Granulomatous osteonecrosis in Crohn's disease

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HJ Freeman, D Owen, M Millan. Granulomatous osteonecrosis in Crohn's disease. Can J Gastroenterol 2000;14(11):951-954. A 25-year-old white woman was diagnosed with Crohn's disease involving the small and large intestines. She had a complex clinical course that required treatment with multiple pharmacological agents, including intravenous, oral and rectal corticosteroids. She also received parenteral nutrition with lipid emulsions. Finally, repeated intestinal resections and drainage of perianal abscesses were required. Her disease was complicated by gallstones, urolithiasis and hip pain. After osteonecrosis was diagnosed, joint replacements were performed. Review of the pathological sections from the resected hip, however, resulted in detection of granulomatous inflammation with multinucleated giant cells – the histological 'footprint' of Crohn's disease in the gastrointestinal tract. Because prior specialized perfusion fixation pathological studies of the intestine in Crohn's disease have shown that granulomas are located in the walls of blood vessels, a possible mechanism for the pathogenesis of osteonecrosis in Crohn's disease is chronic microvascular ischemia of bone.

Key Words: *Avascular necrosis; Corticosteroids; Crohn's Disease; Granulomatous bone disease; Osteonecrosis; Ulcerative colitis*

L'ostéonécrose granulomateuse dans la maladie de Crohn

RÉSUMÉ : Une femme de race blanche, âgée de 25 ans, a reçu un diagnostic de maladie de Crohn atteignant le grêle et le côlon. Elle présentait une évolution clinique complexe qui a nécessité l'administration de plusieurs agents pharmacologiques dont des corticostéroïdes par voies intraveineuse, orale et rectale. Elle a en outre reçu une alimentation parentérale au moyen d'émulsions de lipides. En dernier lieu, des résections intestinales répétées et le drainage d'abcès péri-anaux ont été requis. Sa maladie a été compliquée par le présence de calculs biliaires, d'urolithiase et de douleurs à la hanche. Après un diagnostic d'ostéonécrose, la patiente a dû être opérée pour prothèse articulaire. À l'examen des sections pathologiques des portions de hanche réséquées, on a décelé la présence d'une inflammation granulomateuse à cellules géantes multinucléées et la trace histologique de la maladie de Crohn dans le tractus digestif. Parce que des études d'anatomopathologie par fixation de perfusion sur ces portions d'intestin touchées par la maladie de Crohn ont montré que les granulomes sont situés dans les parois des vaisseaux sanguins, le mode pathogénique possible de l'ostéonécrose dans la maladie de Crohn serait peut-être une ischémie microvasculaire chronique de l'os.

Osteonecrosis, or nontraumatic (aseptic, avascular) bone necrosis, may result in significant patient morbidity (1). Several disorders have been associated with osteonecrosis (eg, systemic lupus erythematosus, rheumatoid arthritis, air embolism, pancreatitis and chronic alcoholism), and some patients have also been treated with corticosteroids. After corticosteroid treatment, however, it is not clear whether the osteonecrosis is necessarily a drug complication, a complication of the disease process or both (1-5).

Osteonecrosis has been rarely reported in Crohn's disease (6-10). In some patients, treatment with corticosteroids and parenteral nutrition, particularly with lipid emulsions, has been implicated in its pathogenesis (7). In others, there was no prior history of corticosteroid therapy, suggesting that osteonecrosis may be a rare skeletal complication associated with inflammatory bowel disease per se rather than a complication of therapy (11).

Other very distinctive but rarely reported skeletal abnormalities can occur in some patients with inflammatory bowel disease. Osteomyelitis of the pelvic bones (12), for example, may have serious clinical consequences, including involvement of the contiguous spinal and neurological structures. In addition, granulomatous bone disease has been described in Crohn's disease, marked by the presence of the characteristic multinucleated giant cell – the histological 'footprint' of this intestinal disorder (13,14). In the present report, a patient

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with Crohn's disease treated with corticosteroids and parenteral nutrition developed clinical features attributed to osteonecrosis. Later pathological studies of the resected hip, however, revealed granulomatous inflammation with multinucleated giant cells, characteristic of granulomatous bone disease.

CASE PRESENTATION

A 25-year-old white woman with abdominal pain and diarrhea was initially diagnosed with Crohn's disease of the distal ileum and ascending colon in 1978. She was treated with intravenous corticosteroids and prednisone, but her pain persisted. In March 1979, an enterocolonic resection was done; this included about 100 cm of small intestine. Pathological examination showed transmural inflammatory disease with ulceration and stricture formation; histological evaluation revealed intestinal granulomas.

