



Aetiology and pathogenesis of bone marrow lesions and osteonecrosis of the knee

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- Bone marrow lesions (BML) of the knee are a frequent MRI finding, present in many different pathologies including trauma, post-cartilage surgery, osteoarthritis, transient BML syndromes, spontaneous insufficiency fractures, and true osteonecrosis.
- Osteonecrosis (ON) is in turn divided into spontaneous osteonecrosis (SONK), which is considered to be correlated to subchondral insufficiency fractures (SIFK), and avascular necrosis (AVN) which is mainly ascribable to ischaemic events.
- Every condition has a MRI pattern, a different clinical presentation, and specific histological features which are important in the differential diagnosis.
- The current evidence supports an overall correlation between BML and patient symptoms, although literature findings are variable, and very little is known about the natural history and the progression of these lesions.
- A full understanding of BML will be mandatory in the future to better address the different pathologies and develop appropriately-targeted treatments.

Keywords: bone marrow lesions; subchondral pathology; bone marrow oedema; subchondral insufficiency fractures; osteonecrosis; knee; MRI

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Introduction

Bone marrow lesions (BMLs) around the knee are a common MRI finding. BML is defined as an alteration of the signal intensity of the bone marrow, with high signal on fluid-sensitive sequences (T2/proton density with fat suppression and short tau inversion recovery (STIR)) with or without low T1WI signal.

BMLs can originate from the subchondral or non-subchondral bone. This article will focus specifically on those involving the subchondral bone. BML is present in a wide range of pathologies including traumatic contusion and fractures, post-cartilage surgery imaging alterations, osteoarthritis (OA), transient BML syndromes, spontaneous insufficiency fractures (SIFK) and true osteonecrosis (ON). These pathologic patterns present different prognoses, and thus a careful diagnosis is mandatory in order to address them with the proper treatment.

MRI plays a fundamental role in guiding the diagnosis based on recognisable typical patterns even at early stages. These patterns rely on location, co-existent abnormalities, age and obviously (but not always) clinical history, clinical aspects and MRI which may be useful in the differential diagnosis.

Traumatic BML

Trauma-induced BMLs can be associated with acute direct or indirect trauma such as bone contusions, or with subacute lesions as a result of overload, such as stress fractures and repetitive microtrauma occurring during physical activity.¹

BMLs are strictly related to trauma mechanism and force, and are often associated with knee ligament tears,² although the presence of subchondral oedema-like lesions was also shown in 41% of asymptomatic collegiate basketball players subject to repetitive microtrauma.³

The most common subchondral contusions are those seen after pivot shift injuries, and are often associated with ACL tears.² BMLs are mainly sited on the mid-portion of the lateral femoral condyle and the posterior lateral tibial plateau (Fig. 1). This can be a result of a valgus stress on the knee with the femur in external rotation relative to a fixed tibia, which explains why the lateral compartment is more involved than the medial one.⁴ Other location-specific patterns are those related to hyperextension injuries,⁵ which may lead to ligament tears and cause subchondral contusions in the anterior tibia and femur, and those related to spontaneously-reduced lateral patellar dislocation in teenagers around the time of physal closure. The latter is characterised by one or a combination of the following: a kissing impaction in the medial patellar facet or the median ridge, a medial patellar traction contusion of the medial retinaculum, impaction contusion in the anterior lateral femoral condyle, and an osteochondral grade 4-5 defect in the

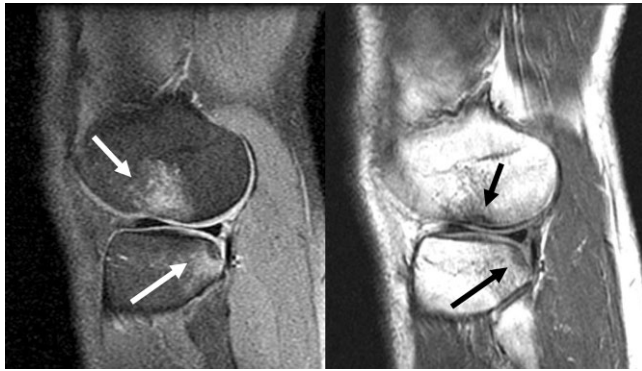


Fig. 1 Bone marrow oedema-like signal related to anterior cruciate ligament tear. On a sagittal fluid-sensitive image (PD with fat suppression) oedema around the sulcus of the lateral femoral condyle is visible (white arrows). On sagittal PD without fat suppression, there are subchondral impaction fractures in addition to bone contusions (black arrows).

