Multimodal conservative treatment of migrating bone marrow edema associated with early osteonecrosis of the hip

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Abstract
Bone marrow edema syndrome is a severely disabling painful condition without a defined treatment and related to pathogenetic mechanisms not yet clearly recognized. We report the case of a 59-year-old post-menopausal woman, affected by bone marrow edema associated with early osteonecrosis of the femoral head with secondary appearance of a rare migrant bone edema of the hip acetabulum. Clinical evaluation and magnetic resonance imaging were used to monitor the outcome of the patient. Pre-treatment clinical evaluation revealed pain upon stepping with the left limb, reduced range of motion of spine and hip, and hip pain during passive rotation. Magnetic resonance imaging showed diffuse signal alteration of the head and neck of the left femur in relation to bone edema, associated with an unclear small cephalic area of the femoral head suggestive of initial osteonecrosis. A further computed tomography scan was performed that did not reveal any alterations in bone profile, interruption of the cortex, or trabecular bone collapse. We immediately started a multimodal conservative treatment administering neridronate (100 mg, intravenously) combined with calcium and vitamin D supplementation and biophysical therapies (magnetotherapy and extracorporeal shockwave therapy). We also instructed the patient not to bear the load on the affected lower limb during standing and walking, using crutches. After 2 months, a notable regression of pain with improvement in mobility was observed. Magnetic resonance imaging revealed complete regression of edema at the head and neck of the femur; however, the new appearance of acetabular bone edema of the ipsilateral acetabular roof was detected. After 4 months, a third magnetic resonance imaging showed the disappearance of the femoral head and acetabular roof defects as well as the complete clinical recovery of the patient. An early diagnosis and intervention are essential to conservatively treat cases of bone marrow edema syndrome.

Keywords
Bone marrow edema syndrome, osteonecrosis, hip, magnetic resonance imaging, neridronate

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Introduction

Bone marrow edema (BME) syndrome is a clinical entity characterized by pain in the affected body segment (usually weight-bearing joints) and increased interstitial fluid within the bone marrow in the absence of a single identifiable cause. Many terms have been used to indicate this type of syndrome, usually with slightly different clinical findings, including but not limited to transient BME, BME lesions, transient osteoporosis, and regional migratory osteoporosis. In particular, transient osteoporosis of the hip (TOH) is a self-limiting condition whose etiology has been examined without conclusive results. To date, one of the most interesting models proposed refers to a prolonged inflammatory response to noxious spurs, which becomes exaggerated leading to excessive tissue growth. Increased bone turnover, demineralization, and consequent venous hypertension and increasing intraosseous pressure could lead to a weakened bone, prone to microfractures, collapse. The management of TOH and avascular osteonecrosis (AVN) can be challenging since early diagnosis and prompt intervention appear to be essential to permit an effective therapeutic strategy. Only if the symptoms of BME are markedly refractory to therapy, core decompression (CD) should be considered. However, there is currently insufficient evidence to support this. Some authors therefore recommend CD only after the pain has not been reduced using conservative methods, although these approaches are no longer recommended in principle.

Here, we describe the clinical case of a post-menopausal woman with BME associated with early osteonecrosis of the hip who benefited from a multimodal conservative therapeutic approach.

Case report

A 59-year-old post-menopausal woman was referred to our clinic (Orthopedic Rehabilitation Unit, Humanitas Research Hospital, Milan) for low back pain after a couple of months, radiating to the left hip and posterior tight, with episodes of paraesthesia and sharp pain located throughout the lower limb extending to the left foot. The patient was a chronic cigarette smoker (approximately 15 cigarettes per day since juvenile age) with no history of any relevant disease other than a family history of skeletal fragility. The patient did not recall any traumatic event occurring in her life.

When she presented for the visit, a simple X-ray of the pelvis and left hip had already been taken, showing modest joint space reduction and cortical shell sclerosis. There was no evidence of diffuse osteopenia. She also brought to view the result of lumbosacral magnetic resonance imaging (MRI) that showed interapophyseal arthritis and yellow ligaments thickening with disc protrusions at L4-L5 and L5-S1. Clinical evaluation revealed pain in stepping with the left limb, reduced range of motion (ROM) of both the lumbar spine and the left hip, pain during passive hip intrarotation and extrarotation, and partial muscle weakness of the left limb without radicular signs. We measured patient left hip pain and function by Visual Analogue Scale (VAS; 0–10, with 0 corresponding to no pain and 10 corresponding to worst pain possible) and ROM, respectively. At the first visit, the VAS was 8 and hip ROM was 40° in flexion and 20° in abduction, rotations limited to minimal degrees. These symptoms did not seem to be consistent with the MRI findings of lumbar spine arthrosis and a further exam was therefore performed. The MRI evaluation of the hip showed diffuse signal alteration of the head and neck of the femur in relation to BME, associated with a subcortical hypointense curvilinear stria of the femoral head, compatible with an osteonecrotic focus in the absence of trabecular collapse.

