

Osteomyelitis and osteonecrosis in inflammatory bowel disease

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HJ Freeman. Osteomyelitis and osteonecrosis in inflammatory bowel disease. *Can J Gastroenterol* 1997;11(7):601-606. Osteomyelitis and osteonecrosis are skeletal disorders seen in patients with inflammatory bowel disease (IBD). Osteomyelitis usually occurs in the pelvic bones, especially in complicated Crohn's disease, presumably by direct extension from a pelvic inflammatory mass, abscess or fistulous tract. Diagnosis of osteomyelitis may be difficult and can lead to spinal extension of the septic process with a resultant neurological deficit, including paraplegia. Osteonecrosis or avascular necrosis has been reported in patients with either ulcerative colitis or Crohn's disease, often, but not exclusively, during or following steroid treatment. The disease is often multifocal, but its natural history is unknown, especially if diagnosed early with modern imaging methods, such as magnetic resonance. In IBD patients, the relationship between osteonecrosis and steroid use is unknown. An adverse steroid effect on bones, especially the femoral heads, may develop in some patients with IBD but, to date, this hypothesis remains unproven. Critical evaluation of published data reveals no consistent association between osteonecrosis and steroid treatment in IBD patients.

Key Words: Arthritis, Avascular necrosis, Bone abscess, Bone disease, Crohn's disease, Granulomatous ulcerative colitis

Ostéomyélite et ostéonécrose dans la maladie inflammatoire de l'intestin

RÉSUMÉ : L'ostéomyélite et l'ostéonécrose sont des troubles du squelette que l'on observe chez les patients atteints de maladie inflammatoire de l'intestin (MII). L'ostéomyélite survient habituellement au niveau des os du bassin, surtout dans la maladie de Crohn compliquée et résulte probablement d'une extension directe d'une masse, d'un abcès ou d'une fistule inflammatoire au niveau du bassin. Le diagnostic de l'ostéomyélite peut être difficile à poser et peut s'étendre vers la colonne vertébrale avec le déficit neurologique qui s'ensuit, y compris la paralysie. L'ostéonécrose ou la nécrose avasculaire a été signalée chez les patients qui souffrent soit de colite ulcéreuse soit de maladie de Crohn, souvent, mais non exclusivement durant la corticothérapie. La maladie est souvent multifocale, mais son histoire naturelle est inconnue, surtout si elle est diagnostiquée tôt au moyen de méthodes d'imagerie moderne comme l'imagerie par résonance magnétique. Chez les patients atteints de MII, le lien entre ostéonécrose et corticothérapie reste inconnu. L'effet indésirable de la corticothérapie sur les os, surtout au niveau des têtes fémorales peut s'installer chez certains patients et à ce jour, l'hypothèse n'a pu être prouvée. L'évaluation critique des données publiées ne révèle aucune association concluante entre l'ostéonécrose et la corticothérapie chez les patients atteints de MII.

About 25% of patients with inflammatory bowel disease (IBD) will develop a rheumatological complication, many of which directly involve bone (1-3). Some common disorders seen in Crohn's disease or ulcerative colitis include central or axial arthropathies, ankylosing spondylitis and sacroiliitis, as well as peripheral (or 'enteropathic') arthropathies. These disorders primarily involve joint spaces, synovia and soft tissues; only later, or secondarily, are bone changes seen, such as joint space erosions, sclerosis, narrow-

ing and ligamentous ossification. In some patients, increased joint disease activity is related to an exacerbation of the underlying intestinal disorder; in others, there is no evident link to intestinal disease activity, and the disorders appear completely independent.

In some, but not all, patients with IBD and ankylosing spondylitis, human leukocyte antigen B27 has been observed (1,2). In addition, subclinical inflammatory changes in the intestine have been observed in over half of patients with

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spondyloarthropathy (4-9), with evolution to frank IBD in about 7% (10). Finally, a transgenic mouse model of human IBD with arthropathy has been reported to be relevant to future immunopathogenesis studies (11,12).

