Skeletal Radiol (2001) 30:407–410

CASE REPORT

Jason S. Weisstein
Lynne S. Steinbach
Carol A. Diamond
Shirley J. Huang
Richard J. O'Donnell

Pseudo-osteomyelitic crisis upon presentation of Gaucher disease

Received: 21 November 2000
Revision requested: 13 December 2000
Revision received: 27 February 2001
Accepted: 28 February 2001

J.S. Weisstein, M.D., M.P.H.,
R.J. O'Donnell, M.D.
Department of Orthopaedic Surgery,
Orthopaedic Oncology Service,
University of California,
San Francisco, 1701 Divisadero Street,
Suite 280, San Francisco,
CA 94115-1652, USA

L.S. Steinbach, M.D.
Departments of Radiology
and Orthopaedic Surgery,
University of California, San Francisco,
505 Parnassus Avenue, San Francisco,
CA 94143, USA

C.A. Diamond, M.D.
University of Wisconsin,
Department of Pediatrics,
Division of
Pediatric Hematology/Oncology,
600 Highland Avenue, H4/4 CSC,
Madison, WI 53792, USA

S.J. Huang, M.D.
Department of Pathology,
The Permanente Medical Group,
Inc., 1200 El Camino Real,
South San Francisco,
CA 94080-3299, USA

R.J. O'Donnell, M.D. (✉)
Department of Musculoskeletal Oncology,
The Permanente Medical Group,
Inc., 1200 El Camino Real,
South San Francisco,
CA 94080-3299, USA

Abstract We report on a 4-year-old boy adopted from Paraguay who presented with an acute onset of thigh pain. Initial clinical, imaging, and histopathologic findings suggested florid osteomyelitis. However, the development of pancytopenia on intravenous antibiotics prompted further investigation and the ultimate diagnosis of Gaucher disease. In retrospect, characteristic changes on conventional radiographic and MR images, as well as growth of a contaminant organism, pointed to the diagnosis of pseudo-osteomyelitis rather than osteomyelitis.

Keywords Gaucher disease · Bone crisis · Pseudo-osteomyelitis · Osteomyelitis · Radiography · MRI

Introduction

Gaucher disease is caused by the deficient activity of β-glucocerebrosidase, resulting in the accumulation of glycosphingolipid in cells of the monocyte-macrophage system. The clinical spectrum is fairly wide; some individuals may be completely asymptomatic, without the need for any treatment, while others may have severe hematologic, hepatic, splenic, and orthopaedic manifestations [1]. Musculoskeletal involvement is often associated with significant morbidity, represented by osteonecrosis, deformity, fracture, chronic pain, infection, and "aseptic" pseudo-osteomyelitis or bone crisis [2, 3, 4]. The last is a well recognized bone manifestation but elusive to diagnose, and has been misdiagnosed as infection, rheumatic fever, sickle-cell anemia, leukemia, Legg-Calvé-Perthes' disease, and "growing pains" [2, 5].

Differentiation of bone crisis from actual osteomyelitis is difficult on both clinical and radiographic grounds [6, 7], but critical because unwarranted surgical intervention may lead to chronic osteomyelitis and intractable draining sinuses [6, 8]. Conventional imaging techniques have proven to be of limited utility in distinguishing pseudo-osteomyelitis from osteomyelitis [9]. Magnetic resonance (MR) imaging, however, offers the potential for assisting in this differential diagnosis [10, 11, 12]. This is especially true in difficult or unusual cases, such as when a bone crisis occurs at the time of initial presentation, as the following case report illustrates.

