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Bone infarcts: Unsuspected gray areas?

Pierre Lafforgue ^{a,b,*}, Sophie Trijau ^b

^a Aix-Marseille université, faculté de médecine, 27, boulevard Jean-Moulin, 13005 Marseille, France

^b Service de rhumatologie, hôpital Sainte-Marguerite, 270, boulevard de Sainte-Marguerite, 13009 Marseille, France

There is agreement to label as bone infarcts avascular necrosis (AVN) occurring in the metaphyses or diaphyses of long bones, the terms AVN or osteonecrosis being used at the epiphyses. One might expect bone infarction to hold no mysteries. Oddly enough, however, scientific evidence about bone infarcts is extraordinarily scant. The prevalence of bone infarcts is unknown. The main sites of involvement are the distal femur, proximal tibia, and distal tibia. In patients without sickle cell disease or Gaucher's disease, involvement of the upper limbs and lesions confined to the diaphysis are so rare as to warrant a reappraisal of the diagnosis. Although widely viewed as a generally silent event, bone infarcts causes symptoms in half the cases. Standard radiographs are normal initially then show typical high-density lesions in the center of the marrow cavity. A periosteal reaction is common and may be the first and only radiographic change. Magnetic resonance imaging consistently shows typical features and therefore, in principle, obviates the need for other investigations. Bone infarcts are multifocal in over half the cases and, when multifocal, are usually accompanied with multiple foci of epiphyseal avascular necrosis. Thus, bone infarcts, whose prognosis is good per se (with the exception of the very low risk of malignant transformation), are usually a marker for systemic avascular necrosis. Consequently, patients with bone infarcts must be investigated both for known risk factors and for other foci of avascular necrosis, which may, in contrast, have function-threatening effects.

Bone infarcts are often mistakenly viewed as a radiological oddity that has no clinical impact. However, although the radiological diagnosis is usually considered easy, errors are common, and some of their aspects remain poorly known. Bone infarction was described as a manifestation of caisson disease before being reported in other settings in 1939 [1,2]. Very few studies have specifically addressed bone infarcts. They included fewer than 20 patients and were published many years ago, with the most recent – to the best of our knowledge – having been reported in 1990 [3–6]. Furthermore, the few relatively recent publications are anecdotal case reports [7–14] that fail to shed new light on the topic. We recently identified 109 cases in 31 patients that, when combined with our earlier case series reported in 1990, provide updated information on bone infarction.

1. Definition

The name bone infarct has not been defined in detail. Traditionally, the term “bone infarct” is reserved for the death of bone and marrow tissue due to ischemia, without infection, and located in the metaphysis and/or diaphysis of a long bone. The same process located at the epiphysis is known as “avascular necrosis” (AVN) or osteonecrosis, which is also the term generally used to designate ischemic cell death of carpal and tarsal bones. For ischemic aseptic cell death affecting flat bones, such as the pelvis, ribs, and skull, both “bone infarction” and “osteonecrosis” terms are used in the literature.

Bone infarction occurring as a chronic non-inflammatory condition is the most common situation and the focus of this article, as opposed to acute bone infarction with an inflammatory response. Chronic bone infarction affects bone marrow areas containing large numbers of adipocytes. Symptoms are minimal and the date of onset therefore usually unclear. Acute bone infarction is ischemic necrosis of hyperplastic bone marrow in patients with sickle cell disease or Gaucher's disease, which can affect any part of the skeleton and causes excruciating pain. The manifestations of acute bone infarction are identical to those of acute osteomyelitis, even

* Corresponding author. Service de rhumatologie, hôpital Sainte-Marguerite, 270, boulevard de Sainte-Marguerite, 13009 Marseille, France.
E-mail address: pierre.lafforgue@ap-hm.fr (P. Lafforgue).