Metabolic bone diseases, including osteoporosis, develop in an estimated 30% of IBD patients (13-16). In these patients, osteopenic bone disease is probably multifactorial. Anorexia may result in impaired intake of calcium and vitamin D. Associated hepatic or biliary tract disease may cause impaired conversion of vitamin D to its active metabolites. Reduced mucosal surface area due to small intestinal disease or repeated intestinal resections may result in impaired absorption and malnutrition. Although steroid therapy may contribute to bone loss, IBD patients may initially present with low bone mass before commencement of steroid therapy (17). There is a poor correlation between bone mass and steroid intake (15,18-20). Recent studies in a rat model of colitis indicate that bone loss may also be attributable to the inflammatory process (21). Bone formation and modelling may be suppressed, possibly due to systemic factors, such as the inflammatory cytokines (ie, interleukin-1 and tumour necrosis factor-alpha). These inhibit bone formation by suppressing osteoblast proliferation (22-24) and enhancing bone resorption (25-27).

Other very distinctive, but rarely reported, skeletal disorders can occur in patients with IBD. These include osteomyelitis and osteonecrosis (or avascular necrosis of bone). Both cause significant morbidity and must be differentiated from the musculoskeletal disorders described above and other rare entities, including periosteal new bone formation (28-30) and granulomatous bone disease (31,32). Osteonecrosis has recently assumed significance related to litigation based on the misconception that osteonecrosis is caused by corticosteroids in IBD patients. As a result, use of highly effective and inexpensive corticosteroid medications, such as prednisone, to treat IBD may be curtailed in favour of earlier 'curative' surgical treatment, including ablative procedures with pelvic pouch reconstruction, that can also cause morbidity and mortality. Moreover, pharmaceutical companies have focused much of their marketing efforts, including some multicentre studies on budesonide therapy for Crohn's disease in Canada (33,34), on 'safe' but expensive corticosteroids for IBD (35). These recent studies, however, lack specific data on the effects of these agents on skeletal metabolism. In a recent report (36), however, four cases of aseptic bone necrosis were noted during budesonide controlled ileal release therapy.

This review examines osteomyelitis and osteonecrosis in IBD, complications that result from these two skeletal disorders, and published data on osteonecrosis and steroid use, particularly in ulcerative colitis and Crohn's disease.

OSTEOMYELITIS

While many inflammatory intestinal tract disorders occur adjacent or very close to the bony pelvic structures, osteomyelitis involving the pelvic bones is rare. In over 600 patients with osteomyelitis, only 5% had involvement of the

bony pelvis (37). Usually the infection is spread by contiguous extension from a soft tissue focus or, less commonly, from an intra-abdominal or intrapelvic abscess. The resulting osteomyelitis is usually located in the bony ilium, probably because it is the largest of the pelvic bones with a large blood supply.

The precise frequency of osteomyelitis in IBD is unknown but the first cases were described in Crohn's disease by Goldstein et al in 1969 (38), London and Fitton in 1970 (39) and Meltzer in 1973 (40). Since then, only a few other cases have been reported in IBD patients (41-53). This seems surprising because of the frequent presence of an associated pelvic inflammatory mass, abscess or fistulous tract in Crohn's disease. Osteomyelitis in ulcerative colitis is even more rare (54).

Most cases of osteomyelitis involve the bony structures on the right side of the pelvis, specifically the bony right ilium. Undoubtedly, the location is related to the nearby or adjacent terminal ileum and cecum, especially common sites of clinically defined involvement in Crohn's disease. In most patients with Crohn's disease and osteomyelitis, a localized abscess or fistula is also present, suggesting that infection resulted from seeding to contiguous bone. Exceptions, however, do occur. In one report (42), for example, osteomyelitis of the femur was seen in Crohn's disease complicated by an *Escherichia coli* septicemia. The patient had received corticosteroids and immunosuppressive medications.

With sacral osteomyelitis in Crohn's disease, presacral and perirectal abscesses are usually present. In most of those patients, the diagnosis of Crohn's disease was made before diagnosis of osteomyelitis, which is not surprising because osteomyelitis usually occurs exclusively in patients with Crohn's disease complicated by sepsis. In contrast, Schwartz et al (44) detailed a case of sacral osteomyelitis as the presenting clinical manifestation in Crohn's disease that was detected only at laparotomy despite extensive preoperative radiographic studies.

