Bone Infarcts and Tumorigenesis

Subjects: Orthopedics

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Bone infarct, also known as aseptic or avascular necrosis of the bone (AVN), is characterized by osteocytes and bone marrow element death that results from inadequate blood supply, which causes local ischemia.

Keywords: secondary osteosarcoma ; bone infarct ; avascular necrosis

1. Introduction

Bone infarct, also known as aseptic or avascular necrosis of the bone (AVN), is characterized by osteocytes and bone marrow element death that results from inadequate blood supply, which causes local ischemia [1]. The disease most often affects bone epiphyses but may also affect metaphyses and diaphyses. Bone epiphyses are more vulnerable to necrosis due to the lack of connection between the bone epiphyses and local blood vessels and the consequent lack of collateral circulation leads to bone ischemia. Disturbed circulation and ischemia lead to the necrosis of osteocytes and damage to the bone structure. Given that no pathogenic microorganisms are involved in this process, it is also known as sterile bone necrosis.

Sterile bone necrosis encompasses nearly forty different conditions. Nonetheless, they all are characterized by similar anatomopathological lesions and clinical courses [2]. The most common types of bone necrosis are shown in **Table 1**.

Table 1. The most common types of bone necrosis [2][3][4][5][6][7][8].

Disease Name	Bones Affected by the Disease
Scheuermann's disease	**vertebral body border plates**
Haglund's syndrome	**exostosis of the posterior calcaneal tuberosity**
Mueller–Weiss syndrome	**tarsal navicular bone**
Freiberg disease	**2nd and 3rd metatarsal head**
Osgood Schlatter disease	**patellar tendon insertion on the anterior tibial tuberosity**
Legg–Calvé–Perthes disease	**femoral head**

2. Ethological and Risk Factors for Bone Infarcts

Bone infarcts occur in both children and adults. Contributing factors may be divided into two groups, one of which are the traumatic factors. The second group includes other factors unrelated to trauma—non-traumatic factors [1][9][10].

In the first group, fractures and dislocations lead to vascularization abnormalities, eventually leading to the development of ischemia in the affected areas [11][12].

Causes of AVN unrelated to trauma include a variety of factors, such as chronic diseases, medications, and excessive alcohol consumption. The daily consumption of alcoholic beverages can cause fat deposit formation in blood vessels over time, leading to alterations in blood supply [11]. Hyperlipidemia, obesity, diabetes, and smoking were also identified to increase the risk of AVN. Many medications elevate the chances of developing osteonecrosis. Corticosteroid effects were found to be time- and dose-dependent [12][13]. Among other drugs, osteoporosis medications, especially bisphosphonates, can contribute to AVN, specifically in the jawbone. The risk is even higher in people who have received a large amount of bisphosphonates intravenously to counteract bone metastases [14][15]. Non-traumatic causes also include non-modifiable factors, such as male gender and northern and urban residence [12].

Certain medical conditions also play an essential role in the etiology of the bone infarct. These include hemoglobinopathies (e.g., thalassemia, sickle cell anemia), decompression sickness, certain autoimmune diseases, coagulopathies (antiphospholipid syndrome, protein C, and protein S deficiency), infections (HIV), and other, such as Gaucher disease and chronic liver diseases [12][16][17][18]. Medical treatments and procedures that increase the risk of AVN may include cancer treatments, radiation, dialysis, and kidney and other organ transplants [18]. Genetic polymorphisms were also found to increase the risk for this condition [17][19].

3. Bone Infarcts-Clinical Picture and Diagnosis

The primary symptom of bone infarcts is a pain in the affected bone area [12]. Initially, the pain intensifies during physical activity and disappears when it is discontinued but may be present at rest in more chronic cases. In some cases, pain may be accompanied by reduced mobility in the illness joint [20].

The patient's history and imaging findings are usually unambiguous enough to establish an AVN diagnosis and rule out other causes of joint and bone pain. X-ray allows for diagnosis confirmation in advanced cases but may be useful in the initial differential diagnosis [12][20]. Bone scintigraphy offers the advantage of detecting abnormalities present at the earlier stages of the disease thana classic X-ray. The affected bone tissue presents with "donut-like" changes ('cold' in 'hot') [21]. Nonetheless, its use is limited because of a specificity lower than MRI. MRI has both higher sensitivity and specificity than X-ray and allows for identifying early signs of the disease [12]. Still, positron emission tomography (PET) is superior to MRI as a more sensitive imaging method, detecting early changes and allowing for the prediction of disease prognosis [10][22][23]. Its use is limited by low availability in comparison with the aforementioned methods.

