Definition of bone necrosis by the pathologist

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Summary

Osteonecrosis is a common disorder that may go clinically unrecognized or may result in the collapse of the architecture of bone, determining severe anatomic alterations of the involved site. Osteonecrosis is not a specific disease entity, but rather the result of a number of conditions ultimately leading to an impairment of blood supply to the bone tissue, although there is evidence that modifications of bone remodelling activity and weakening of bone structure with formation of microfractures are implicated as well. According to the site involved and to the factors promoting its development, the morbid anatomy and histopathology of osteonecrosis show a different appearance. This review discusses the main skeletal manifestations of osteonecrosis, including subarticular avascular necrosis of the femoral head and of the knee, as well as osteonecrosis of the jaw.

KEY WORDS: bone, necrosis, histopathology.

Necrosis is the cell death due to an irreversible external injury, which is recognizable microscopically by alterations in the nucleus (swelling, pyknosis, karyorrhexis, karyolysis) and in the cytoplasm, which becomes eosinophilic. Osteonecrosis, that is the death of bone, is a common disorder that may go clinically unrecognized, or may result in the collapse of the architectural bony structure, leading to joint pain, bone destruction, and loss of function. Synonyms of osteonecrosis are avascular necrosis, ischemic necrosis, subchondral avascular necrosis, and aseptic necrosis of bone. The term “aseptic necrosis” was first used by the German pathologist Georg Axhausen, who studied the evolution of bone grafts and described the process of repair by which new bone is laid down on dead bone graft (1).
Osteonecrosis is not a specific disease entity, but rather it is the final common pathway of several conditions leading to bone death. This review covers the histopathologic aspects of the main conditions characterized by osteonecrosis with a discussion of their pathogenesis.

Histopathology of osteonecrosis

It has long been accepted that the histologic sign indicative of osteonecrosis is empty osteocytic lacunae, but it is now clear that artefactual loss of staining of osteocytic nuclei may result from suboptimal tissue fixation. On the other hand, loss of osteocytes is not complete until two to four weeks after the onset of ischemia, according to studies conducted on both human material and experimental bone infarction in animals (2-4). This indicates that the histological recognition of bone death may be delayed if based on this feature alone, even in properly processed material. In addition, occasional empty lacunae are seen in the interstitial lamellae between osteones in the cortical bone, and their number increases with age, probably as a result of diminished blood supply. They are patchily distributed within cortical bone, in contrast to the complete loss of osteocytes observed in severe ischemic episodes (5).
The earliest microscopic signs indicative of bone ischemia are seen in the marrow spaces, where starting from the second day there is loss of nuclear staining of marrow cells and large round and ovoid spaces filled with fat appear (6). The fatty and haemopoietic marrow becomes then ghosted and the small vessels show evidence of necrosis (Figure 1); after 15 days the osteocytic lacunae are empty and the trabecular surface is devoid of cells. At the border of the necrotic zone there is proliferation of capillaries accompanied by fibroblasts and foamy histiocytes, which are responsible for the breakdown of necrotic fatty marrow, while dead bone is partly removed by osteoclasts and substituted by newly formed trabeculae; alternatively woven bone is laid down on the surface of dead trabeculae. Phemister coined the term “creeping substitution” to indicate this slow replacement of aseptic dead bone in contrast with the massive resorption or sequestration of dead bone associated with osteomyelitis (7, 8).

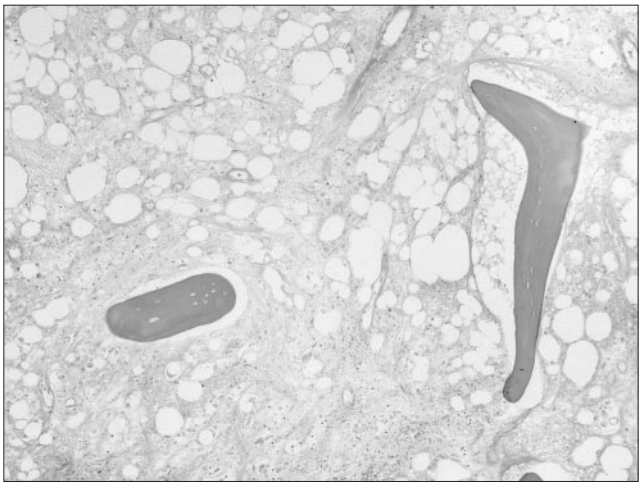

Figure 1 - Osteonecrosis following fracture of the femoral head. There is diffuse coagulative necrosis of marrow cells and osteocytic lacunae in bone trabeculae are empty (haematoxylin and eosin, 10x obj.).