The significant clinical feature in each aforementioned case of osteomyelitis was severe and persistent pain in the affected area. This can be overlooked in a patient chronically ill with other complications of Crohn's disease. Moreover, diagnosis may be difficult if pain is present in the abdomen, pelvis or affected area because it might be attributed to either an abscess or fistula. In addition, diagnosis may be elusive in some patients with sacroiliitis and/or spondylitis complicating IBD because either of these can result in disabling and severe back pain.

Diagnosis may be difficult, even if occult osteomyelitis is suspected. The typical radiographic osseous changes of osteomyelitis may not appear for days or even weeks. Isotopic bone scans may offer sensitivity approaching 100%, and other imaging modalities, including computerized tomography (CT), may be helpful to detect sequestra and altered anatomy (45). In a study of 80 consecutive patients with symptomatic Crohn's disease referred for CT imaging, two had unsuspected sacral osteomyelitis (46). Magnetic resonance imaging (MRI) may also be extremely useful. It is

more precise than other imaging modalities for definition of extent of an inflammatory process and differentiation of osteomyelitis from cellulitis (48).

Pelvic sepsis may be further complicated by extension of the septic or inflammatory process into the spinal canal – causing transient or even permanent neurological complications – particularly if concomitant sacral osteomyelitis is documented. There are now several descriptions in the English literature of Crohn's disease with fistula formation extending into the spinal canal causing serious sequelae, such as a spinal epidural abscess. Aitken et al (49), for example, first described an epidural abscess in a 36-year-old male with Crohn's disease of the terminal ileum and a pelvic inflammatory mass resulting in paraplegia. In addition, Sacher and co-workers (50) reported an 11-year-old male with Crohn's disease of the colon and a right psoas abscess complicated by a spinal epidural abscess from L2 to S4. Finally, Hershkowitz et al (51) described a 19-year-old male with epidural and subdural empyema originating from a rectal fistula.

The precise pathogen in osteomyelitis may be difficult to define because the clinical course of osteomyelitis often necessitates antibiotic use to treat other septic complications. Often, the organisms involved in pelvic osteomyelitis originate from bowel flora, but, unfortunately, cultures obtained from draining sinuses, adjacent abscesses or infected cavities may be misleading. A bone biopsy may best document the specific bacterial agent involved with osteomyelitis. In a comprehensive review of osteomyelitis, the frequency of positive cultures in relation to the sources of specimens was 60% for bone aspirates and 65% for bone pus obtained at the time of surgical treatment (52).

Finally, in a recent review, osteomyelitis was almost an exclusive septic complication of Crohn's disease (53). In one report (54), however, a 16-year-old female with brucellosis and ulcerative colitis was described with multiple abscesses and osteomyelitis; the presence of multifocal osteomyelitis suggested hematogenous seeding of bone rather than direct extension from an abdominal source.

In summary, osteomyelitis is a serious but fortunately rare skeletal complication of IBD, particularly complicated Crohn's disease. In addition to difficulties in diagnosis and management, however, there is a need to be alert for the insidious development of serious clinical sequelae of osteomyelitis, including transient or permanent neurological complications due to extension of the pelvic or bony septic process into the spinal canal.

OSTEONECROSIS (AVASCULAR NECROSIS)

Osteonecrosis, or nontraumatic (aseptic, avascular) bone necrosis, is estimated to account for over 10% of joint replacements (55). Although several clinical entities have been associated with osteonecrosis, as summarized in Table 1, the incidence and pathogenesis of each condition is not well defined. Osteonecrosis has rarely been reported in patients with IBD, either during or after corticosteroid treatment (56-61) (Table 2). In addition, other treatments for IBD have been implicated in the pathogenesis of osteone-

TABLE 1
Causes of osteonecrosis in adults

Idiopathic	
Congenital	
Legg-Calve-Perthes disease	
Hemoglobinopathy (sickle cell crisis)	
Infectious/inflammatory	
Septic osteonecrosis	
Pancreatitis	
Traumatic osteonecrosis	
Mechanical vascular disruption	
Fat embolism syndrome	
Coagulopathy	
Toxic or drug-associated causes	
Alcohol abuse	
Corticosteroids	
Endocrine/metabolic causes	
Gout	
Cushing's syndrome	
Neoplastic causes, including lymphoma	
Vascular causes	
Connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus)	
Arteritis and vasculitis	
Radiation injury	
Gaucher's disease	
Others, including dysbarism	