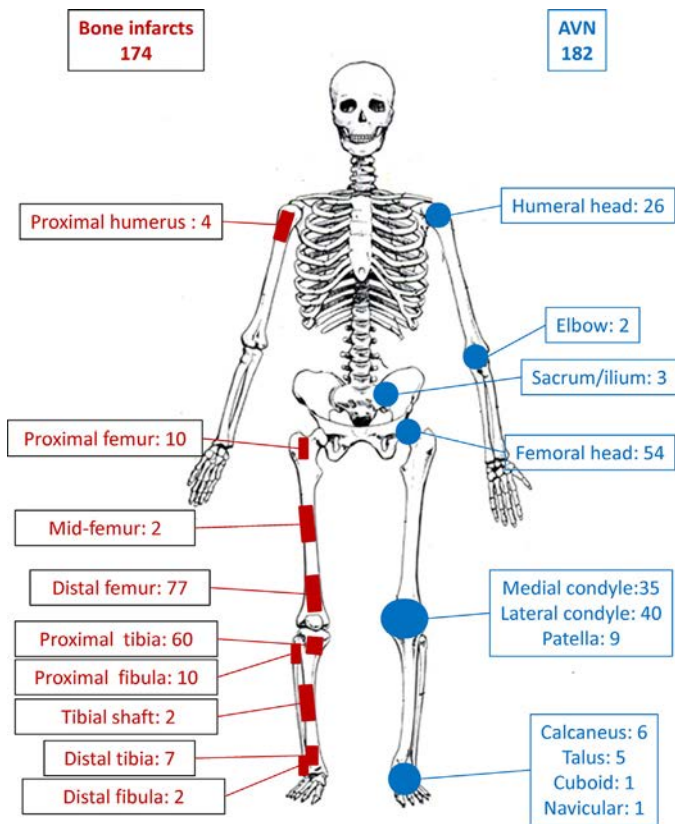


Fig. 1. Distribution of bone infarcts and other forms of avascular bone necrosis in 51 patients (adapted from [5] and additional personal observations).

regarding the laboratory and imaging findings [15–17]. Acute bone infarction contributes to the functional impairments seen in patients with sickle cell disease or Gaucher's disease.

2. Epidemiology

The prevalence of bone infarcts is unknown. Anecdotal case reports frequently describe bone infarcts as rare or very rare, and only about 25 cases have been reported over the last 25 years [7–14]. Obviously, few cases will be deemed worthy of publication, and the literature therefore provides no information on prevalence. Over 26 years, we have seen 51 patients with bone infarctions¹. This number is small compared to that of patients with femoral head AVN seen over the same period. However, it undoubtedly constitutes an underestimation, since the cases were identified manually, as the ICD-9 has no specific code for bone infarcts. The cases are distributed equally between males and females, and most of the patients are 25 to 50 years of age [5–14].

The most common sites of involvement are the metaphyses or metaphyseal-diaphyseal regions of the knee (distal femur, proximal tibia, and proximal fibula), which accounted in our experience for 85% of all bone infarcts (Fig. 1). The proximal femur is the next most common site. The upper limb is only very rarely involved, with the main location being the proximal humeral metaphysis. Bone infarcts confined to the diaphysis are also exceedingly rare. Therefore, considerable circumspection is in order when considering a possible diagnosis of bone infarct affecting the upper limb or confined to the diaphysis.

Bone infarction is usually multifocal. This characteristic was pointed out in the very first publications, then confirmed in most of the reported cases. Our 51 patients had 174 bone infarcts in all and only 14 patients had a single focus. The same 51 patients also had 189 foci of AVN located in the epiphyses of long bones or small tarsal bones. This multifocal distribution of the lesions highlights the systemic nature of the necrotic bone disease.

3. Diagnosis

Bone infarcts are classically identified in one of two ways: either fortuitously when imaging studies are performed to investigate another disease, such as knee osteoarthritis; or non-fortuitously during an imaging workup for epiphyseal AVN. However, although many bone infarcts are asymptomatic, others cause bone pain. In our experience, the infarct was the only detectable cause of pain in 45% of cases. The corresponding proportion among published cases is difficult to determine. Thus, the widespread belief that bone infarcts are asymptomatic is in large part unfounded.

