Bone marrow edema – premonitory sign in malignant hemopathies or nonspecific change?

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Abstract
Bone marrow edema (BME) is defined as an excess of fluids that builds up in the bone marrow (BM), commonly found because of osteoporosis, trauma, infections, ischemia or neoplasia. Histologically, BME is characterized by accumulation of extracellular eosinophilic fluid. Magnetic Resonance Imaging (MRI) is the only method that highlights the presence of BME caused by various diseases, including the one associated with hematological malignancies. The classic MRI protocol for the study of BM and BME includes T1- and T2-weighted sequences, the STIR sequence, and in some cases, administration of intravenous contrast agents in T1-weighted sequences. Fifty-four patients were investigated; there were identified 30 patients with MRI features of BME. Out of the 30 patients with BME, 24 were known to have a malignant hematological disease (multiple myeloma, leukemia, lymphoma); for the remaining subjects, imagistic findings and other laboratory investigations led to multiple myeloma diagnosis. Of the 30 patients, six showed characteristic lesions of the underlying disease as well as BME; four patients had only BME. BM is a structure that is commonly investigated using MRI scans, regardless of the examined bone segment. T1-weighted images and T2-weighted with fat suppression are essential for BME evaluation. Moreover, MRI allows monitoring disease progression and treatment response in patients with malignant hemopathies.

Keywords: MRI, malignant hemopathies, bone marrow edema.

Introduction
Bone marrow edema (BME) represents an increase of interstitial water content. Therefore, some authors prefer the name of “BME-like” signal or anomaly, a term first used by Wilson et al. in 1988 [1]. BME can be a constant sign in osteoarthritis, rheumatoid arthritis or osteoporosis [2–4].

The physiopathology of BME is still unclear [1, 5–7] and depends of the pathological condition that determines it. It was suggested that local vascular changes are a trigger [1, 6–9]. It is widely acknowledged that the hyper-perfusion phenomenon in bone marrow (BM) contributes to its formation [4]. Cytokines play an important role in BME [3]. This may explain the link between BME and the occurrence of pain in the segment [10], and the effect of cortisone treatment or anti-tumor necrosis factor-α (anti-TNF-α) [3]. The peri-tumoral edema is correlated at the prostaglandins level with the expression of the cyclooxygenase-2, which is involved in the synthesis of prostaglandins [3].

Histologically, BME is characterized by accumulation of extracellular eosinophilic fluid and the presence of inflated fat cells that begin to disintegrate [7]. BME is in most cases the debut component of histological anomalies.

Magnetic Resonance Imaging (MRI) is the method of choice for BM disease [11–13], including the presence of BME. MRI is a non-invasive technique [10, 12–15] complementary to bone biopsy, allowing simultaneous multi-segment investigation [5, 16, 17], that can determine the concentration of fat and water at this level as well as bone vascularization and metabolism [8, 14, 16, 18]. The information is used in the diagnosis and staging of disease as well as monitoring response to treatment [2, 10, 14, 16, 19].

BME is a nonspecific MRI change commonly found because of osteoporosis, trauma, infections, ischemia or neoplasia [1, 3, 9, 20]. Thus, MRI can detect BME pattern associated in algodystrophy with microfractures in the trabecular bone and simultaneous damage of the joint and periarticular soft tissue, and in osteoarthritis with fibrosis, hyperemia, necrosis and the presence of subchondral cysts, as well as ligament injuries or synovial inflammation [1, 3, 4, 9, 11].

Materials and Methods
A total of 54 patients were MRI investigated between 2010 and 2014.

Classical MRI protocol for studying BM and BME include T1- and T2-weighted sequences, STIR sequence, in some cases, administration contrast media in T1-weighted sequence [12].
Patients who showed at least one edematous bone lesion were included in the study.

Bone marrow biopsies (BMB) with histological and immunohistochemical (IHC) examinations were performed for the patients diagnosed with lymphoma, also for the patients without a hematological malignancies.

**MRI protocol**

**T1-weighted sequences**

In T1-weighted sequences, fat has a short relaxation time (will appear bright white), and the water has a long T1 relaxation time (signal intensity is lower than fat). Therefore, BME has a reduced signal compared to the rest of normal BM and muscle structures. Difficulties in diagnosis appear when the edema is diffuse or when examining young patients, that still have a high amount of hematopoietic marrow [3, 8, 10, 12, 13, 15, 17, 18] (Figure 1).