4. Treatment and Management

The main aim of bone infarct treatment is the prevention of further loss of bone mass. The choice of intervention depends on the severity of the bone damage. Pharmacological treatment is mainly symptomatic [17][20]. Studies regarding nonsurgical treatment included small groups, and their quality is low—therefore, they might be regarded as experimental [17]. The medications commonly used in the treatment of AVN are listed in **Table 2**.

Table 2. Medications used in the treatment of AVN [12][17][20].

Classes of Drugs	Examples	Role in Osteonecrosis Management
Non-steroidal anti-inflammatory drugs	Ibuprofen or naproxen	Help relieve pain and inflammation associated with AVN
Osteoporosis medications	Alendronic acid	Some studies indicate that osteoporosis drugs can slow the progression of AVN.
Hypolipidemic drugs	Statins, fibrates	Prevention of micro and macro angiopathies
Anticoagulants and antiplatelet agents	Warfarin, acetylsalicylic acid	Inhibition of thrombus formation and anti-aggregation effects

Most patients who suffer from AVN will seek help in the advanced stages of the disease when the symptoms begin to interfere with their activities. In such patients, surgical treatment might be considered [24]. Selected surgical procedures used to treat AVN are presented in **Table 3**.

Table 3. Surgical procedures used to treat AVN [9][12][17][19][24].

Treatment	Characteristics
Spinal decompression	During this procedure, the surgeon removes part of the inner layer of bone. In addition to reducing pain, this treatment has the effect of stimulating osteogenesis and neovascularization.
Bone graft (transplant)	The procedure helps to strengthen the area of bone affected by the lesions. During the procedure, some healthy bone taken from another part of the body is used.
Bone osteotomy	During this procedure, a bone wedge above or below the stressed joint is removed—This helps to shift weight away from the damaged bone. Changing the shape of the bone may allow the joint replacement surgery to be pushed back.
Joint replacement (alloplasty)	This treatment is used when other treatments do not help; it involves replacing the damaged parts of the joint with plastic or metal parts.

5. Possible Associations between Tumorigenesis and Bone Infarct

Several patient cases were published in the past linking osteonecrosis to malignant diseases. The first case of an infarct-associated sarcoma was described in 1960. This was followed by several other reports, though most describe single-patient cases or relatively small case series. Bone infarcts were portrayed as the primary cause of the tumorigenesis or secondary to it [25][26]. Infarct-related sarcomas are extremely rare even when compared with bone malignancies secondary to Paget's disease or radiation [27][28]. Diagnosis and management are challenging, given the disease's rarity and the paucity of available data to guide clinicians [29][30]. In addition, little is known about the pathogenesis of the disease, risk factors for the malignant transformation of the necrotic tissue, and its natural course.

6. Discussion

Ischemia of the bone is a relatively common finding in orthopedic practice. Many conditions and medications were shown to increase the risk of bone infarcts, including conditions that promote the formation of blood clots (e.g., sickle cell anemia, pregnancy, Cushing disease), steroids, alcohol abuse, diving, radiation therapy, and others [12][17][29][31]. In fact, in roughly 70% of cases, the cause of bone infarct remains unknown [30][32][33][34][35]. Not all infarcts are symptomatic, and patients remain symptom-free for a long time, which is especially true for diaphyseal and metaphyseal AVN [29][32]. That results in diagnostic and treatment delays and poorer clinical outcomes [36].

Available epidemiological studies demonstrate that less than 1% of malignant tumors affect the bone. In the USA, only 3300 cases of primary bone tumors are diagnosed each year [32]. Secondary bone tumors, including infarct-associated tumors, are even rarer, making up to 0.6–1% of all sarcomas of the bone [34][36][37]. The first cases of infarct-associated sarcomas were described by Furey et al. in 1960 [38]. In the literature, less than 150 cases of AVN-related tumors were described, inducing over 120 MFH cases [34][39]. Most patients affected were male and in their fifth or sixth decade of life [34][39][40][41]. A majority of these tumors were located in the lower limbs, especially the tibia and femur, though two case reports concerned humoral lesions [29][30][41][42]. Many cases came from small case series or single-patient case descriptions [29][30][31][32][33][34][35][36][39][40][41][42][43][44][45]. It should be underlined that silent infarcts, which are more likely to be a background for carcinogenesis and tumor development, do not present with noticeable symptoms [32]. It is possible that a growing tumor would obscure radiological signs of the past infarct. Therefore, the true epidemiology of AVN-associated tumors is likely to be underestimated [34]. On the contrary, epiphyseal bone infarcts are more likely to be discovered early, since they are usually symptomatic. Tumorigenesis, being a lengthy process, is unlikely to occur in such cases, and as a result, symptomatic infarcts are less likely to be a background for secondary malignancies [30][34][41][46].