In May 1980, she was hospitalized for abdominal pain and diarrhea. She was treated with intravenous corticosteroids (hydrocortisone 100 mg every 8 h) and parenteral nutrition (including lipid emulsion). She improved, and after three weeks the hydrocortisone was changed to prednisone 40 mg daily and sulphasalazine 1 g bid. Over the next three months, prednisone was tapered and discontinued. She was a chronic smoker and was advised to cease cigarette consumption, but continued to smoke throughout her subsequent illness. In September 1980, her pain recurred. She was treated with 6-mercaptopurine 50 mg daily, sulphasalazine 4 g daily and prednisone 20 mg daily; the latter was slowly tapered and discontinued over the next six months. In May 1981, she passed a renal calculus. In October 1982, abdominal pain and diarrhea recurred. The dose of 6-mercaptopurine was increased to 100 mg daily, and prednisone was restarted at 25 mg daily. Attempts at reducing her prednisone were associated with increased abdominal pain and recurrent diarrhea.

In February 1983, she was hospitalized and given intravenous hydrocortisone 100 mg every 8 h for two weeks then changed to prednisone 40 mg daily. In August 1983, a second renal stone was passed; prednisone was tapered to 10 mg daily and discontinued during the next month. The patient ceased use of 6-mercaptopurine because of its cost. In April 1985, abdominal pain and diarrhea recurred and prednisone 40 mg daily was restarted; this dose was reduced to 15 mg daily. In May 1985, azathioprine 100 mg daily was started. By August 1985, azathioprine was reduced to 50 mg daily and prednisone to 10 mg daily.

In April 1986, she was hospitalized again; she had terminated use of her medications about two months earlier. She was treated with intravenous methylprednisolone 40 mg every 8 h for two weeks, which was changed to prednisone 40 mg daily; prednisone was reduced by 5 mg every two weeks. Colonoscopy showed inflammatory changes of Crohn's disease in the colon. Barium radiographs showed a stricture in the region of the anastomosis. In February 1987, revision of the anastomosis was done with resection of an additional 10 cm of strictured distal small bowel along with a cholecystectomy for cholelithiasis. In July 1987, her pain and diarrhea recurred; prednisone was reinitiated at 40 mg daily and decreased each week by 5 mg daily to 20 mg daily. In September 1987, colonoscopy revealed ongoing colonic ulceration. She was treated with corticosteroid (betamethasone sodium phosphate; Betnesol, Roberts Pharmaceutical, Canada) enemas and oral 5-aminosalicylate 2400 mg daily.

In January 1988, she was admitted for recurrent abdominal pain. She was treated with intravenous methylprednisolone 40 mg every 8 h, 5-aminosalicylic acid (Asacol, Proctor & Gamble Pharmaceuticals, Canada) 2400 mg daily and corticosteroid enemas. After 10 days, she was discharged on prednisone 60 mg daily and Asacol 3200 mg daily; prednisone was then reduced by 5 mg each week. Colonoscopy showed linear sigmoid ulcerations, but there was no visible small bowel disease. By March 1988, the prednisone treatment was discontinued.

In May 1988, she first reported shoulder and knee arthralgias, but radiographs were normal. Between May 1988 and June 1991, she required four additional hospitalizations for recurrent abdominal pain and diarrhea. Each time, she was treated with intravenous methylprednisolone 40 mg every 8 h, corticosteroid enemas, Asacol 3200 mg daily and metronidazole 1500 mg daily. The methylprednisolone was gradually changed to prednisone 40 mg daily and then reduced by 5 mg every 10 days. In addition, 6-mercaptopurine 100 mg daily was prescribed, but in November 1988 she discontinued this medication. Colonoscopy in November 1988 showed persistent inflammatory change in the sigmoid colon. In October 1989, a perianal abscess was drained. In January 1990, a Bartholin's gland abscess was drained. In May 1990, ureteral lithotrypsies were done for ureteral stones. The total dose of corticosteroids administered during the patient's course could not be precisely defined, in large part, due to limited compliance; however, the 'total prednisone equivalent' was estimated in excess of 20 g.

In July 1991, at the age of 38 years, left hip pain developed for the first time. Radiographs were normal, but nuclear imaging bone scans suggested bilateral avascular necrosis of the hips. A magnetic resonance imaging scan showed changes of osteonecrosis in the femoral heads. In March 1992, core decompression of the left hip was done. In July 1992, decompression of the right femoral head with vascularized fibular graft to the right femoral head was done. At that time, avascular necrosis of the left shoulder was detected. In April 1993, a left hip replacement was done, followed in December 1993 by a left shoulder replacement.