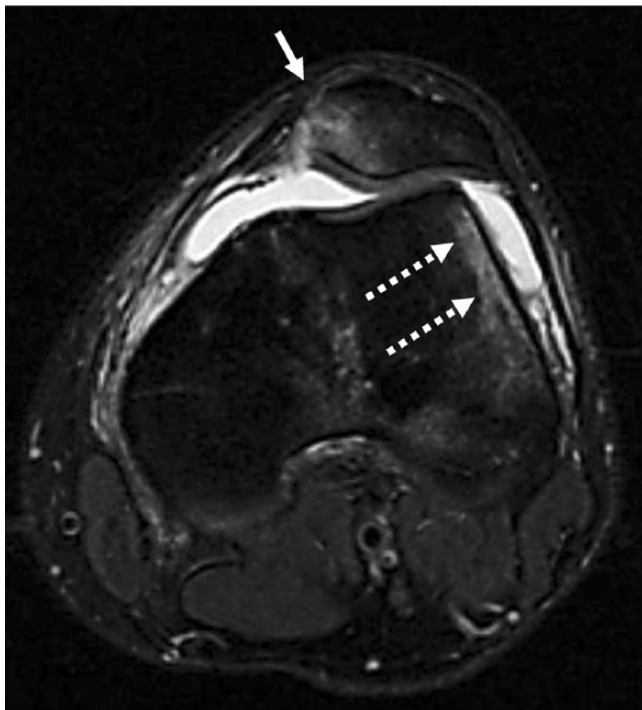


Fig. 2 Typical contusions related to spontaneously reduced lateral patellar dislocation. On axial fluid-sensitive sequence (T2 fat suppression) there is oedema in the medial patella (arrow), and in the anterior aspect of the lateral femoral condyle (dotted arrows).

lateral femoral condyle associated with a sequestered intra-articular fragment⁶ (Fig. 2).

Subchondral osseous injuries following a single direct impact or resulting from repetitive microtrauma show histopathological features. The underlying bone is locally impacted, presenting (micro)fractures of the subarticular spongiosa with osteocyte necrosis and empty lacunae, haemorrhage and oedema.⁷ These histological findings correspond to the MRI pattern. If the traumatic impact is

more severe, a subchondral fracture may cause a local depression and collapse of the cartilage surface. Fractures affecting the osteochondral unit (either with a chondral or osteochondral fragment or purely subchondral) may show accompanying bone marrow lesions. Osteoarthritis signs may appear in the course of bone remodeling as the subchondral bone becomes stiffer. In this case, the cartilage overlying such areas is also directly affected, with chondrocyte apoptosis and necrosis, chondrocyte proliferation and loss of superficial proteoglycans.⁸

The natural history of post-traumatic bone contusions have been poorly investigated, especially at long-term. BML evolution is influenced by several factors. While BML to isolated MCL tear may spontaneously heal in two to four months, it has been reported that BML in a complex knee injury with ACL tear has a slower resolution.⁹ Moreover, BML in ACL lesion is predominantly present at three years follow-up when associated with a disruption or a depression of the normal contour of the femoral cortical surface, while lesions without cortical involvement tend to resolve spontaneously in 95% of cases.¹⁰ In addition, the location of the lesion may affect the evolution of BML. In fact, 67% of lateral femoral condyle ACL injury-associated bone bruises have been shown to evolve from osteochondral damage, whereas no cartilage defects were found in cases of BML of the posterolateral tibial plateau.¹¹ Post-traumatic BML in an ACL-injured knee in the lateral femoral condyle had a quicker resolution compared to lateral tibial BML (median of three *versus* six months).¹²

According to the few studies reported in the literature, there is no agreement regarding a correlation at short-term follow-up between BMLs, pain and functional status, even though it has been reported that BML may negatively affect pain, functional recovery, and return to previous sport level, especially if the alteration is still detectable three months after the injury.^{13,14} Similarly, it still remains unclear if the initial joint injury and BML are directly correlated to long-term function and OA development.