The pathophysiology of the malignant transformation of necrotic bone tissue remains a field of hypotheses and assumptions that still need to be investigated in depth. It has been hypothesized that the reparative process and chronic inflammation lead to the transformation into sarcoma [32][35][40]. In general, the development of sarcoma in the AVN of the bones is a relatively slow process. One study of Caisson workers demonstrated that sarcoma developed 17–22 years after quitting their job. A similar timeframe applied to a case described by Endo et al., wherein the malignancy was detected 13 years after the infarct was visualized on an X-ray performed for to another reason. The close follow-up of that patient led to the detection of malignancy relatively early, before it transformed into high-grade osteosarcoma [32].

Nonetheless, the exact time interval between bone infarct and the development of bone sarcoma is unknown, since AVN timing is usually impossible to determine. In all of the cases described by Stacy et al., all patients were diagnosed when the symptoms related to the malignancy itself became apparent, and only subtle signs of previous AVN indicated that it was secondary to infarction. The situation was the same in all but one case [34]. In addition, none of the studies included in this research have proven that there is a connection between any condition, medication, or other risk factors promoting oncogenesis in patients who suffered a bone infarct [32][33][40][41][42][44]. It is yet to be established if such tumors develop by chance or if some populations need closer follow-up to allow for early detection and treatment, which could improve the long-term prognosis. Alhamdan et al. have made a suggestion that SCT patients are more likely to develop secondary malignancies in infarcted areas. Still, there is no proven connection between these two, but this concept warrants further investigation [40].

Imaging is key to diagnosis and determining signs of a previous bone infarct [32][34]. A radiologist assessing the tumor might see a well-defined, calcified band representing the previous infarct's margins. A mixed pattern of lucencies and sclerotic changes found in the tumor's proximity might also indicate that the disease is secondary to osteonecrosis [34]. Such changes are observed both in classic radiographs, MRIs, and CT [30][31][32][33][34][35][36][39][40][41][42][43][44][45]. Nonetheless, an X-ray is usually insufficient to assess the tumor properly, and MRI and CT are indispensable. For staging

and the determination of the presence of metastases or multifocal lesions, scintigraphy and SPECT might be considered [31][34][41].

More recently, molecular markers and genomic analyses have helped determine the histological characteristics of infarct-associated tumors [32][41][42]. Immunohistochemical stains are especially useful in rare histological tumors. Myxofibrosarcomas express CD34 protein, whereas low-grade osteosarcomas express CDK4, MDM2, and mutations of the p53 protein. INI1 was retained in osteosarcoma [32][41][42]. Most of the included studies, however, did not share results of immunohistological or molecular examination.

Secondary osteosarcomas typically develop in individuals over 50 years of age, which translates to challenges in the management of the disease [36]. The overall prognosis is unfavorable in patients with sarcomas arising at the bone infarct site. Past reports have suggested that aggressive and multimodal treatment might result in 2-year survival rates comparable to primary osteosarcomas (60–70% vs. 50–80%, respectively) [30][31][34][35][47]. Unfortunately, not all patients can complete a high-dose course of ChT, due to their comorbidities, and some instead receive a shorter, low-dose regimen or none [28][36]. Some patients might not respond to such management either [41]. Therefore, overall-survival rates are much lower. In a review from 1992 by Torres and Kyriakos, only 22% of patients were alive five years after MFH diagnosis [29]. Domos et al. reported that 46% of their patients died within seven months of the diagnosis, and taking together their data and other cases published until 2004, 57% of patients were dead within 19.2 months [30].

Conversely, in the recently published case series by Stacy et al., patients who had localized disease survived 11 months to 25 years, and, in a review prepared by Laranga et al., five-year survival reached 62% (CI 28–84), and the median survival was 74 months, compared to 12 months in the cases described previously in the literature. The results were worse for patients treated with surgery only (50% lived for five years post-diagnosis and, for the case reports described previously, 50% lived for two years) [34][36]. These data suggest that surgery combined with adjuvant treatment and even surgery alone offer better results than in the past decades. However, given the small case numbers, definite conclusions cannot be drawn [29][30][34][36]. To date, there is no standardization of treatment for this type of malignancy. This might be important, especially for patients with metastases, who still have the worst prognosis, with reported survival rates at 1-year post-discovery close to 0% [29][30][31][34].

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