Pathogenesis

The aetiological factors of osteonecrosis are known only in some conditions, like fracture, caisson disease, sickle cell disease, but less clear in others, like systemic lupus erythematosus, corticosteroid administration, alcoholism; idiopathic forms are frequent as well.
Osteonecrosis involves more frequently the convex articular surfaces because of the smaller diameter of the terminal vessels of this region and the absence of collateral vascularization. Other intrinsic factors contributing to the development of osteonecrosis are the reduced vascularity of fat marrow in comparison with haemopoietic marrow and the non-extensive quality of bone tissue. Impairment of the blood flow may be caused by vascular compression (external pressure), trauma or occlusion of the vessels by nitrogen bubbles (in caisson disease) or rigid sickle cells (in sickle-cell anaemia). The mechanism of ischemia and necrosis in other non-traumatic osteonecrosis is not clear and several possible mechanisms have been proposed. Most authors think that bone necrosis results from primitive vascular problems, including vessel infarction, stenosing arteritis, arterio-sclerotic disease, extraosseous arterial involvement or extraosseous venous abnormality, or hypercoagulability and hypofibrinolysis. However, there is little histological evidence of vascular thrombosis, as there is little evidence of alterations in the coagulation mechanisms to support these theories.
Frost has been the first to report the almost constant presence of trabecular microcracks in aseptic bone necrosis, with the possible exception of necrosis associated with work in compressed air, as the result of failure of healing of this microdamage with resultant fatigue fracture (9). Diminished resistance of the affected bone is thought to determine secondary vascular impairment at the capillary level either through compression from relatively inelastic fat cells or through the rupture of small intratrabecular vessels. Interestingly, evaluation of transiliac bone-biopsy specimens from patients with aseptic osteonecrosis and normal kidney function revealed a marked reduction in osteoblastic appositional rate and in bone-formation rate at the cell and tissue level, indicating that non-apparent metabolic disturbances are present in these patients (10). Alterations in the remodelling of bone tissue may contribute to the development of osteonecrosis in several ways, for example by inducing a healing defect of microfractures and thus facilitating subchondral fractures ultimately leading to osteonecrosis (10).

Clinico-pathologic presentations

Regardless the aetiology and pathogenesis, bone necrosis results in different clinico-pathologic presentations related to the involved site. Infarcts occurring in the shaft of long bones are likely to be asymptomatic and are usually incidental findings on X-ray films, in which case they need to be differentiated from cartilaginous tumours. Clinically manifesting bone infarcts are usually seen adjacent to a joint, particularly in the femoral head (11), followed in frequency by the humeral head (12), the knee (13), the small bones of the hand and the foot (14-17), and the vertebrae (18). Many of these conditions, especially the idiopathic osteonecrosis occurring in childhood or adolescence, have historical names. Finally, in recent years a peculiar type of osteonecrosis of the jaws has emerged as a complication of the use of bisphosphonate drugs.