BML after surgery for cartilage repair

Increasing awareness of the role played by BML in joint homeostasis has recently led to investigations into the meaning of such MRI findings in patients with cartilage treatments.¹⁵

Perifocal bone marrow oedema-like signals are a frequent finding after both chondral and osteochondral surgical procedures (e.g. microfracture, autologous chondrocyte implantation, osteochondral autograft or allograft transplantation, chondral/osteochondral scaffolds), ranging from about 40% to 80%.^{16,17} BML is detectable around and above the treated site, usually together with the signs of the surgical procedure itself, but it does not present as specifically distinctive¹ (Fig. 3). From an histological point of view, subchondral bone cysts on one side, and upward subchondral bone plate migration or intralesional osteophyte formation on the other,

are subchondral bone alterations found after cartilage repair surgery.¹⁸ Deteriorations of the subchondral micro-architecture such as changes in bone mineral density, bone volume, and trabecular thickness can also be found, suggesting that the entire osteochondral unit can be altered, either as a short-term maturation result, or as long-term tissue evolution¹⁹ (Fig. 3).

The aetiopathology and evolution of these findings is still unclear, with evidence of both a reduction and increase in its incidence over time. In a study aimed at clarifying the evolution of BML detected after cartilage surgery,²⁰ BMLs were present in the first post-operative phases, markedly reduced at two and three years, and then again increased at mid- to long-term follow-up. This trend could be the expression of tissue modifications over time; the initial reduction could be explained by the maturation phase, which for such cartilage treatments is commonly

acknowledged to stabilise at around two years. On the other hand, the tissue obtained as a result of cartilage procedures may be not sufficient to protect the subchondral bone from mechanical forces, leading to progressive abnormal subchondral bone stimulation.

Despite the aforementioned findings shedding some light on both frequency and evolution, no correlation has been found between BML and clinical outcome, thus making the clinical significance questionable and difficult to interpret.^{16,17,20} The high MRI sensitivity might allow early changes to be detected, such as a tissue reaction which is abnormal but still not severe enough to affect the clinical outcome, even at mid- to long-term follow-up. Nonetheless, BML is a common finding after cartilage surgery, and there is a need for a better understanding of the evolution of post-surgical BML over time, as well as its importance as a prognostic factor over time.

BML in osteoarthritis

Subchondral BML is a common finding in patients with both early and advanced OA, associated with thinning of the cartilage with or without meniscus damage and focal cartilage defects. The oedema can precede cartilage lesion formation. If there is also a well-defined low T1W signal, this may evolve into a well-defined subchondral cyst.^{21,22} The differential diagnosis in this case may be challenging, since it may be difficult to distinguish this BML from an insufficiency fracture or ON (Fig. 4).

An OA-related joint imbalance may account for the higher prevalence of BML which has been associated with overloading, such as in the medial compartment in varus knees or the lateral compartment in valgus knees. This strongly supports the hypothesis of a possible role of repeated trauma in the genesis of these lesions, and a higher incidence of BML (as seen on MRI) has even been