TABLE 2
Osteonecrosis in inflammatory bowel disease (IBD)

Patient age (years)/sex	IBD type	Osteonecrosis location	Steroids	Reference
27/female	CD	L/R humerus	Yes	56
16/female	CD	L/R humerus, L femur, L talus	Yes	57
14/female	CD	L/R femur	Yes	57
16/male	CD	L/R femur	Yes	57
29/male	UC	L/R femur, R talus	Yes	58
30/male	CD	L/R femur, R humerus	Yes	58
26/female	UC	L/R femur	Yes	58
29/female	UC	R femur	Yes	58
22/male	CD	L/R femur	Yes	58
27/male	UC	R femur	Yes	58
36/male	UC	L/R femur	Yes	58
46/male	CD	L/R femur, R lunate	Yes	59
21 male	UC	L/R femur	Yes	60
38/male	CD	L/R femur	No	61
23/male	CD	L/R femur	No	61

CD Crohn's disease; L left; R Right; UC Ulcerative colitis

rosis, including parenteral nutrition, particularly with lipid emulsions (57). Moreover, some IBD patients may have another cause of osteonecrosis, including another disease, trauma or chronic alcoholism. Finally, patients with IBD and no prior history of corticosteroid use have developed osteonecrosis (61).

There are six published reports of osteonecrosis in patients with IBD (56-61). In 1971, Brom et al (56) described a 27-year-old female with Crohn's disease, periostitis, arthritis and aseptic necrosis of both humeral heads. Although the patient was treated with intravenous and oral corticosteroids, it was thought that the bone changes were due to Crohn's disease. Shapiro and colleagues (57) described two females, aged 14 and 16 years, and one 16-year-old male with Crohn's ileocolitis and multifocal osteonecrosis. All patients received corticosteroids as well as parenteral nutrition with infused lipids for four to six weeks. After remission, steroids were gradually discontinued. Because congenital hyperlipidemia in rabbits (62) and hyperlipidemia in humans (63) have been seen with osteonecrosis, it was hypothesized that the combination of lipid infusion and steroids might be additive in children with Crohn's disease, because both factors can increase serum lipid levels, causing fat embolism and altered diffusion of oxygen to metabolically active bone tissue, and, ultimately, bone ischemia and necrosis (63).

Vakil and Sparberg (58) described seven patients with osteonecrosis (five with ulcerative colitis and two with Crohn's disease) in a group of 161 IBD patients treated with steroids. Osteonecrosis developed in the seven patients within six months after initiation of steroid therapy. It was suggested that IBD may predispose patients to steroid-associated osteonecrosis. This result was consistent with the findings of Cruess (64), who reported that steroid-associated osteonecrosis occurred within six to eight months of therapy initiation, whereas osteopenic complications occurred two to three years later. In contrast, Culp et al (59) reported lunate and femoral head osteonecrosis in a 46-year-old male with Crohn's disease two years after a one-month course of 7.5 mg/day prednisone. In addition, Madsen and Andersen (60) described a 21-year-old male with ulcerative colitis and multifocal osteonecrosis after steroid treatment; MRI was used for diagnosis. The authors argued that early diagnosis might make earlier treatment possible so that collapse of subchondral bone and progression of the disease may be averted. Finally, in a report published in 1993 (61), two males, aged 38 and 23 years, with Crohn's disease and no history of prior corticosteroid treatment were diagnosed with osteonecrosis, suggesting that osteonecrosis might be a disease complication rather than be due to IBD treatment.

In summary, osteonecrosis is a disorder of unknown pathogenesis that has been reported (55) to complicate several clinical disorders, including IBD (61). Usually, one or both femoral heads are involved, but any bone may be affected, and frequently it is a multifocal process. Clinical diagnosis is difficult, and the natural history of osteonecrosis is unknown. If changes are radiologically defined, the process is not likely to be reversible. Surgical decompressive proce-

dures have been used but their role is unclear, especially if detected with MRI. Patients with radiologically defined bone necrosis and collapse will likely require joint replacement to maintain function and mobility.