Osteonecrosis of the femoral head

According to the experience of the Hospital for Special Surgery (New York), 20% of the femoral head resection for non-traumatic causes are performed for subchondral avascular necrosis; about 60% of idiopathic cases are bilateral and the majority of these patients have been treated with corticosteroids or are alcoholists (19). The median age of patients treated for subarticular avascular necrosis is 54 years while that of patients treated for ostearthritis is 67. In a review of the experience of the Hospital for Joint Diseases (New York), from approximately 2000 total hip replacement carried out between 1984 and 1989, the presence of osteonecrosis was identified in 345 patients (377 specimens, 18.9%) (20).
Before 1960, osteonecrosis of the femoral head in absence of fracture of the femoral neck was considered an unusual event. In 1962, Mankin and Brower reviewed the literature and could find only 27 reported cases, while nowadays this condition is recognized as an important cause of osteoarthritis (21). Most patients are males, 30 to 60 years old, and there is often history of corticosteroid treatment or alcoholism. The reported incidence of bilateral involvement is between 50% and 70% (21).
In addition, osteonecrosis is observed as a secondary complication of osteoarthrosis of the hip in about 10% of femoral head removed for joint replacement (22, 23). Secondary osteonecrosis appears more frequently as a superficial “shallow” lesion involving 2-3 mm in depth beneath the articular surface (36.5% of cases), while less frequently the lesion is larger and shows a wedge shape similar to that of primary subarticular avascular necrosis (23). The first type is probably a result of bone eburnation of osteoarthrosis, which interferes with blood flow, while the second type appears to be an independent event presumably caused by similar causal factors involved in primary osteonecrosis (22, 23).
A fracture of the femoral neck is always followed by ischemic necrosis of the femoral head, due to the interruption of the blood supply. These fractures are occasionally seen in the young age following major trauma, but they are more common in the osteoporotic or osteomalacic bones of the elderly women after very minor trauma. Following the process of fracture repairing, or starting from the viable subfoveolar bone, the infarcted femoral head undergoes revascularization and reparative processes take place. This is sometimes followed by a collapse of the femoral head, a complication that usually occurs after a 1.5-2 year period from the fracture of the femoral neck, and that leads to late secondary changes (24-26).
Catto has described the morphologic modifications associated with osteonecrosis of the femoral head due to sub-capital fracture, which according to her papers occur four different steps, but this description can applied to other forms of osteonecrosis as well. In the first stage there is necrosis of the bone marrow, without evidence of reparative processes; in the second stage the reparative processes become evident at the periphery of the necrotic region; in the third stage there is collapse of the articular surface; and in the fourth stage there is evidence of secondary osteoarthritis (27, 28). These classical anatomical descriptions form the basis of the classification schemes for staging of osteonecrosis developed for imaging techniques:
– Stage I. At external examination the shape of the femoral head is unaltered, but on frontal section there is a wedge shaped subarticular area of necrosis in which the marrow is yellow-opaque. The infarct is well delimited from the surrounding bone by a thin hyperaemic border. Histologically, the articular cartilage is viable, while the marrow elements of the subarticular bone are substituted by granular eosinophilic material and ghosts of necrotic adipocytes can be identified. The trabecular bone shows empty osteocytic lacunae and at the margin of the infarct there is increased osteoblastic and osteoclastic activity, accompanied by a proliferation of capillaries and fibroblasts in the marrow spaces, which correspond to the hyperaemic rim seen macroscopically;

– Stage II. As in stage I, the articular surface is unaltered, but due to the progression of reparative processes, the infarcted area appears better demarcated on section (Figure 2), and a peripheral rim of sclerosis is visible radiologically. The proliferating capillaries and fibroblasts extend into the necrotic area, and dead bone trabeculae are removed by osteoclasts and substituted by viable new ones, laid down by osteoblasts, resulting in the sclerotic rim;
– Stage III. At this stage there is an evident modification of the shape of the articular surface due to the collapse of the necrotic bone. On frontal section, there is a linear fracture usually located just below the articular cartilage, at the bony end plate level, or less frequently within the necrotic area or at its periphery (Figure 3). Histologically, the fracture area shows an admixture of fragmented bony trabeculae and cartilage with reparative tissues, including reactive woven bone, cartilage and granulation tissue, that is the appearance of unstable fracture elsewhere in the skeleton. Focal necrosis of the repair tissue around the area of fracture-collapse may occur and it should not be interpreted as recurrent osteonecrosis, since it is likely not related to a recurrent ischemic event but rather to the injury resulting from the fracture itself (29);
– Stage IV. At this stage the shape of the femoral head is severely deformed, due to the progressive detachment of bone and cartilage fragments from the infracted area (Figure 4). Bony and cartilaginous debris can be seen in the capsular and synovial tissues. This is accompanied by the development of signs of osteoarthritis, including eburnation of bone around the infarct. When osteoarthritic changes are fully developed, it may not be possible to recognize the initial cause as that of subarticular avascular necrosis.

Osteonecrosis of the knee

Spontaneous osteonecrosis of the knee was described as a distinct entity in 1968 (30). The typical clinical presentation is in elderly women, often obese and showing osteoporosis, who complain of sudden onset of pain in the knee, almost always of the medial condyle of the femur and associated with localized tenderness at the joint line. There is no history of systemic dis-

