Bone necrosis that results in a reactive interface visible on MRI as a band of low signal intensity surrounded by a focal peripheral edematous area	Stoica et al.[21] (2009)
CRPS	Typical pattern of (periarticular) BME (decreased on T1-weighted and increased on T2-weighted sequences) caused by a combination of hyperemia, increased bone metabolism, and inflammation; clinical signs include soft-tissue edema, skin changes, joint effusions, skin and intra-articular contrast enhancement, muscle atrophy, and fibrosis of periarticular structures	Rupasov et al.[23] (2017)
Infectious lesions		
Osteomyelitis	BME on fluid-sensitive sequences and replacement of fat signal on T1-weighted images	Sax et al.[24] (2020)
Infectious arthritis	Periarticular BME with concomitant changes in the cartilage, joint capsule, and soft tissues in severe cases; only periarticular BME in milder cases	Starr et al.[4] (2008)
Metabolic or endocrine lesions		
HADD	T2-weighted images show foci of low signal intensity corresponding to the calcification, and increased signal intensity around the foci, representing BME	Kuroda et al.[25] (2004)
Gout	BME correlates with tophi, which show a low to intermediate signal intensity on T1-weighted images and variable intensity on T2-weighted images	Carter et al.[26] (2009)
Iatrogenic lesions		
Post-radiation therapy	Areas of increased signal intensity in STIR images may represent edema, hemorrhage, or an early reflux of nonirradiated cells	Romanos et al.[28] (2013)
Neoplastic lesions		
Osteoid osteoma	Nonspecific findings such as hip joint effusion, perinidal BME, and soft-tissue mass	Gaeta et al.[95] (2004)
Osteoblastoma	T1-weighted fat-saturated sequence shows strong enhancement of the nidus with extensive perifocal BME	Kintzelé et al.[96] (2020)
Chondroblastoma	BME, periosteal and soft-tissue reactions, and varying signal intensity on T2-weighted sequence	Gao et al.[97] (2019)

*MRI = magnetic resonance imaging, BME = bone marrow edema, STIR = short tau inversion recovery, CRPS = complex regional pain syndrome, and HADD = hydroxyapatite deposition disease.

TABLE II Schematic Representation of the Etiological Classification of Proximal Femoral BME*

Classification	Characteristics	Studies
Reversible		
TBMES	• Caused by a local ischemic episode • Hip pain • Decreased range of motion • Limping gait	Berger et al.[12] (2003), Trevisan et al.[13] (2002), James et al.[30] (2008), Bilgici et al.[38] (2010), and Geith et al.[39] (2017)
RMES	• Spontaneous development or caused by a minor trauma • Clinical presentation like TBMES	James et al.[30] (2008), Balakrishnan et al.[41] (2003), Korompilias et al.[42] (2008), and Ergun and Lakadamyali[43] (2008)
Progressive		
ONFH	• Idiopathic or secondary ischemic lesion • Clinical presentation like TBMES and RMES • Hip pain and joint degeneration	Fernandez-Canton[45] (2009), Moya-Angeler et al.[46] (2015), and Zeng et al.[47] (2020)
SIF	• Secondary to osteoporosis or osteopenia • Usually, unilateral	Davies et al.[36] (2004), Bangil et al.[56] (1996), and Yamamoto et al.[57] (2001)
OA	• Hip pain • Joint destruction	Boutry et al.[61] (2002) and Watanabe et al.[63] (2002)

*BMES = bone marrow edema syndrome, TBMES = transient BMES, RMES = regional migratory BMES, ONFH = osteonecrosis of the femoral head, SIF = subchondral insufficiency fracture, and OA = osteoarthritis.

"crescent sign," joint space narrowing, subchondral cysts, and osteophytes at a later stage[52]. The crescent sign seen in conventional radiographs, despite not being a unique feature of ONFH, is usually associated with this disease and is the result of cumulative microfractures induced by fatigue within the necrotic zone[53]. Vande Berg et al. showed that, in hips with ONFH, a low signal