The diagnosis relies only on imaging studies and, among these, on radiography and magnetic resonance imaging (MRI). The findings on standard radiographs depend on the time since the infarction [1,3,5,18,19] (Fig. 2). Initially, for an unknown but probably prolonged period, the radiographs may remain normal, with the diagnosis being established only by MRI. The early radiographic changes are non-specific and may erroneously cause concern when they consist of ill-defined areas of lucency or sclerotic areas in the center of the medullary canal [3,6,19]. A periosteal reaction



Fig. 2. Radiographic features. a: a periosteal reaction may be the only radiographic finding; b: magnetic resonance imaging confirming the bone infarct in the same patient as in (a); c: radionuclide bone scan showing symmetrically increased uptake in the distal femoral and proximal tibial metaphyses and a bull's eye sign at both hips in the same patient as in (a); d: typical appearance with a calcified lesion in the center of the bone marrow sparing the cortical bone and extending into the femoral metaphysis and diaphysis. Note the minimal periosteal reaction over the medial aspect of the metaphysis; e: typical appearance of a distal tibial infarct in a patient with multiple foci of glucocorticoid-induced avascular bone necrosis. (Note the calcifications related to avascular necrosis of the talus).

¹ Personal unpublished case series, including ref. [5].

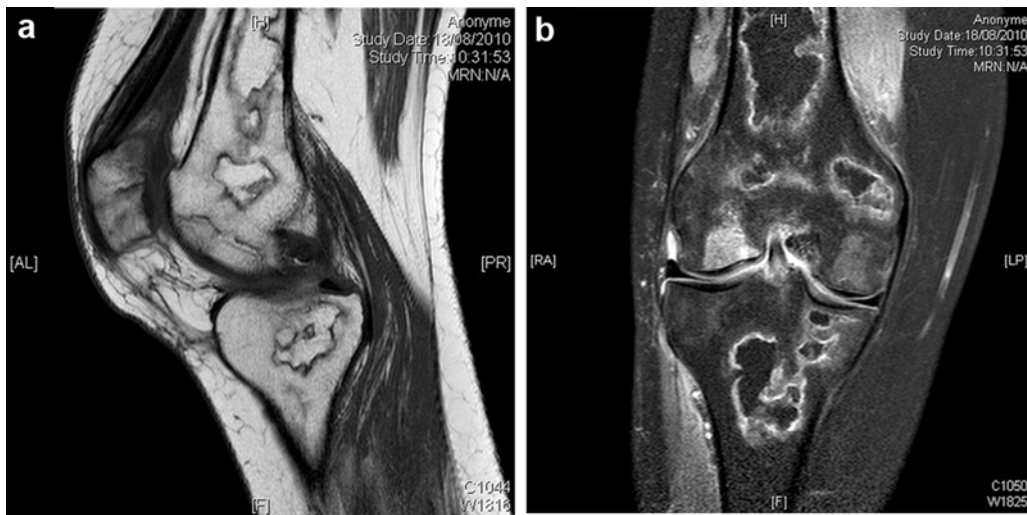


Fig. 3. Magnetic resonance imaging: bone infarcts in the distal femur and proximal tibia with avascular necrosis of the medial condyle and distal tip of the patella in a patient with multiple foci of glucocorticoid-induced avascular bone necrosis. a: sagittal T1-weighted image; b: coronal STIR image.

parallel to the femoral or tibial diaphysis is common (55% of our patients and visible, although not described by the authors, in several reported cases [5,11]). The periosteal reaction may coexist with the typical radiographic features or be the only sign. Awareness of this feature is very low, and bone infarct should be included among conditions to be sought routinely in patients with a periosteal reaction. Finally, a classical sign is the presence of heterogeneous sclerotic images in the metaphysis or metaphyseal-diaphyseal region, at the center of the medullary canal, sparing the cortex and either surrounded by shell-like sclerosis or resembling a plume of smoke.

The MRI features are characteristic (except in acute bone infarction due to sickle cell disease or Gaucher's disease) [5,6,18,20] (Figs. 2b and 3). No false-negative MRI scans have been reported. The MRI signs of bone infarction are those seen in femoral head AVN but located in a metaphysis or diaphysis. There is a medullary lesion surrounded by a scalloped, serpiginous, tortuous border. This border generates low signal on T1-weighted images and high signal or a double contour (parallel lines of low signal and high signal) on T2-weighted or STIR images. Within the area demarcated by the border, the bone marrow initially keeps its normal fatty-tissue signal then becomes heterogeneous, with foci of low signal. This MRI

pattern is sufficiently characteristic to establish the diagnosis of bone infarction, although no well-designed studies have proven its diagnostic value. MRI must be performed when the standard radiographs are normal or atypical. Furthermore, MRI is helpful to detect and evaluate AVN in the adjacent epiphysis, which is common.