CORTICOSTEROIDS AND OSTEONECROSIS

The critical elements in the pathogenesis of osteonecrosis are unknown. However, a possible association with corticosteroids was first described in 1957 (65), followed by English language reports (66-69). Later, a more definite association was described following renal transplantation, with a recorded prevalence of up to 20% (70,71), and in patients with systemic lupus erythematosus (prevalence of up to 40%) (72-75). Although osteonecrosis was seen in other conditions treated with corticosteroids, its prevalence was so low that a strong statistical relationship could not be defined, except possibly in patients with malignant lymphoma (76-79). Although corticosteroids alone have not been shown to cause osteonecrosis in animals (80), other criteria need to be considered before suggesting that an adverse pharmacological event has occurred in IBD.

For example, a consistent association between corticosteroids and osteonecrosis in patients with IBD is still needed. The published literature to date is contradictory. Of the six reports (56-61) on osteonecrosis in IBD, all are either single cases or series of cases, with three (57), seven (58) or two (61) patients. In the first series (57), the authors noted that, in their experience, osteonecrosis was not seen in children with IBD who were receiving corticosteroid doses without intravenous lipids. In the second series (58), seven patients with either ulcerative colitis or Crohn's disease were described but modes of treatment other than corticosteroids, including parenteral lipid infusions, were not detailed. An estimated 4.3% of IBD patients seen in those authors' tertiary centre developed radiologically defined osteonecrosis; whether patients with already established osteonecrosis were included was not clear. It was suggested, however, that IBD may predispose patients to osteonecrosis. In a final report (61), osteonecrosis occurred in two patients with no prior corticosteroid use.

Definition of a specific dose-response gradient, to include the total cumulative dose, the highest dose or the duration of drug treatment, is crucial. In disorders treated with high doses of corticosteroids (eg, renal transplant recipients), there is some evidence for a dose-response gradient. In contrast, for disorders (such as rheumatoid arthritis) treated with low steroid doses even for prolonged periods, osteonecrosis is rare. Moreover, there are reports of osteonecrosis after only short term steroid treatment, especially in the neurosurgical literature (81,82). In an evaluation of 22 papers on steroids in renal transplant recipients and patients with systemic lupus erythematosus (83), a relationship with total daily dose of prednisone was described (ie, 4.6% increase in osteonecrosis risk for every 10 mg/day increase in prednisone). In contrast, a prospective study of 54 systemic lupus erythematosus patients showed that the duration of prednisone treatment, total cumulative dose and mean daily dose did not

differ in patients with or without osteonecrosis (84). However, the mean daily prednisone dose in months of maximal treatment was more in those with osteonecrosis. Interestingly, osteonecrosis was reduced or even avoided after altering other components of the treatment regimen, except for steroid dose, in transplant recipients (85). Finally, osteonecrosis is rare in some disorders treated with high steroid doses (eg, temporal arteritis, chronic active hepatitis). To date, then, data do not support that osteonecrosis is caused by steroids, except in some diseases, specifically renal transplant recipients or patients with either systemic lupus erythematosus or, possibly, malignant lymphoma.

A consistent *temporal relationship* between corticosteroid treatment and osteonecrosis is not evident in IBD patients. Cruess (64) had initially suggested that osteonecrosis in some diseases occurred within six to eight months of initiation of steroids. Subsequently, Vakil and Sparberg (58) noted that osteonecrosis was only seen in their patients during or within six months of steroid treatment, even though the medication may have been initiated years earlier. In con-

trast, osteonecrosis was attributed to corticosteroids in one report over two years after a course of treatment (59). Thus, no temporal relationship between steroid administration and osteonecrosis is evident in the reported IBD patients.

Finally, a *biological explanation* is still needed to define the clinical observations. A number of theories of causation have been proposed (56-61) but none has ever been examined in patients with IBD.

Osteonecrosis is a disorder of multiple etiologies and unknown pathogenesis that appears to be an unpredictable development in patients with IBD. Osteonecrosis seems to be associated with high doses of administered steroids in specific clinical disorders: renal transplant recipients or patients with systemic lupus erythematosus or malignant lymphoma. However, to date, evidence to define a direct relationship with corticosteroids in other disorders, including even the rare published reports in IBD patients, has been contradictory. In those with IBD, osteonecrosis has been specifically related to the disease process, rather than an adverse effect of pharmacological treatment.

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