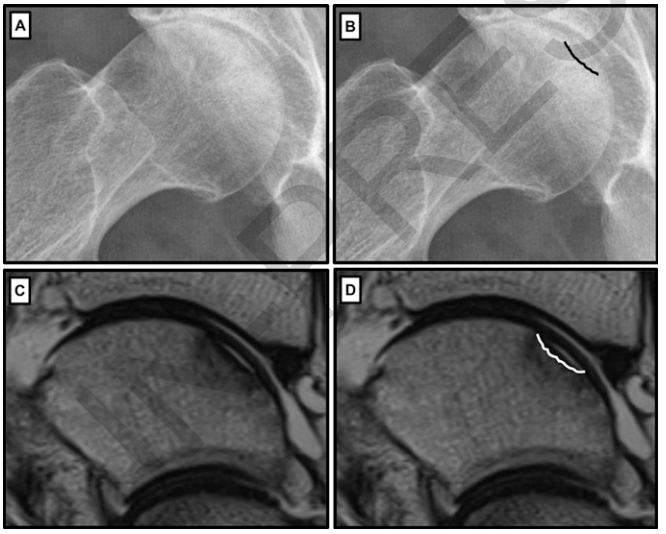

Fig. 2

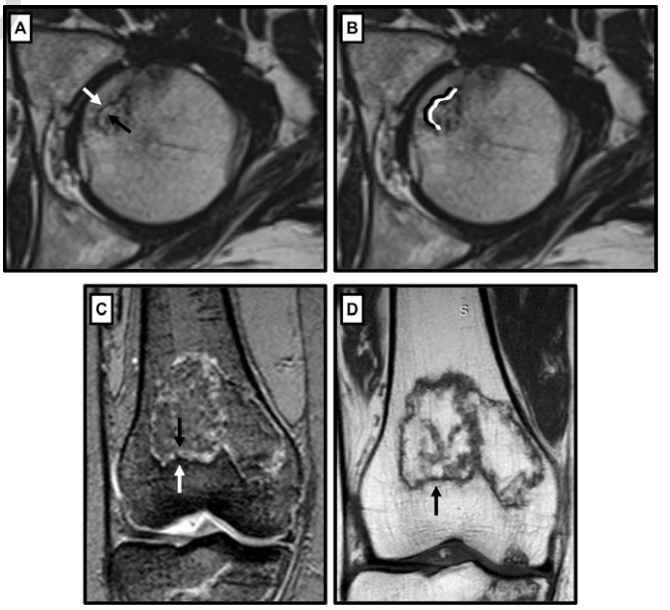

Fig. 3

Figs. 2-A through 2-D Examples of the crescent sign in ONFH. **Figs. 2-A and 2-B** Frog-leg lateral radiographs of the hip in a 55-year-old woman with ONFH demonstrate a crescent sign, which is a curvilinear lucent subchondral line (black line) associated with ONFH. **Figs. 2-C and 2-D** T2-weighted sagittal MRI sequences of the talus in a 66-year-old man showing a subchondral hypointense line indicating an osteochondral lesion related to ONFH (white line). **Figs. 3-A through 3-D** Examples of the double-line sign seen on MRI scans. **Figs. 3-A and 3-B** T2-weighted MRI sequences of the left hip in a 64-year-old man with ONFH. An inner high-signal-intensity line represents reparative granulation tissue (black arrow in **Fig. 3-A** and highlighted in white in **Fig. 3-B**) and an outer low-signal-intensity line represents adjacent sclerotic bone (white arrow in **Fig. 3-A** and highlighted in black in **Fig. 3-B**). **Figs. 3-C and 3-D** Double-line sign in a 53-year-old woman with osteonecrosis of the knee. **Fig. 3-C** T2-weighted fast-field-echo acquisition is effective at highlighting the double-line sign, with the hyperintense inner line (black arrow) and the hypointense outer line (white arrow). **Fig. 3-D** In this T1-weighted sequence, it is possible to detect only the outer hypointense line (arrow).