The usefulness of radionuclide bone scanning has not been specifically evaluated. The main contribution of this investigation lies in its ability to detect other skeletal foci (Fig. 2c). Similarly, the role for computed tomography seems limited. Similar to radiography, computed tomography may be normal or show a medullary lesion surrounded by a sclerotic border and sparing the cortex (Fig. 4).

A number of differential diagnoses should nevertheless be considered. An isolated periosteal reaction requires an evaluation for a tumor or infection. In this situation, MRI is performed routinely and establishes the correct diagnosis. Chronic osteomyelitis may produce radiographic changes similar to those seen in bone infarction, but the diagnosis is easily made based on the setting, laboratory evidence of inflammation when present, and MRI findings. Although enchondroma is often visible as a calcified metaphyseal lesion, the appearance of the calcifications differs from that seen in bone infarction. On standard radiographs, an enchondroma has a round

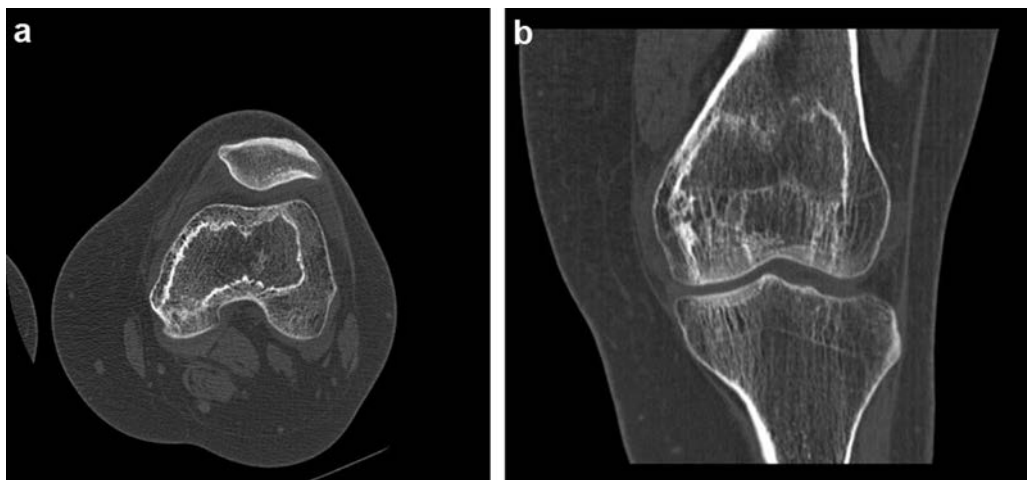


Fig. 4. Computed tomography: the lesion in the center of the bone marrow is surrounded by a compact rim; on the coronal slice, this lesion is seen to extend toward the femoral condyles.

Table 1

Risk factors of bone infarction identified in 51 patients (adapted from [5] and additional personal observations).

Glucocorticoid therapy	28
Alcohol abuse	18
Dyslipidemia	30
Lupus/Antiphospholipid syndrome	5
HIV infection	2
Caisson disease	1
Sickle cell/Thalassemia disease	1
None	4

The total is greater than 51 because some patients had more than one cause.

or oval shape, with no rim of sclerosis; the calcifications are centrally located, dense, multilobulated clumps. The cortex may be thin and expanded. A bone infarct, in contrast, has no specific shape and is surrounded by a rim of sclerosis; the calcifications within the lesion are rarely compact, and the shape of the bone is never altered. Despite these differences, in our experience, images suggestive of enchondroma are sometimes mistaken for bone infarcts. The MRI features of the two lesions differ markedly. Finally, histological examination of the lesion is not generally necessary provided the radiographic and MRI signs of bone infarction are well known.