**T2-weighted sequences**

In T2-weighted sequences, the difference between fat and water signal intensity is reduced; the consequence is a poor differentiation between normal BM signal, the fatty marrow and BME. However, in circumscribed lesions an increased signal of BME lesions may be observed compared to the rest of the normal BM [3, 8, 10, 12, 13, 18] (Figure 1).

**STIR (short-time-inversion-recovery)**

STIR sequence emphasizes the difference between water and fat signal, canceling the fat signal. Thus, the identification of BME is clearer compared to standard sequences. STIR images are complementary to T1- and T2-weighted sequences. In BME, the signal is more intense than that of red BM, because the concentration of water and fat is higher in case of edema [3, 8, 10, 12, 13, 15, 18, 19] (Figure 1).

**T1-weighted sequence with intravenous contrast media**

The area of BME is loaded with contrast substance differentiated according to the cause of the change. It will present in time and under treatment variations in concentration, respectively in the intensity of charging signal. It can therefore become an indicator of treatment response in malignant hemopathies [3, 8, 10, 13, 15, 18].

Post-contrast images increase the cost and duration of the MRI examination and should be used only in cases in which it is assumed the existence of small circumscribed BM lesions [9], that are hidden by BME or to quantify BME, as well as in cases of uncertain injuries in diagnosis.

**Histological and IHC protocols**

BMB (>1 cm length) was prelevated from postero-superior iliac crest, after local anesthesia. After fixation in 10% buffered formalin, BM sample was decalcified for 3–4 hours in EDTA disodium salt, processed and paraffin embedded. The sections of 4 μm were stained with Hematoxylin–Eosin (HE). IHC staining was carried out on paraffin-wax sections using MaxPolymer Novolink (Leica, UK), in accordance with the manufacturer’s instructions. Hodgkin’s lymphoma panel included: Reed–Sternberg cells marker CD30 (clone 1G12, dilution 1:40, Novocastra, Leica, UK); Reed–Sternberg cell marker CD15 (clone MMA, dilution 1:80, Cell Marque, USA); B-cell marker CD20 (clone L25, dilution 1:250, Novocastra, Leica, UK); B-cell marker PAX5 (clone SP34, dilution 1:300, Cell Marque, USA), and T-cell marker CD3 (clone LN10, dilution 1:400, Novocastra, Leica, UK). The panel for multiple myeloma (MM) included: plasma cell marker CD38 (clone SPC32, dilution 1:80, Novocastra, Leica, UK); kappa light chain (polyclonal, dilution 1:750, Novocastra, Leica, UK); lambda light chain (polyclonal, 1:1500, Novocastra, Leica, UK), and B-cell marker CD20 (clone L25, dilution 1:250, Novocastra, Leica, UK).

**Results**

There were investigated with MRI a total of 54 patients, who were aged between 26 and 79-year-old, with a mean age of 52.5 and female/male ratio of 6.5/1. After MRI examination, it was noted that 24 (44.4%) patients showed no signs of BME. Those were excluded from the study. The remaining 30 (55.6%) patients showed at least one edematous bone lesion, this representing the group of interest for the study.

The regions investigated by MRI in the study group were: cervical spine in six (20%) cases, thoracic spine in six (20%) cases, lumbar spine in 16 (53.4%) cases and knee in two (6.6%) cases (Table 1).

Of the total examinations, eight (26.6%) exams were completed using T1-weighted sequences with intravenous contrast administration, the rest (73.4%) were native exams (Table 2).

Of the 30 cases, 24 (80%) patients were noted as having a malignant hematological disease, while six (20%) patients were subsequently diagnosed as having multiple myeloma (MM).

From those diagnosed with malignant hemopathy, two (6.7%) subjects were diagnosed with classical Hodgkin’s lymphoma, 20 (66.6%) with MM and two (6.7%) subjects showed a form of leukemia (Table 3).

In the study group, four (13.3%) patients had only BME, six (20%) showing the rest of the lesions characteristic of the underlying disease (Figure 2) (Table 4).