TABLE III Treatment Strategies for BME*

Treatment Strategies	Pathology	Phase	Level of Evidence	Studies
Physical modalities				
Mechanical unloading	Osteonecrosis	Early	IV	Barp et al.[64] (2019)
PEMF	ONFH		IV	Massari et al.[65] (2006)
ESWT	ONFH		V	Wang et al.[68] (2015)
Surgical therapy				
Core decompression	ON	Early	IV	Beckmann et al.[84] (2013)
Red marrow grafting	ONFH		V	Millikan et al.[85] (2015)
Subchondroplasty	OA		I	Ververidis et al.[86] (2019)
PRP	OA		II	Nguyen et al.[87] (2017)
Osteotomies	ONFH	Late	I	Quaranta et al.[88] (2021)
THA	OA		III	Fukui et al.[89] (2015)
Pharmacological options				
Iloprost	BMES	Early	IV and I†	Tosun et al.[74] (2020) and Disch et al.[75] (2005)
Bisphosphonates				
Alendronate	Osteonecrosis		I	Agarwala et al.[76] (2005)
Zoledronic acid	TOH		V, IV, and III†	Asadipooya et al.[34] (2017), Evangelatos et al.[78] (2020), and Fabbriciani et al.[90] (2012)
Clodronate	OA		I	Frediani et al.[79] (2020)
Ibandronate	BMES		II	Bartl et al.[82] (2012)
Neridronate	CRPS-1		I	Varenna et al.[83] (2013)
Denosumab	Idiopathic BME		IV	Rolvien et al.[91] (2017)
Teriparatide	TOH		III	Fabbriciani et al.[90] (2012)

*PEMF = pulsed electromagnetic fields, ESWT = extracorporeal shock wave therapy, ONFH = osteonecrosis of the femoral head, ON = osteonecrosis, OA = osteoarthritis, PRP = platelet-rich plasma, THA = total hip arthroplasty, BMES = bone marrow edema syndrome, CRPS-1 = complex regional pain syndrome 1, and TOH = transient osteoporosis of the hip. †Levels of evidence are given in the same order as the studies in the next column.

intensity in the subchondral area with a thickness of ≥4 mm on T2-weighted images suggests an irreversible lesion with a specificity of approximately 92%[54]. The crescent sign refers to a linear cleft that is due to subchondral fracture in the setting of ONFH (Fig. 2). It is typically a radiographic finding, but it can also be seen on computed tomography (CT) and MRI. On radiographs, the crescent sign is seen as a curvilinear lucent subchondral line, corresponding to the subchondral hypointense line seen on MRI. This sign can occur at the femoral and humeral heads, scaphoid, lunate, and talus.

On T2-weighted MRI scans, a "double line" sign can be seen as an inner bright line representing granulation tissue and an outer dark line representing sclerotic bone[54] (Fig. 3). This sign can be found at the periphery of a necrotic area and represents the border between the viable and nonviable bone. The double-line sign is seen better on T2-weighted sequences (Figs. 3-A and 3-B) than on T1-weighted sequences (Fig. 3-D), in which it is possible to detect only the outer hypointense line. The T2-weighted fast-field-echo sequence effectively highlights the double-line sign, with the hyperintense inner line and the hypointense outer line (Fig. 3-C).

SIF

In contradistinction to the previously described diseases, SIF may completely resolve or progress toward epiphyseal collapse[54,55]. SIF involves bone fragility, usually secondary to osteoporosis or osteopenia without any evidence of osteonecrosis, which leads to subchondral fractures in the femoral head[56,57]. Patients with SIF usually develop symptoms in their 50s and are usually unilaterally affected[36,57]. Diverging from ONFH, the proximal segment of the femoral head in SIF is generally vital and contains repair tissue with associated edema[37]. SIF is also characterized by viable bone and bone marrow elements associated with edema, granulation tissue, and immature bone without any evidence of prior bone infarction[36,58,59]. The rates of SIF progression are not clear; therefore, conservative treatment is the first line of treatment, leaving surgical procedures for patients with progressive destruction of the femoral head[60].

Osteoarthritis

Osteoarthritis may be the most recognized cause of hip pain, as all of the classic signs (subchondral cysts, subchondral bone sclerosis, osteophytes, and joint line narrowing) involve the acetabulum and femoral head[61]. Nevertheless, on rare occasions, it may also present a BME pattern, which is associated with a rapidly progressive joint destruction[61-63]. A combination of MRI changes may be seen as a deformity of the subchondral bone plate, impaction fractures of the trabecular bone, and extensive marrow infiltration[32,63]. BME has proved to be an important marker: the degree of