PATHOLOGY REVIEW

In 1999, the findings from this case were reviewed, and available bone sections from the hip replacement in April 1993 were re-examined by one of the authors and later by another author. As noted in the original pathological report, pathological changes of osteonecrosis were evident (Figure 1). No fat cell infiltration was noted in the bone marrow; this has been previously recorded in animal studies as a histopathological change in corticosteroid-associated osteonecrosis. In addition, however, granulomatous inflammation in the

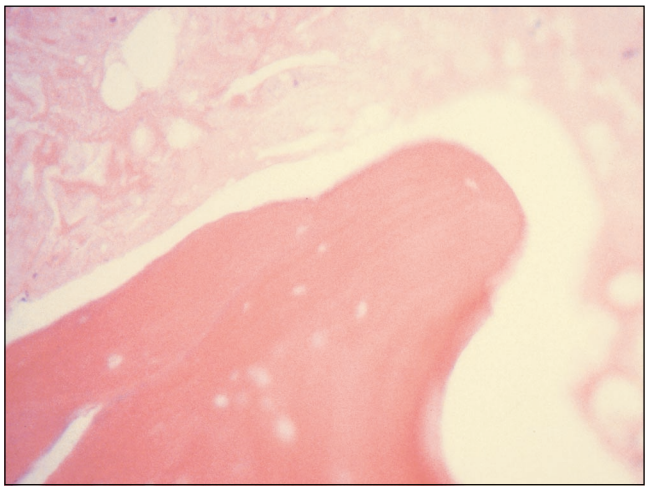

Figure 1) *Osteonecrosis of the right hip. Note absence of osteocytes within bone lacunae ('empty spaces'), characteristic of nonviable bone (hematoxylin and eosin, original magnification ×50)*

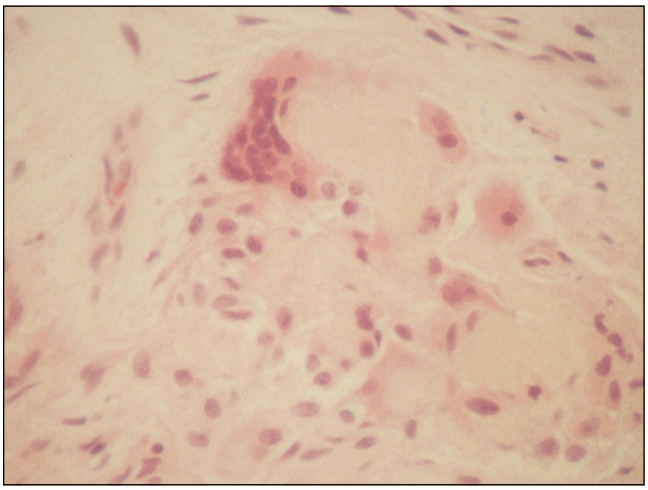

Figure 3) *Higher power of granuloma in Figure 2 showing multinucleated giant cells (hematoxylin and eosin, original magnification ×260)*

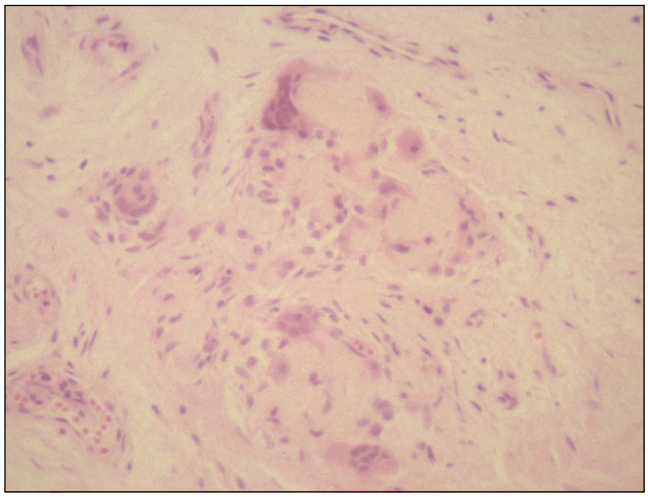

Figure 2) *Circumscribed noncaseating granuloma in the right hip with multinucleated giant cells (hematoxylin and eosin, original magnification ×120)*

bone was present, with granulomas containing multinucleated giant cells (Figures 2 and 3). The granulomas were located within viable bone of the femoral head beneath the articular surface adjacent to the infarct. Discrete granulomas were noted, and none of the giant cells contained 'foreign material'. No caseation or central necrosis was evident. No perivascular inflammation was noted, although limited sampling at the time of specimen dissection precluded a comprehensive examination of the tissues. Review of the patient records (in light of the pathological observations), including chest radiographs, excluded other causes of systemic granulomatous disease, including tuberculosis.