Figure 1. Baseline MRI of the hip in a 59-year-old postmenopausal woman affected by bone marrow edema. (a) Diffuse bone edema involving both the head and neck of the femur, with an unclear small cephalic area suggestive for initial osteonecrosis. The presence of a “crescent line” by nuclear magnetic resonance is also visible. (b) MRI of the hip showed diffuse signal alteration of the head and neck of the femur in relation to edema, associated with a subcortical hypointense curvilinear stria of the femoral head.
We then instructed the patient not to bear the load on the left lower limb during standing and walking, which were permitted with the aid of crutches. Gait retraining was performed during physiotherapy sessions, together with leg mobilization and training in order to prevent muscle loss. Necessary adjustments were also made to the shoe in collaboration with a podiatrist. In order to confirm the presence of necrosis and exclude fractures or malignancy, a further computed tomography (CT) scan was performed, which did not reveal any alterations in the bone profile, nor interruption of the cortex or trabecular bone collapse.

After a multidisciplinary evaluation of the clinical case and considering the potential reversibility of the disease, we decided to immediately start a multimodal conservative treatment, while keeping the patient under tight radiological and clinical monitoring. Non-steroidal anti-inflammatory drugs were prescribed for pain relief and bone edema. Blood analysis revealed a state of active bone remodeling (S-telopeptide 487.0 ng/L, S-total calcium 2.55 mmol/L, S-ALP 99 U/L, S-phosphorus 1.25 mmol/L). The therapeutic protocol consisted of intravenous administration of neridronate at 100 mg intravenously, every 3 days for a total number of four administrations, along with long-term caloric treatment, while keeping the patient under tight radiological and clinical monitoring. Non-steroidal anti-inflammatory drugs were prescribed for pain relief and bone edema.

The ESWT protocol consisted of three treatments administered weekly using a lithotripter with electromagnetic source and equipped with “in-line” ultrasound probe for targeting (SLK, Storz Medical, Tagerwilen, Switzerland). Each session of therapy consisted of a mean of 4800 impulses, at an Energy Flux Density (EFD) value of 0.20 mJ/mmq for the two first sessions and EFD 0.35 mJ/mmq for the last treatment. ESWT treatments were very well tolerated without anesthesia, and no side effects were recorded.

For the magnetotherapy, we proposed to our patient a portable pulse generator (Biostim, IGEA, Carpi, Italy) supplied by the coil with single voltage pulses at 75 Hz, each lasting 1.3 ms. The peak amplitude of magnetic field was 2 ± 0.2 mT. The device was used at home for at least 6 h/day (put in place during the hours of night sleep) for a period of 2 months.

Since the woman had hypercholesterolemia, a lipid-lowering treatment with oral atorvastatin 10 mg was also started.

After 2 months, the patient reported a notable regression of pain with clinically relevant improvement of mobility (VAS = 3), which was allowed without crutches. Furthermore, no restriction in hip ROM was noted during the physical examination, with the exception of limitation to approximately 120° in flexion and to the maximum degrees of internal rotation of hip ROM. MRI revealed complete regression of edema at the level of the head and neck of the left femur and the subcortical hypointense curvilinear line of the femoral head. However, MRI also showed the new appearance of acetabular bone edema as a widespread signal alteration of the bone spongiosa of the left acetabular roof associated with a streak of altered signal with a horizontal course (Figure 2).

The woman was advised to maintain load reduction on the left limb, and clinical and radiological re-evaluation after 2 months was planned. After a further 2 months (4 months since beginning treatment), the patient was clinically completely healed, no longer had pain (VAS = 0), and had recovered full-hip mobility (full ROM). A third MRI showed the disappearance of the femoral head defects and demonstrated the disappearance of the diffuse drop in T1 signal intensity of the acetabular roof. No signs of fracture or long-term bone complication were observed (Figure 3).