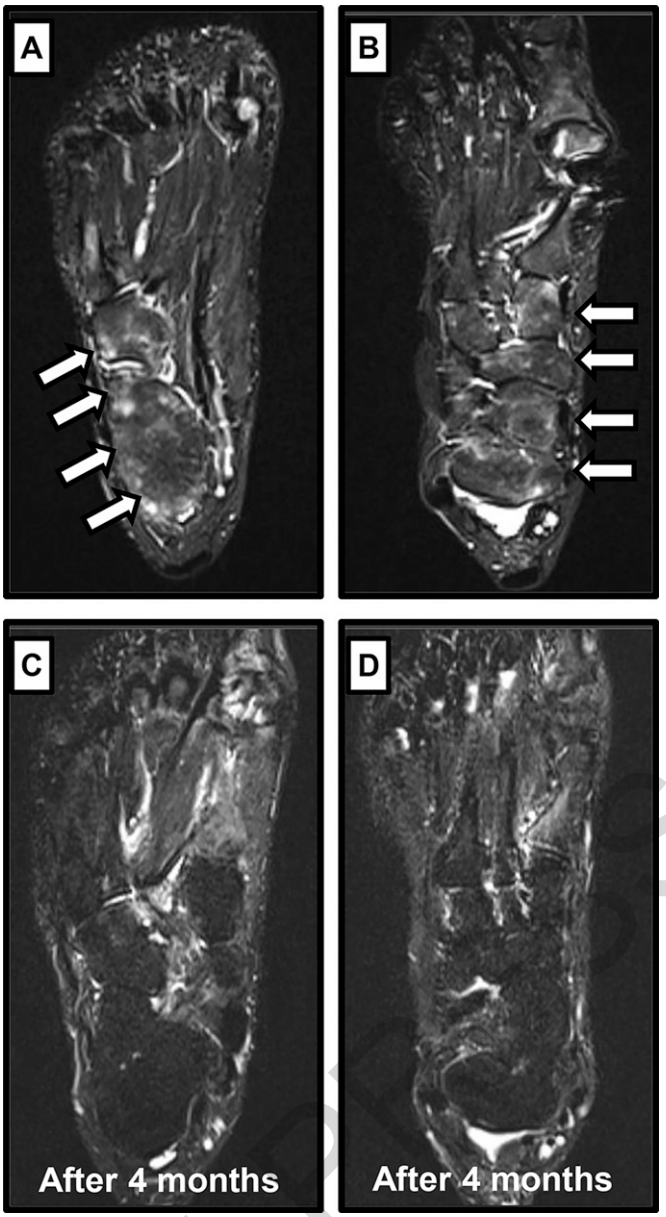

Fig. 4

Figs. 4-A through 4-D The effect of BME treatment with neridronate in a 58-year-old woman with complex regional pain syndrome-1 (CRPS-1). **Figs. 4-A and 4-B** Axial STIR sequence MRI scans show the typical "patchy" distributed BME in the calcaneus, talus, cuboid, and cuneiform bones (arrows) in the baseline evaluation. **Figs. 4-C and 4-D** Axial STIR sequence MRIs made 4 months after treatment show that BME was no longer detectable in the same sites.

edema in patients with advanced hip osteoarthritis is associated with the severity of pain, the radiographic grading of osteoarthritis, and the number of microfractures in the examined subchondral regions of the femoral head[35].

Treatment Strategies

Three different strategies exist for BME treatment: physical modalities, pharmacological options, and surgical therapy (Table III).

Physical Modalities

In the early stages of diseases characterized by evidence of BME on MRI, a conservative treatment that is based on mechanical unloading and abstention from physical activity for a prolonged period is usually appropriate[64]. Among the physical modalities, treatment with pulsed electromagnetic fields (PEMF) has anti-inflammatory effects on bone tissue, reducing the production of free radicals and stimulating osteoblasts to add new bone matrix[65]. The PEMF-induced increase in bone turnover leads to a reduction in BME and consequently in pain perception, shortening the natural course of the disease[66]. Extracorporeal shock wave therapy (ESWT) has also been shown to have a beneficial effect because of its angiogenic, analgesic, and anti-inflammatory properties[67]. Specifically, it has been shown to be effective in treating the early stages of ONFH, leading to a reduction in BME and consequently in pain and to improvement in hip function[68]. Also, the addition of hyperbaric oxygen therapy results in an accelerated recovery of hip function compared with pharmacological therapy alone in BME treatment[69].

