Improvement of Chronic Osteomyelitis After Granulocyte Colony Stimulating Factor

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Abstract *Background:* chronic osteomyelitis represents a persistent bone and bone marrow infection easy to diagnose in the presence of pain, erythema, swelling, and a draining sinus but more difficult to detect in the absence of the preceding features and with a painful orthopaedic prosthesis. *Case Description:* we report upon an elderly gentleman with myelodysplasia requiring revision surgery for a fractured prosthetic left knee. He had clinical, laboratory, and radiological features of chronic osteomyelitis that improved only with administration of granulocyte colony stimulating factor (G-CSF). *Literature Review:* G-CSF has been successfully employed to treat resistant osteomyelitis in three young patients with primary defects of monocyte and neutrophil killing. A randomized trial confirmed the efficacy of G-CSF in the treatment of chronic osteomyelitis in twenty patients with diabetic foot ulcers and a rat model confirmed the efficacy of G-CSF in acute osteomyelitis. *Clinical Relevance:* our case highlights the usefulness of G-CSF treatment for immune suppressed patients with resistant chronic osteomyelitis.

Introduction

Chronic osteomyelitis is a severe and persistent infection of bone and bone marrow due to haematogenous or contiguous soft tissue spread, fractures and their internal fixation, joint replacements and ineffective treatment of acute osteomyelitis. Ulcers associated with peripheral vascular disease such as in diabetes or sickle cell anaemia may represent local predisposing factors whereas inherited or acquired immune deficiencies represent systemic predispositions [1]. Neutrophil function may be impaired in myelodysplasia [2] whereas granulocyte colony stimulating factor (G-CSF) is known to improve neutrophil function in several neutrophil disorders [3]. We report the case of an elderly gentleman with myelodysplasia requiring revision surgery for a fractured prosthetic left knee; he had clinical, laboratory and radiological features of chronic osteomyelitis that improved only with administration of G-CSF.

Case Report

An 82 year old gentleman was admitted in February 2010 with pyrexia (38.7°C) and severe pain due to a prosthesis induced fracture of the lateral femoral condyle of the left knee. In 1996 and 2001 he had left and right total knee replacements for osteoarthritis and in January 2008 refractory anaemia with multi-lineage dysplasia was diagnosed on a bone marrow biopsy. An MRI confirmed osteomyelitis (Fig. 1). Blood cultures and two aspirations from the area of interest never yielded any bacterial or yeast growth. Despite empirical antibiotic treatment the ALP (mostly the bone iso-enzyme) never went below 400 IU/l and the CRP never went below 150 mg/l (Fig. 2), although partial responses were witnessed, implicating a bacterial cause despite repeated negative blood cultures. As the orthopaedic team

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Fig. 1 MRI scan of left knee and femoral shaft from February 2010. Axial T1 weighted images: **a** with gadolinium enhancement, **b** without gadolinium enhancement. There is enhancing tissue of the central marrow material on the *left*. *Bottom (c)*: axial T2 weighted images showing high signal in the marrow and surrounding soft tissues

was reluctant to operate on what they believed a septic patient (not due to osteomyelitis) we administered G-CSF (Lenograstim) (263 µg S/C for 7 days) on the 25th of April with significant falls in CRP and ALP (Fig. 2), along with clinical improvement. Encouraged by this a second course of G-CSF with the same dose and duration, was given in May with further reductions of CRP and ALP that finally allowed revision surgery. The patient was discharged home after 4 weeks of physiotherapy. Throughout this prolonged

admission the patient's neutrophil count never fell below $1.0 \times 10^9/l$ and always rose to $16 \times 10^9/l$ after C-GSF. An MRI of the left knee and femoral shaft in August 2010 did not show osteomyelitis (Fig. 3). The patient was re-admitted mid-September for watery diarrhoea for which no causative organism was found. CT scan showed thickened bowel walls from ileum to rectum. Reactive amyloidosis was suspected but after a persistent deterioration the patient died.