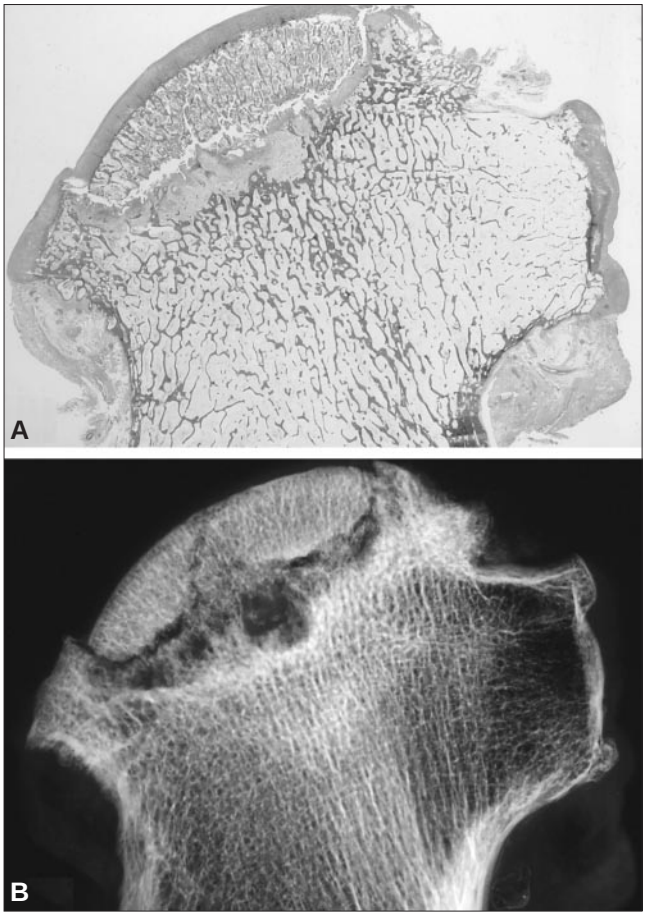

Figure 3 - A – Scanning view of a frontal section of an infarcted femoral head stained with haematoxylin and eosin. A subchondral fracture is present at the periphery of the infarcted area, which has caused the collapse of the articular surface. The trabeculae in viable bone adjacent to the infarct are thickened. B – Specimen radiograph of the same frontal section in A, showing the fracture line and the rim of bone sclerosis at the periphery of the infarct.

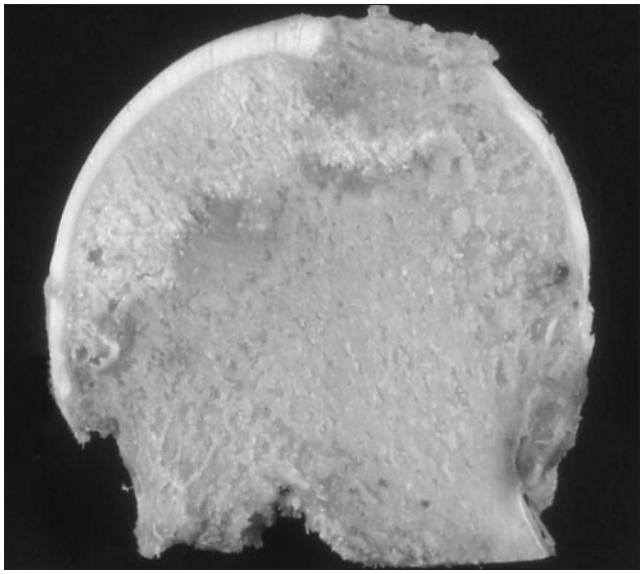

Figure 2 - Frontal section of a femoral head showing a wedge-shaped subarticular area of necrosis, which is well separated from the viable bone by a rim of granulation tissue. The convex shape of the femoral head is maintained.

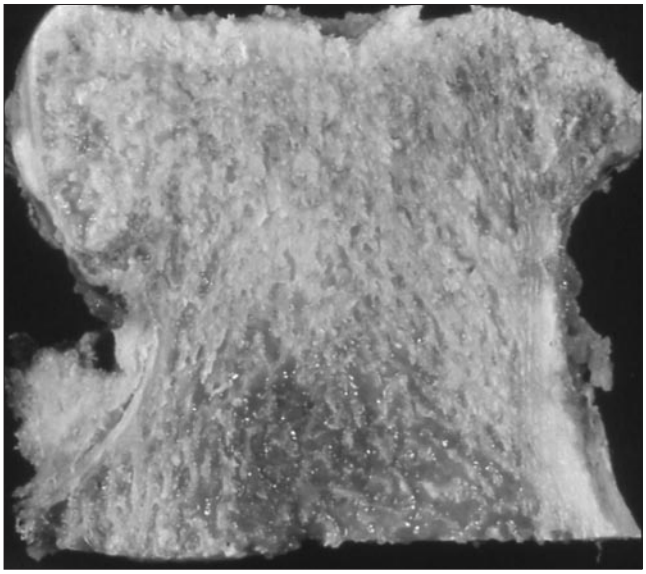

Figure 4 - Frontal section of a femoral head showing severe deformity due to the progressive detachment of bone and cartilage fragments from the infarcted area.