Pharmacological Options

The first therapeutic strategy to be implemented for the treatment of any clinical condition caused by BME is to reduce pain and the duration of disease. To date, treatment options are limited[70,71]. Several researchers have agreed that iloprost, a prostacyclin analog, can reduce BME and induce a substantial improvement in symptoms[72-74]. For example, Disch et al. observed that iloprost treatment in patients with isolated BME or in those with BME associated with proximal femoral necrosis resulted in a sustained improvement in symptoms in both groups, as well as a substantial improvement with respect to range of motion, pain, and extension of the edema area[75]. Therefore, the authors proposed that the main goal of iloprost therapy should be to prevent the further spread of necrosis by reducing edema formation[75]. Bisphosphonates have shown promising results in the management of ONFH; among them, oral alendronate is known to delay disease progression, prevent collapse, improve clinical outcomes, and potentially avoid arthroplasty[76]. More recently, Agarwala et al. demonstrated that the combination of oral alendronate and intravenous zoledronic acid is superior to oral alendronate-only therapy in preventing radiographic progression and collapse in osteonecrosis, since zoledronic acid is more bioavailable after administration[77]. In this regard, Evangelatos et al. conducted an experimental study to evaluate the efficacy and safety of zoledronic acid infusion in patients with transient osteoporosis of the hip (TOH), as well as the sustainability of the therapeutic effect[78]. Their results showed that a single infusion of 5 mg of zoledronic acid in patients with TOH was safe and led to a resolution of the BME, as well as to a decrease in severe pain within 1 month, a rapid functional recovery, and prolonged remission[78]. Frediani et al. recently evaluated the efficacy of clodronate in reducing pain and BME in knee osteoarthritis[79]. Their results showed that intramuscular administration of a therapeutic dose of clodronate followed by a maintenance dose was effective in the management of symptomatic knee osteoarthritis, improving functional outcomes and reducing pain and BME; furthermore, prolonged treatment increased the long-term efficacy