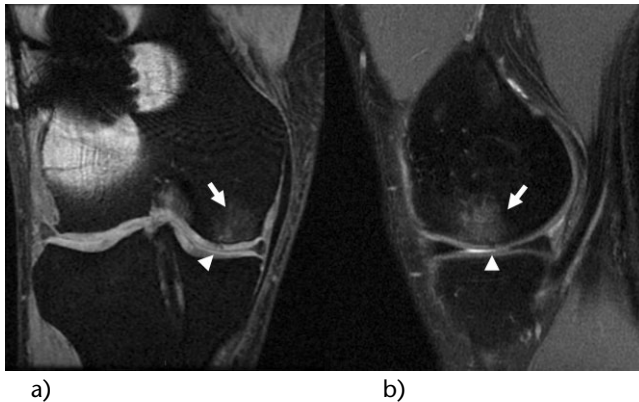


Fig. 3 Oedema-like signal on coronal and sagittal PD fat suppression (white arrows) in the medial femoral condyle of a patient, ten years after a hyaluronan-based matrix-assisted autologous chondrocyte transplantation. The implant presents a cartilage-like signal, and only a few signs of the initial procedure are still present (white arrowhead).

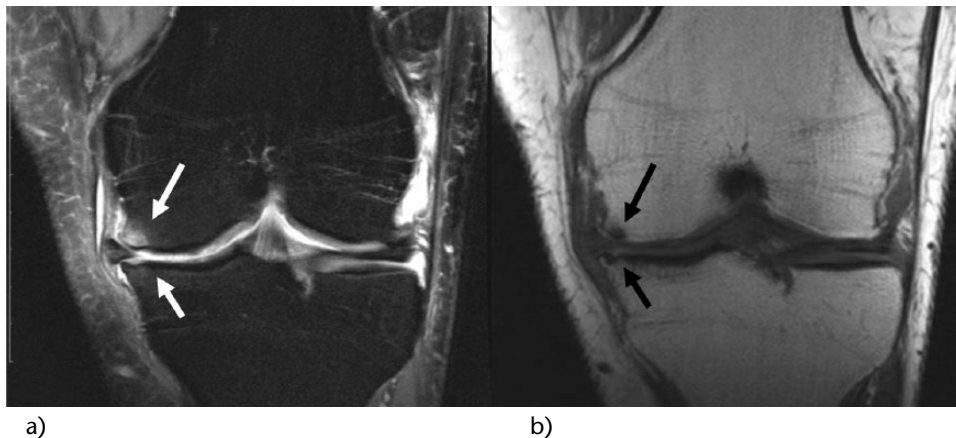


Fig. 4 Advanced osteoarthritis. On the coronal PD fat suppressed image (a) there is subchondral bone marrow oedema-like signal at the periphery of the medial femoral condyle, and also the medial tibial plateau (white arrow). Other components of osteoarthritis including cartilage loss and osteophytes are also seen. There is medial meniscus extrusion (arrowhead). On the coronal T1WI (b) there are low-signal intensities (black arrows). At this point it is hard to determine whether these are insufficiency fractures or early cyst formation.

documented in a healthy population subject to a temporary artificial misalignment.²³

BML pattern associated to OA corresponds histologically to a mixture of different findings, including bone marrow necrosis, fibrosis, microfractures and bone remodeling as well as fibrovascular ingrowth.²⁴ Specific changes in bone mineralisation, remodeling and defects within BML features adjacent to the subchondral plate have been shown,²⁵ with reduced mineral density in BML areas, which appear sclerotic compared to unaffected regions.

The clinical correlation of BML in the setting of OA is still under debate: pain was found to be correlated with the development or enlargement of pre-existing BMLs,²⁶ and a systematic review found four high-quality studies *versus* one demonstrating this association, supporting moderate evidence for an association between BML and pain.²⁷

The evolution of BML in the setting of OA is extremely variable. Subchondral lesions may regress or resolve completely within 30 months' follow-up,²⁸ but some studies showed the persistency of BML in the majority of patients.^{29,30} It has been demonstrated that the severity and enlargement of BML is a negative prognostic factor for cartilage loss, pain, and even predictive for arthroplasty.^{28,31,32}

Transient bone marrow lesion syndromes, subchondral insufficiency fractures and osteonecrosis