Of the total of 30 cases, 10 (33.3%) patients showed specific post-treatment modifications (Figure 3) (Table 4).

In 14 (46.6%) cases were found nonspecific compli-
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Table 1 – Investigated segments

<table>
<thead>
<tr>
<th>Segment type</th>
<th>No. of examinations</th>
</tr>
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<tbody>
<tr>
<td>Cervical spine</td>
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</tr>
<tr>
<td>Thoracic spine</td>
<td>6</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>16</td>
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<tr>
<td>Knee</td>
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Table 2 – Performed MRI investigations

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<td>Native MRI</td>
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<tr>
<td>MRI with contrast</td>
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Table 3 – Patients’ batch

<table>
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<th>Type of malignant hemopathy</th>
<th>No. of patients</th>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Leukemia</td>
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</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
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</table>

Table 4 – Bone marrow edema – associations

<table>
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<th>BM edema – associations</th>
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<td>Without other associated lesions</td>
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</tr>
<tr>
<td>With the characteristic lesions of the underlying disease</td>
<td>6</td>
</tr>
<tr>
<td>With treatment-related lesions</td>
<td>10</td>
</tr>
<tr>
<td>Associated with nonspecific changes</td>
<td>14</td>
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</table>

MRI identified the presence of diffuse BME in 11 (36.7%) cases and circumscribed lesions in 19 (63.3%) cases (Figure 5).

Figure 2 – BME lesions associated with specific lesions of Hodgkin’s lymphoma: (a) T1-weighted sequence; (b) T2-weighted sequences; (c) STIR sequences; (d) T1 with contrast.

Figure 3 – BME associated with MM lesions after treatment – fatty degeneration: (a) T1-weighted sequence; (b) T2-weighted sequences; (c) STIR sequences.

Figure 4 – BME associated with cervical vertebral body fracture in a patient with MM: (a) T1-weighted sequence; (b) T1 with contrast.

Figure 5 – BME without any other associated damage in a patient with MM: (a) T1-weighted sequence; (b) T2-weighted sequences; (c) STIR sequences; (d) T1 with contrast.

Histology and IHC

BMB of Hodgkin’s lymphoma patients showed a compact polymorphous reactive infiltrate with small-sized lymphocytes, histiocytes, eosinophils and plasma cells (Figure 6) very few mononucleated tumor Hodgkin’s cells were detected (Figure 7). Tumor cells were CD15- and
CD30-positive (Figure 8), expressed PAX5 (Figure 9), but CD20- and CD3-negative; small peritumoral lymphocytes were T-cells, CD3-positive. The histology showed a BM-positive Hodgkin’s lymphoma, and the patients were stage IV of disease.

For the remaining six patients without a diagnosed hematological disease, but with MRI showed at least one edematous bone lesion, BMB revealed a malignant plasma cells infiltrate (between 40% and 90% of the marrow cellularity) (Figure 10), CD38-positive (Figure 11) and CD20-negative, with a clonal nature: five cases with kappa light chain secretion (Figure 12) and one case with lambda light chain secretion.
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After treatment, the MRI aspect shows fatty degenerated areas in BM [2, 8, 10, 13, 23].

Radiotherapy induces also, through cytotoxic changes, a different cellular behavior in the bone metabolism of the irradiated area. This will cause a number of imagistic changes required to report to the physician. Complications of radiotherapy applied in malignant hemopathies are fractures or avascular necrosis in irradiated bone [2, 8, 10, 21]. Fractures are caused by reduced elasticity of the bone structure and can be identified through characteristic changes on MRI images [8, 10, 21]. Post-radiation aseptic necrosis is caused by microvascularization changes, due to fibrosis and endothelial proliferation, leading to ischemia [2] of the area and subsequent death of BM cells.

In early stages, it is identified as areas of diffuse BME [8]. The same aspect is identified in patients treated with high doses of cortisone [8].

Conclusions

BME is a nonspecific MRI change. It can be analyzed for diagnostic purposes only in the context of other associated signs. The required sequences to highlight it are T1-weighted sequences and those with fat suppression. T2-weighted sequences do not have diagnostic and prognostic value. Consequence of treatment, BME occurs constantly. BME can occur also as a primary lesion of onset malignant hemopathies.

References


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Received: July 10, 2014

Accepted: November 17, 2014