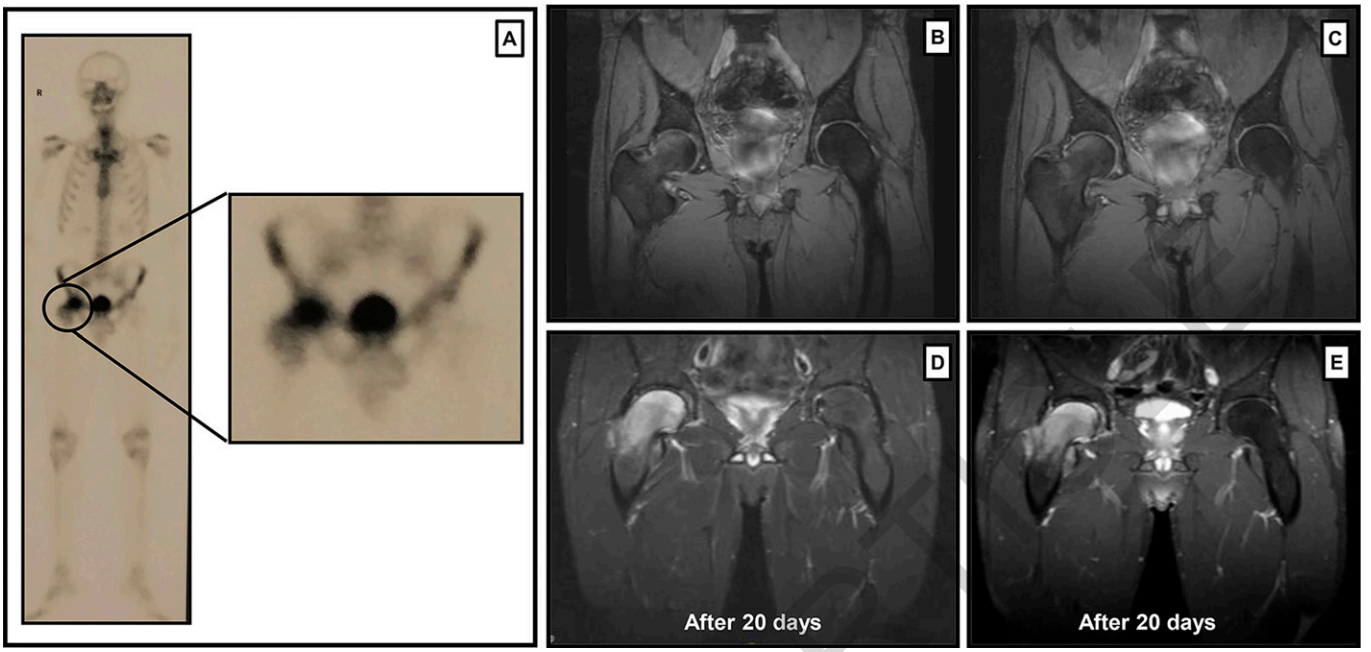

Fig. 5

Figs. 5-A through 5-E Effect of BME treatment with neridronate in a 40-year-old male soldier who reported intense pain in the right coxofemoral region following intense running activity. **Fig. 5-A** When the patient was first seen, the scintigraphy examination in the bone phase showed a late hyperfixation of the osteotropic radiopharmaceutical in the right coxofemoral region, especially in the femoral head and to a lesser extent in the trochanteric region, suggesting a CRPS-1 diagnosis. **Figs. 5-B and 5-C** Pelvic T1-weighted (**Fig. 5-B**) and T2-weighted MRI (**Fig. 5-C**) made at the first examination. **Figs. 5-D and 5-E** After 20 days from the start of treatment with neridronate, the patient reported a marked improvement in pain symptoms, but the T1-weighted (**Fig. 5-D**) and T2-weighted MRI scans (**Fig. 5-E**) showed a residual area of hyperintensity in the right coxofemoral region.

of clodronate compared with the shorter schedule[79]. In contrast, intravenous ibandronate is a potent osteoclast inhibitor with proven efficacy and good tolerability in osteoporosis and metastatic bone disease[80,81]. Bartl et al. conducted a prospective observational study to investigate whether the natural course of BME can be shortened with ibandronate infusion therapy in 30 patients compared with a control group receiving conventional therapy[82]. They showed that the intravenous infusion of ibandronate produced rapid and effective relief of bone pain after 1 month, achieving substantially better pain relief than the results in the control group. Thus, with a low rate of side effects compared with other treatment options, intravenous application of ibandronate represents an effective, safe, and economical option for the treatment of BMES[82]. In contrast, neridronate was effective in the treatment of type 1, as demonstrated by Varenna and colleagues[83]. Their randomized, double-blinded, placebo-controlled study showed that intravenous administration of 100 mg of neridronate was associated with a reduction in pain symptoms and an improvement in functional status in patients with CRPS-1 of the hand or foot[83]. As an example, one of our patients, a 58-year-old woman with CRPS-1, had the typical "patchy" distribution of BME in the calcaneus, talus, cuboid, and cuneiform bones and was treated with neridronate infusion therapy (100 mg) (Fig. 4). At the end of therapy, 4 months after the first examination, BME was no longer detectable in the same sites. Another patient, a 40-year-old male soldier, reported severe pain in the right coxofemoral region following intense running activity (>5 km per day for >20 days) (Fig. 5). He subsequently was seen with sudden hyperesthesia, allodynia, functional limitation (walking with canes for support of the left leg), and skin discoloration at the hip and thigh on the right side. The scintigraphic examination (Fig. 5-A) showed, in the bone phase, a late hyperfixation of the osteotropic radiopharmaceutical in the right coxofemoral region, especially in the femoral head and to a lesser extent in the trochanteric region. This condition of osteometabolic hyperactivity, associated with a modest increase in local vascular permeability, was found to be compatible with a diagnosis of CRPS-1. As the patient reported severe pain (a score of 9 on a visual analog scale), and in consideration of the MRI findings (Figs. 5-B and 5-C), he was managed with the following therapeutic regimen: 100 mg of neridronate, 1 capsule/day of alprazolam, 100,000 IU of vitamin D, and Paracetamol (acetaminophen)-codeine as needed. After 20 days from the start of treatment, the patient reported a marked improvement with respect to pain, but the MRI examination (Figs. 5-D and 5-E) showed a residual area of hyperintensity in the right coxofemoral region. This suggests that the improvement reported by the patient is almost always unrelated to the improvement of the condition detectable on imaging.