eases or administration of corticosteroid drugs (13). The lesion often involves only a small subchondral portion of bone, preferentially of the medial femoral condyle, and in most cases there is pathological fracture with collapse and fragmentation of the necrotic segment leading to marked deformities (31). Interestingly, a histopathological analysis of fourteen cases of osteonecrosis of the knee revealed the presence of subchondral insufficiency fracture in most specimens, suggesting that the primary event leading to spontaneous osteonecrosis of the knee is a subchondral insufficiency fracture due to osteoporosis or other metabolic diseases (32).

Osteonecrosis of the jaw

Osteonecrosis of the jaw presents mainly in two clinical settings, either as a complication of the treatment with bisphosphonate drugs, or following radiotherapy for head and neck carcinoma, as osteoradionecrosis.

Osteonecrosis of the jaw is a well recognized complication of the use of bisphosphonates in the treatment of cancer-related hypercalcemia, as well as in bone involvement by multiple mieloma and metastatic carcinomas. It was first reported in 2003 (33) and can be defined as the unexpected development of necrotic bone in the oral cavity of a patient receiving bisphosphonate treatment and who has not received radiotherapy to the head and neck. It may develop spontaneously, but usually appears after dental surgery procedures, heals poorly or does not heal over a period of 6 to 8 weeks (34). Most of the reported case (95%) have been associated with pamidronate or zoledronic acid given intravenously to control metastatic bone disease (35).

A recent survey of 1203 oncology patients (904 multiple myeloma and 229 breast cancer patients) reported that 6,9% of multiple myeloma patients and 4,3% of breast cancer patients developed osteonecrosis of the jaw (36). The most common malignancies associated with osteonecrosis of the jaw are multiple myeloma and breast cancer, followed by prostate cancer, lung cancer, uterine leiomyosarcoma, plasmocytoma and leukemya (36). The most important predisposing factors for development of osteonecrosis are the type of bisphosphonate, the total dose, the time of exposure to the treatment, dental surgery and dental infection. The hazard of developing osteonecrosis was significantly higher in zoledronic acid treatment: 1% within the first year increasing to 21% at three years. Patients who developed osteonecrosis received a median number of 35 infusions (range 13 to 68) and median time of exposure to bisphosphonates was 39.3 months (range 11 to 86) (36).

The role of bisphosphonates in the development of osteonecrosis of the jaw has not yet been fully understood. These drugs interfere with bone resorption by inhibiting osteoclastic activity, through selective concentration at the interface of the active osteoclast and the bone resorption surface. Osteoclast activation is the first event of the remodelling process, which is followed by resorption and formation. This cycle is critical to maintain bone viability. If osteoclastic function is too severely impaired and the remodelling process does not take place, this may predispose to the development of osteonecrosis of bone. In addition, bisphosphonates have anti-angiogenic properties which may contribute to the development of osteonecrosis (37, 38). Another hypothesis that has been proposed is based on the fact that teeth are readily infected by bacteria (come from outside or contained in saliva) that cause caries and periodontal disease. Because the teeth are separated from bone by no more than two millimetres of periodontal connective tissue, such infections have easy access to the underlying bone (39). Why the effect of bisphosphonates on jaw bones would be different to other bones is unclear. Bisphosphonates may be highly concentrated in the jaws because these bones have a greater blood supply than other bones and a faster turnover rate related both to their daily activity and the presence of teeth. Coupled with chronic invasive dental diseases and treatments and the thin mucosa over bone, this anatomic concentration of bisphosphonates causes this condition to be manifested exclusively in the jaws (40).