There is a wide spectrum of conditions primarily characterised by BML, which can be reversible or irreversible. Transient conditions include regional migratory osteoporosis (RMO), transient osteoporosis (TOP) and complex regional pain syndrome (CRPS) (also known formerly as reflex sympathetic dystrophy or algodystrophy). On the other side there are irreversible conditions, which are represented by spontaneous osteonecrosis of the knee (SONK) and avascular necrosis (AVN). Subchondral insufficiency fractures of the knee (SIFK) can be reversible, but also progress to SONK and rapidly destructive OA.³³ All transient conditions have a similar MRI presentation of diffuse subchondral bone marrow high-signal intensity with indistinct margins, reaching but preserving the joint surface (Fig. 5). Gender, age, and clinical history help to differentiate between the three diagnoses: CRPS occurs after an initiator which can be a major or a minor traumatic injury or pain, including that associated with meniscal tears and arthroscopy. TOP is seen in the femoral head during pregnancy and in the peripartum.³⁴ Migratory osteoporosis usually migrates between different joints including hips, knees, and metatarsal heads of the middle-aged over a course of weeks to years. There is likely to be an overlap between these entities. TOP can progress to RMO and in many cases an insufficiency fracture can be identified.³⁵

Ahlback first described ON of the knee in 1968.³⁶ Since then, the improvement of knowledge in this field has led to the identification of three distinct categories of ON: SONK, AVN, and post-arthroscopic ON.

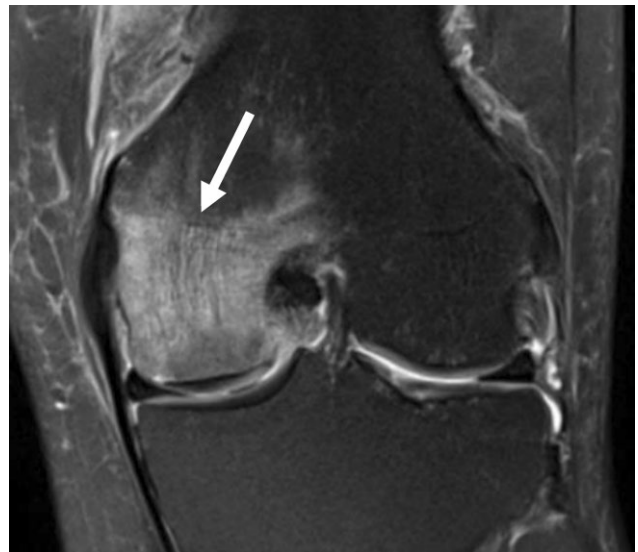


Fig. 5 Coronal PD fat suppression image of the knee demonstrates reversible bone marrow oedema-like signal in the medial femoral condyle. The oedema-like signal is extensive and demonstrates indistinct margins (see arrow).

Post-arthroscopic ON is the least common form, with no age or sex predominance, which may occur after meniscectomy, cartilage debridement, and radiofrequency surgery.³⁷ However, this also falls into the spectrum of CRPS/SIFK, when the pain initiator is surgery.³⁸

Avascular necrosis (AVN, an osteonecrosis mainly ascribable to ischaemic events) usually affects patients below 45 years of age. It can be secondary to systemic diseases, corticosteroid use, smoking, radiation, alcohol abuse and chemotherapy. These underlying systemic conditions and bone infarcts at other locations can narrow the differential diagnosis between SONK and AVN.

SONK is considered to be the most common form, although few epidemiologic data exist. Only one study indicates a 3.4% incidence in patients aged over 50 years and 9.4% in patients older than 65 years.³⁹ SONK is classically described as a superficial focal subchondral lesion, mainly affecting the medial femoral condyle, rarely bilateral (< 5%), and affecting female patients more commonly than males. Patients usually complain of an acute knee pain located in the medial compartment, which is worse at night, without any history of trauma or risk factors for ON. The aetiology is still not completely understood, but two aetiologic hypotheses have been proposed. A vascular origin was initially suggested, with compromised microcirculation to the subchondral bone resulting in oedema and increased intra-osseous pressure, finally leading to ischaemia and ON.⁴⁰ However, the evidence in favour of this theory is limited to a small number of studies with histological findings suggesting abnormal vascularity, an increased focal bone turnover, and oedema.⁴¹ More recently, SONK has been associated with subchondral insufficiency fractures of the knee (SIFK). SIFK are non-traumatic fractures with no histological evidence of necrosis, usually occurring