Fig. 2 Time course of the patient's illness showing the behaviour of C-reactive protein (continuous line; mg/l) and alkaline phosphatase (dashed line; U/l) in response to rotating antibiotics and to G-CSF

Fig. 3 MRI scan of the left knee and femoral shaft from August 2010. Coronal T1 weighted images **a** with gadolinium enhancement, **b** without gadolinium enhancement. There is no enhancing tissue and no evidence of inflammation

Discussion

We have described the unusual case of a patient with myelodysplasia whose chronic osteomyelitis unresponsive to antibiotics improved after two courses of G-CSF. The diagnosis of chronic osteomyelitis is relatively obvious in a patient with a history of osteomyelitis who experiences a recurrence of pain, erythema, and swelling associated with a draining sinus. However, a painful orthopaedic prosthesis may delay its recognition [1] as in our patient who presented with a very painful fractured lateral femoral condyle but did not have a clear cut history of osteomyelitis. Unfortunately, antibiotic therapy alone is usually insufficient to treat chronic osteomyelitis, although empiric or culture-directed antibiotics may remove many of the symptoms [1]. Indeed, during the first months of illness our patient's CRP never went below 150 mg/l and matched similar swings in ALP despite antibiotic treatment. We reasoned that G-CSF, a naturally occurring cytokine that increases proliferation and promotes the activity of myeloid cells through various biochemical effects might help with the chronic infection [3, 4]. It should be said that on admission, the patient's neutrophil level was normal, and throughout the course of the illness never fell below range, in fact always increasing after G-CSF administration. After the two rounds of G-CSF treatment the CRP normalised whereas the ALP improvement was more erratic due to the transient G-CSF induced osteoclastic activity that could briefly increase bone-specific ALP [4].

Granulocyte colony stimulating factor has been used in various settings to promote or hasten healing: forty diabetic patients with normal neutrophil counts who had longstanding ulcer infections and osteomyelitis were randomized 1:1 to receive either antimicrobial therapy (ciprofloxacin and clindamycin) plus 263 µg of G-CSF subcutaneously daily for 21 days or antimicrobial therapy alone. Within 9 weeks of commencing treatment the

diabetic patients that received G-CSF underwent fewer amputations than those who did not receive G-CSF (15 vs. 45%, $P = 0.03$) [5].

In a patient with chronic granulomatous disease (CGD) failing to achieve a satisfactory response to antibiotic treatment for bacterial osteomyelitis, the addition of G-CSF improved granulocytic function and lead to resolution of the bone infection [6]. A 16 year old child with CGD with femoral osteomyelitis due to *Aspergillus nidulans* was poorly responsive to liposomal amphotericin B: the addition of G-CSF alongside surgical debridement and itraconazole cured the osteomyelitis [7]. A child with a primary monocyte killing defect developed *Aspergillus* vertebral osteomyelitis unresponsive to liposomal amphotericin B, intra-lesional amphotericin B, and itraconazole: the administration of granulocyte macrophage-colony stimulating factor (GM-CSF) induced clinical and radiological improvement [8]. These primary neutrophil and monocytic defects resemble the acquired defects seen in myelodysplasia [3]. In an animal model of acute osteomyelitis, *Staphylococcus aureus* was directly inoculated into rat tibias to induce histopathologically evident osteomyelitis: one group received antibiotics only, the second received antibiotics with GM-CSF. Rats were followed up for 3 months with plain radiographs and 67 Ga-citrate scintigraphy. A scintigraphic comparison of the two groups 48 h after treatment revealed a decreased uptake in the group receiving GM-CSF. At 3 months, there was one death and one chronic osteomyelitis with fracture in the first group. Physical examination, plain radiographs, and histopathologic findings were normal in all rats from the second group [9].

Our case provides further evidence that administration of G-CSF may help improve the clinical and biochemical picture in patients with chronic osteomyelitis. It was beyond our reach to perform functional neutrophil studies, but we believe that an expansion of red marrow in the

femur more than an increase in neutrophil count had contributed to the improvement of this patient's condition. Given the scanty human and animal data on the use of G-CSF in chronic and acute osteomyelitis further research into its use may lead to its consideration as first-line treatment of resistant chronic osteomyelitis, especially in those patients with primary or secondary phagocyte dysfunction.

Conflict of interest None declared.

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