Surgical Therapy

Surgery should be reserved for patients in whom pharmacological treatment and physiotherapy have failed. The earliest hypotheses pertaining to BME formation focused on reduced

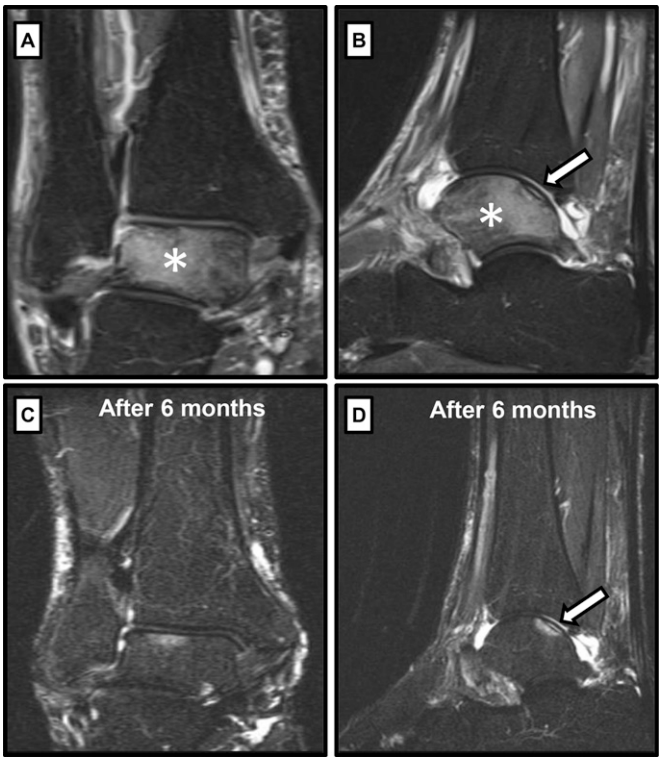

Fig. 6

Figs. 6-A through 6-D Effect of BME treatment with PRP in a 66-year-old man. **Figs. 6-A and 6-B** STIR MRI sequences made at the baseline evaluation show profuse high-signal-intensity BME of the talus (asterisks) secondary to an osteochondral lesion (arrow) of the posterior aspect. **Figs. 6-C and 6-D** STIR MRI sequences made 6 months after treatment show an almost total disappearance of the BME with only a small crescent sign (arrow in Fig. 6-D).

microcirculation leading to ischemia and increased intraosseous pressure[2]. On the basis of this hypothesis, core decompression was introduced as one of the earliest interventions to reduce pain and increase function since it provides surgical drilling of holes in BME sites to relieve pressure[84]. It is effective for symptomatic relief in early stages in all patients who have a painful hip secondary to osteonecrosis and for transient symptomatic relief in patients in an advanced stage[84]. The small number of progenitor cells in the proximal end of the femur with ONFH does not allow sufficient regeneration of bone tissue in the affected area; red marrow grafting, which contains osteogenic precursors that repopulate osteonecrotic bone, is therefore another efficient strategy in the treatment of this clinical condition[85]. On the other hand, subchondroplasty, which is used for the knee but also for hip and ankle treatment, is a procedure developed to treat bone marrow lesions by injecting a calcium phosphate bone-substitute into compromised subchondral bone, under fluoroscopic guidance[86]. Among the new emerging modes of treatment, platelet-rich plasma (PRP) therapy showed moderately good results in selected patients. The application of autologous platelet concentrate allows the local release of the growth factors contained in the platelets, providing an effective stimulus for bone regeneration[87]. As an example, another of our patients, a 66-year-old man with profuse high-signal-intensity BME of the talus secondary to an osteochondral lesion of the posterior aspect, did not undergo surgery, but was treated with immobilization and administration of PRP (Fig. 6). The STIR sequence MRI performed 6 months after treatment showed almost complete disappearance of the BME.

Recommendations and Overview

BME currently remains a complex phenomenon because of the heterogeneous clinical conditions in which it is manifested. In fact, BME occurrence can be due to a variety of causes, and there are several ways in which it can appear on MRI. Thus, it is difficult for the clinician to make a correct diagnosis and, consequently, determine the most appropriate treatment. Therefore, the aims of this review were to provide a more detailed review of the many clinical conditions associated with the detection of BME on MRI and to focus our attention on possible treatment strategies. In fact, it is essential to identify the different clinical manifestations early and to establish which pharmacological strategies can be used to avoid the surgery that is required in the late and advanced stages of the disease. It is necessary to identify a treatment profile that unites different contexts, a sort of "neoadjuvant" therapy that allows BME to be reduced before surgery or a treatment that allows surgery to be avoided completely.

In conclusion, a standardized protocol needs to be developed and followed so that a clinician can identify the correct etiology of BME, rapidly make an accurate diagnosis, and determine the most effective therapeutic strategy. Finally, we believe that continued research in this field is needed to determine other potential diagnostic tools that can complement and improve the assessments that are made on the basis of MRI findings.

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