Discussion

In this case report, we describe the favorable outcome of a multimodal therapeutic approach to a patient with migrating BME associated with early osteonecrosis of hip joint. Our multidisciplinary team (physiatrist, orthopedic surgeon, bone specialist, and physiotherapist) collaborated in the planning of treatment and rehabilitation following our clinical experience and the most recent evidence in the literature. As previously mentioned, given the clinical case and the potential reversibility of the disease, the conservative treatment was considered as the first choice of treatment.

The effectiveness of bisphosphonates in subjects with BME is controversial and their current use in clinical practice is based on only a few studies, which were of low quality and heterogeneous in terms of patient populations, therapeutic schedules, and outcome measures. In clinical practice, if load reduction on the affected limb and pain control by simple analgesics are insufficient and if symptoms persist for
several months, their introduction may be considered. Increased bone turnover may be an important determinant of BME and bisphosphonates could induce favorable effects by exerting their inhibitory action on osteoclast activity and bone resorption. Indeed, favorable effects of zoledronate, pamidronate, and ibandronate via intravenous have been already seen. The novelty of this case was the use of neridronate at a schedule approved for the treatment of complex regional pain syndrome type I, which is commonly associated with BME. Indeed, neridronate has been shown to be effective in resolving BME in patients with complex regional pain syndrome type I at either hand or foot as well as bone structural alterations associated with painful knee osteoarthritis. Our clinical case provided a preliminary evidence that neridronate may also be effective in resolving BME at the hip level even when associated with early AVN. The favorable skeletal outcome in our patient may have also been related to the use of atorvastatin for hypercholesterolemia, based on the evidence that statin may offer some protection against having osteonecrosis.

Another novelty provided by this clinical case was the combination of neridronate with ESWT for the treatment of BME. Indeed, there are some published reports showing tentative evidence on the use of biophysical therapies for the treatment of osteonecrosis and BME, which show promising effects. Shockwaves exert trophic effects on musculoskeletal tissues, mediated by several specific factors, including nitric oxide. In addition to these biochemical processes, there is the possibility of a direct role of shockwaves on bone remodeling through biophysical (mechanical) stimuli. In recent years, ESWTs have proved effective and have already been used with promising results, leading to a clinical and functional improvement in cases of bone edema and avascular necrosis of the femoral head, with a progressive normalization of the MRI signal. Consequently, it seemed likely that it could drive the progressive normalization or, at least, prevent the worsening of the initial picture.

With regard to the use of magnetotherapy, it is known that osteocytes respond to the mechanical deformation of the bone through electromagnetic potentials linked to the deformation. Therefore, it should be possible to address bone remodeling using exogenous electromagnetic fields of correct amplitude and frequency.

An unusual and rather interesting detail of this case report, for which no description is recognized in other recent studies, was the unexpected migration of edema through the femoral head to the acetabulum, during a 2-month treatment period, between the first and second MRI exam. Despite this radiological finding, our patient did not report any particular problems related to acetabular involvement. This process, which could pave the way for further degeneration, should have been slowed by the prompt initiation of treatment and partially prevented in its clinical implications.

Although progression to AVN of the femoral head has not been proved and there is conflicting evidence in the literature, BME and AVN are sometimes confused in clinical practice. Radiological signs could be of help for a good differential diagnosis.

The beginning of a conservative, multimodal therapy, even in the presence of a suspected area of necrosis, proved to be a winning strategy for our patient. Therefore, we believe that non-surgical options are worth considering for a greater number of indications. BME can be regarded as a self-limiting disease with a good prognosis, but it can take a lengthy course over months. We cannot exclude that the favorable outcome of BME in our patient reflected the natural history of the disease. Indeed, considering the multimodal approach taken in this case study, the improvement may be attributed to neridronate, atorvastatin, ESWT, or magnetotherapy, and not due to the contribution of any single therapy.

**Conclusion**

A rapid diagnosis and intervention is essential to conservatively treat BME syndrome with positive results facilitating in the early recognition of the presence of necrotic bone lesions. Furthermore, the observation of a migrating secondary bone lesion suggests that the entire clinical situation may already be susceptible to further degeneration by the time of discovery. A multimodal conservative approach can guarantee positive therapeutic results in cases of disease with potential rapid reversibility through the use of different physiological pathways, preventing the possible progression to necrosis.

**Author’s Note**

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