In our experience, biopsy material from affected areas shows partially or completely necrotic bone, with empty osteocytic lacunae and heavily eroded surfaces (Figure 5). A severe acute and chronic inflammatory infiltrate is present in the inter-trabecular spaces of the surrounding bone tissue, with neutrophils, eosinophils, plasma cells and histiocytes. Prominent osteoclastic and osteoblastic activity can be seen at the trabecular surface (Figure 5). In the necrotic area, Actinomyces colonies are identified in most cases (Figure 6). Therefore, the overall picture is that of an osteomyelitic process and it is debated whether there is superinfection of a primarily necrotic bone by the oral flora or bone necrosis is rather a consequence of microbial infiltration of metabolically inactive and poorly vascularized bone. The observation that bone tissue within and adjacent to the affected area is not entirely necrotic speaks against a bisphosphonate-induced necrosis, but rather supports the theory that the process is started by injury and infection, and the reduced remodeling ability due to bisphosphonate treatment hinders the subsequent reparative process.

Osteoradionecrosis can be defined as a chronic effect of radiotherapy which progresses slowly and does not tend to heal spontaneously. In a study by Reuther et al. osteoradionecrosis had an incidence of 8.2%, i.e. 68 (62 males and 6 females) out of 830 patients who received radiotherapy (41). Sader et al. demonstrated a positive correlation between the incidence of osteonecrosis and the therapeutic intensity (42). Osteoradionecrosis was more common in patients treated with combined radio/chemotherapy before surgery, with the time range between treatment and development of osteoradionecrosis being 9 months for the combination radio/chemotherapy and 14 months for radiotherapy alone (42). In

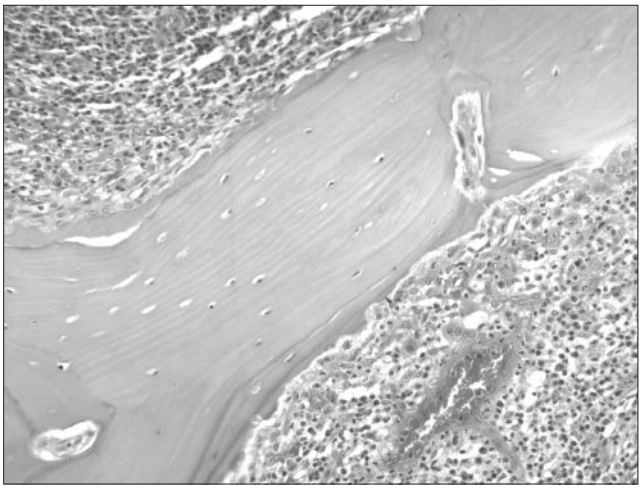

Figure 5 - Bisphosphonate induced osteonecrosis of the jaw. Haematoxylin and eosin stained section showing partially necrotic bone trabeculae, with lacunae containing viable osteocytes, necrotic osteocytes or showing empty lacunae. A severe inflammatory infiltrate is present in the inter-trabecular spaces (20x obj.).

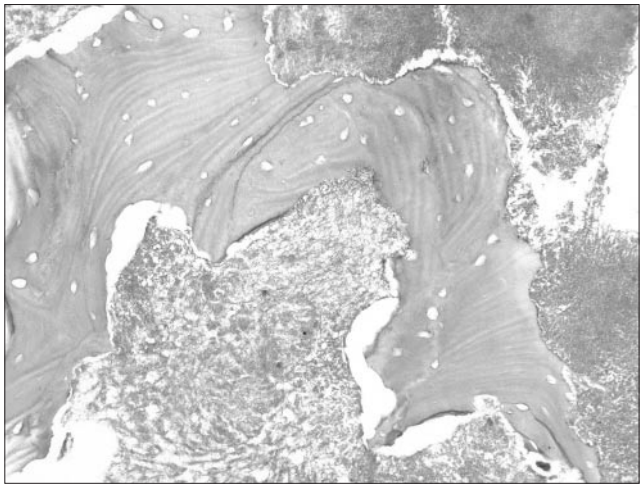

Figure 6 - Bisphosphonate-induced osteonecrosis of the jaw. Haematoxylin and eosin stained section showing completely necrotic bone trabeculae. Actinomyces colonies are present in the inter-trabecular spaces (20x obj.).

addition the extent of osteoradionecrosis shows a direct correlation with the radiation dose. Other risk factors are tumor stage, tumor infiltration of adjacent bone and tooth extraction (42).

The histological features of osteoradionecrosis of the mandible are similar to those of bisphosphonate induced osteonecrosis of the jaw. It has been hypothesized that osteoradionecrosis develops as a consequence of hypoxia due to reduced vascularity and radiation-induced endoarteritis. This may then lead to an infection of the previously weakened bone and tissues and to the development of a chronic non-healing wound.

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