DISCUSSION

The cause of osteonecrosis in patients with Crohn's disease is not known. Indeed, it has only been very rarely reported in Crohn's disease, but in some tertiary care teaching centres, detection rates have been estimated to be about 0.5% to 1% (8,10). In some reports, treatments for the disease, particularly corticosteroids, as well as parenteral nutrition with lipid emulsions, have been implicated (7-9). In contrast, osteonecrosis was also previously reported in patients with no prior corticosteroid therapy or parenteral nutrition (11). In our patient, treatment for Crohn's disease included numerous courses of corticosteroids as well as parenteral nutrition, but the clinical course of the disease became complicated by bone pain and radiological evidence of osteonecrosis. Subsequent review of the resected hip specimen revealed the presence of granulomatous inflammatory changes with multinucleated giant cells. These findings are clearly reminiscent of gastrointestinal granulomas – the histological 'footprints' of Crohn's disease. These pathological findings of granulomas in bone have been previously described in at least two prior reports of granulomatous bone disease in Crohn's disease (13,14). In one case (13), the clinical symptoms were apparently alleviated by an increase in the corticosteroid dose, while in the other case (14), a total hip replacement was done. In both of these earlier reports, however, osteonecrosis was not recorded.

Granuloma formation in tissues, including bone, may have a variety of causes. In immunocompromised patients, including those on long term corticosteroids, infections should be considered at least in the initial clinical assessment. Our patient had no clinical evidence of either tuberculosis or fungal disease, and the granulomas present in bone were noncaseating. Nonspecific granuloma formation may occur after tissue injury in which there is an inflammatory response to necrotic material. These 'foreign body' granulomas often contain irregular fragments of the material provoking the reaction. This finding also was not present in our case, and the granulomas were located in viable tissues and not immediately abutting the infarcted bone. Finally, even most recent authoritative orthopedic pathological descriptions of osteonecrosis do not include granulomas or multinucleated giant cells as a feature of the disorder (15).

The mechanisms involved in osteonecrosis in most clinical settings are not precisely known. In Crohn's disease, it has been previously postulated by others that fibrin microclots may cause hyperviscosity, increased generation of thromboplastin, hyperfibrinogenemia, thrombocytosis and hypercoagulability, possibly related, in part, to malabsorption-associated depletion of vitamin K and decreased protein C and protein S (16). Alternatively, chronic cigarette smoking has been observed to be an important factor, not only in the pathogenesis of Crohn's disease in some patients, but also in the pathogenesis of osteonecrosis. In a Japanese study, an increased risk for osteonecrosis was observed in smokers (17). It has also been speculated that some form of microvascular injury, possibly chronic, is likely necessary before the changes in the bone occur. Significantly, careful pathological studies of the intestine using specialized arterial perfusion-fixation methods have demonstrated a close relationship between vascular structures and granulomas, prompting the intriguing suggestion that the intestinal microvasculature is likely involved early as an integral part of the pathogenesis of Crohn's disease (18). In Crohn's disease involving the small or large intestine, chronic ischemic injury mediated within the microvasculature of the deeper bowel wall layers may well explain the typical focal and patchy changes that are prominent in the inflammatory process. Advanced granulomas located in the walls of blood vessels might be expected to destroy the vessel and occlude its lumen, obscuring the vascular origin of these lesions and causing bone infarcts. It may be speculated that the bone changes observed in osteonecrosis, at least in Crohn's disease, have a similar pathogenesis. Further pathological studies, possibly employing specialized arterial perfusion-fixation methods used in the intestinal studies, might improve understanding of the pathogenesis of osteonecrosis in this clinical setting.

In summary, this report describes a patient with Crohn's disease and a clinical course complicated by hip pain, initially attributed to osteonecrosis. Further pathological review of the resected hip specimen revealed necrotic foci associated with granulomatous inflammatory changes and multinucleated giant cells, typical of granulomatous bone disease in Crohn's disease (13,14). A possible mechanism for osteonecrosis in this clinical setting may be related to ischemic changes associated with microvascular inflammatory occlusion induced by granulomas in blood vessel walls of bone.

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