4. Risk factors – pathophysiology

Few facts are known about the causes of bone infarction. Overall, the risk factors for bone infarction are shared with AVN of the epiphyses, with the only exception of trauma. Radiation-induced bone necrosis is a separate entity that is no longer viewed as a form of aseptic AVN. The earliest identified risk factor is depressurization responsible for caisson disease, in which bone infarcts are labeled type B lesions and epiphyseal AVN type A lesions. The prevalence of ischemic bone necrosis of any type varies from close to 0% among professional divers in the military to 70% in Turkish sponge divers, reflecting the degree of compliance with decompression procedures [21,22]. In France, rules for hiring and monitoring employees who work under hyperbaric conditions are determined by a decree, and manifestations of decompression are among the recognized occupational diseases.

In individuals who are not subjected to supra-atmospheric pressure, glucocorticoid therapy is by far the most common risk factor. Very few studies involved a routine evaluation to identify risk factors for ischemic bone necrosis, and the role for glucocorticoids was recognized only fairly late [5]. Other risk factors were alcohol abuse, dyslipidemia, HIV infection, and sickle cell disease. Only 8% of patients had none of these risk factors (Table 1). Glucocorticoid therapy was a risk factor in over half the anecdotal case reports published to date [6–14].

There are also other unusual causes. Fat necrosis associated with pancreatic disease is a rare cause of acute necrosis of the fatty bone marrow. Patients present with acute polyarthritis, pancreatitis, and panniculitis. The skeletal lesions are osteolytic initially but subsequently acquire the typical radiographic and MRI features of bone infarcts [23]. Similarly, bone marrow necrosis related to sickle cell disease or Gaucher's disease usually produces acute symptoms suggesting osteomyelitis, although some patients have minimal symptoms with the classical presentation of bone infarction [15,17].

We are not aware of any studies designed to elucidate the pathophysiology of bone infarction. However, as bone infarction is a form of ischemic necrosis, a reasonable assumption is that its pathophysiology resembles that of femoral head AVN [24]. In fat necrosis, however, the most likely mechanism is direct toxicity of the pancreatic enzymes for the fat cells in the bone marrow.

5. Course and outcome

The reputation of bone infarct as a generally inconsequential event is well deserved. Nevertheless, two serious complications, both rare, should be borne in mind. There have been fewer than 100 cases of malignant transformation at pre-existing sites of bone infarction (with typical imaging features) [25,26]. This number is substantial, however, relative to the number of published cases of bone infarcts. Publication bias is the most likely explanation, although this hypothesis remains unproven, as the prevalence of this devastating complication is unknown. In our population – the largest reported to date – there have been no cases of malignant transformation. Malignant fibrous histiocytoma is the most common tumor type, although osteosarcoma, fibrosarcoma, angiosarcoma, and other types have been reported also. These histological types derive from the cell types found in the scar tissue surrounding the necrotic focus, where the malignant transformation probably originates [25]. Malignant transformation should be considered if a previously asymptomatic site of bone infarct starts to cause inflammatory pain or shows radiological changes. There have been a handful of cases of bacterial infection at sites of bone infarct [27–29], a complication shared with femoral head AVN. Imaging studies show typical pre-existing bone infarction, ruling out septic necrosis complicating osteomyelitis. The presentation is identical to that of typical osteomyelitis. No data are available about whether infection at sites of necrotic and poorly vascularized bone is potentially more severe or less responsive to antibiotic therapy. A case of cyst formation has been reported [30]; however, despite the histological evidence of necrosis, the appearance of the lesions strongly suggests that this patient did not have bone infarct.

6. Conclusion

Available knowledge about bone infarcts stems chiefly from clinical experience, as opposed to scientific studies, of which very few have been published. Everyday practice establishes that bone infarct is usually an asymptomatic event discovered fortuitously on imaging studies performed for another reason and that the radiographic and MRI features are usually sufficiently typical to allow a definite diagnosis.

Several points highlighted by the few published case series studies are poorly known and therefore deserve to be emphasized. A bone infarct can cause pain in and of itself. A periosteal reaction may be the only radiographic abnormality. Bone infarcts are usually multifocal and frequently coexist with multiple foci of AVN, demonstrating that it indicates a systemic disease responsible for bone ischemia. The clinical implication is that patients with bone infarct diagnosis should be routinely evaluated for known risk factors and for epiphyseal sites of AVN, which govern the functional outcome.

Disclosure of interest

The authors declare that they have no competing interest.

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