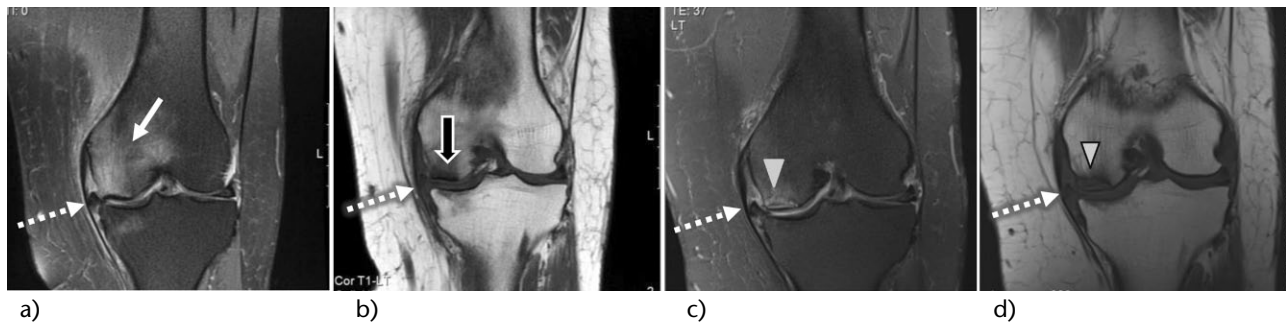


Fig. 6 Progression of an insufficiency fracture over ten months. Coronal PD fat suppression (a) and T1WI (b) at the acute stage show a bone marrow oedema-like signal in the medial femoral condyle (see arrow) and a linear hypo-intensity on T1 with a thickness of < 4 mm (black arrow). Flattening of the articular surface is already present. After ten months (c and d) the oedematous signal has nearly resolved, but there is a subchondral area of low signal on all sequences > 4mm thick representing osteonecrosis (arrowhead). Medial meniscus extrusion is also seen (dotted arrow).

in overweight, elderly female and osteoporotic patients. Once a subchondral fracture occurs and fails to heal, repetitive micromotion of the unstable osteochondral portion can lead to infiltration of synovial fluid, detachment and fragmentation of the osteochondral fragment, followed by ON changes in the disconnected area⁴² (Fig. 6).

The clinical course and earliest stage of SIFK can be unpredictable and does not necessarily progress in every patient. Sometimes reparative mechanisms with new bone formation can occur and avoid bone death. Typically, the initial phase consists of severe pain with functional impairment for at least three to six months, followed by spontaneous resolution with functional and radiographic improvement.⁴³ In the acute stage there is a marked, ill-defined oedema-like signal that is more extensive than the pattern secondary to cartilage loss.⁴⁴ The lack of additional subchondral changes other than BML is 100% predictive of reversibility. The presence of a subchondral area of low signal at > 4 mm thick strongly predicts irreversibility³³ (Fig. 6). The duration of symptoms is variable, and depends on the initial severity and extent of bony involvement and on the entity of ON changes. Clinical progression of severe symptoms and radiological evidence of subchondral bone collapse found in SONK or AVN alter the entire joint homeostasis leading to end-stage OA.

Conclusions

The growing interest seen in years regarding BMLs has enabled a better understanding of the many different aspects of these MRI findings, which can be used, together with the clinical presentation, to provide differential diagnosis and guide the management of affected patients. However, many aspects remain unsolved. A fundamental step in this field will be the comprehension of what determines the different kinds of BMLs, as well as what leads to the possible evolution of a reversible traumatic lesion or insufficiency fracture into an irreversible ON/AVN and OA. A full understanding of BMLs will be mandatory in the future to better address the different pathologies by developing appropriately-targeted treatments.

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CONFLICT OF INTEREST

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