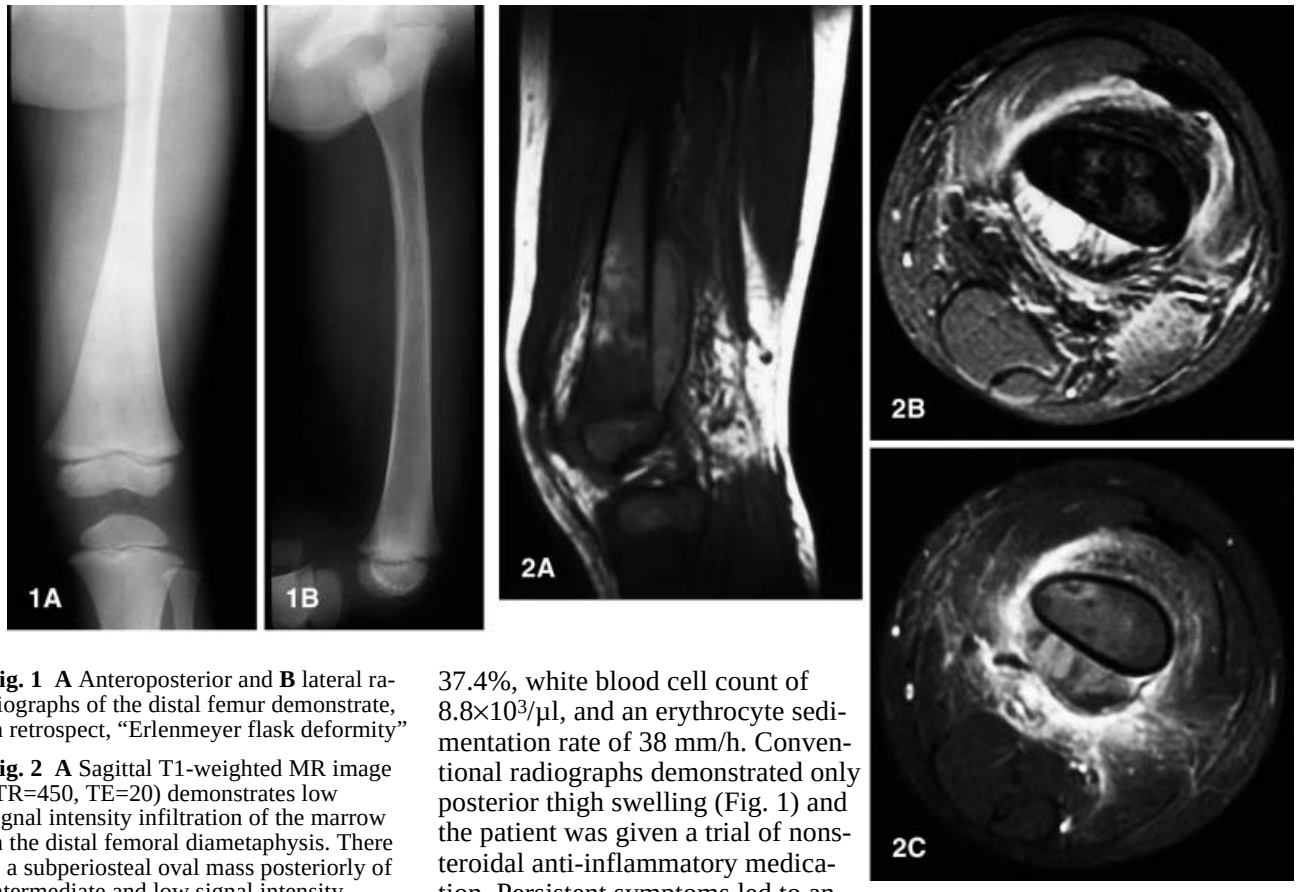

Fig. 1 **A** Anteroposterior and **B** lateral radiographs of the distal femur demonstrate, in retrospect, "Erlenmeyer flask deformity"

Fig. 2 **A** Sagittal T1-weighted MR image (TR=450, TE=20) demonstrates low signal intensity infiltration of the marrow in the distal femoral diametaphysis. There is a subperiosteal oval mass posteriorly of intermediate and low signal intensity. **B** Axial gradient echo (TR=450, TE=16, flip angle=20°) and **C** T1-weighted post-gadolinium (TR=450, TE=16) images show the subperiosteal mass as a high signal intensity region with minimal contrast enhancement. The surrounding soft tissues are of high signal intensity with contrast enhancement in a feathery distribution

Case report

A 4-year-old apparently previously healthy boy, adopted from Paraguay at 6 months of age, presented to his pediatrician after being awakened with the abrupt onset of uncontrollable thigh pain. His history was significant for recent fatigue and sweats, but no fever. Physical examination was positive for distal femoral swelling, erythema, and warmth; passive knee range of motion was limited to 90°of flexion. Abdominal examination revealed no masses or organomegaly. The laboratory evaluation revealed a hematocrit of 37.4%, white blood cell count of 8.8×10^3/μl, and an erythrocyte sedimentation rate of 38 mm/h. Conventional radiographs demonstrated only posterior thigh swelling (Fig. 1) and the patient was given a trial of nonsteroidal anti-inflammatory medication. Persistent symptoms led to an MR study, which showed extensive distal femoral marrow signal changes and a very large posterior thigh mass with surrounding muscle infiltration (Fig. 2).

The patient was admitted to the orthopaedic service with a presumptive diagnosis of distal femoral bacterial osteomyelitis. Operative aspiration of the posterior thigh collection produced bloody, turbid fluid, which prompted open intervention. Extensive soft tissue edema and a markedly thickened periosteum were noted. A bone biopsy showed fibrinopurulent debris admixed with focally nonviable bone spicules consistent with acute to subacute osteomyelitis (Fig. 3). Appropriate stains and cultures were unrevealing except for coagulase-negative *Staphylococcus epidermidis*, which grew from broth only.

The patient was treated with intravenous cefazolin, with symptom resolution and sedimentation rate normalization to 4. Persistent pancytopenia (hematocrit=26.7%; white blood cell count=2.2×10^3/μl; platelet count=105,000/μl) resulted in the antibiotic course being curtailed after 4 weeks, and a bone marrow aspirate and biopsy were performed. Ninety percent of the marrow population was comprised of nodular aggregates of Gaucher cells characterized by abundant eosinophilic cytoplasm with prominent fibrillary striations, giving the cells a so-called crumpled tissue paper appearance (Fig. 4). The cells were intensely positive with periodic acid-Schiff staining. Abdominal CT scanning revealed hepatosplenomegaly. No focal splenic lesions were appreciated, and the pancreas, kidneys, and adrenals were unremarkable. Subsequent assays showed low lymphocytic β-glucocerebrosidase activity. The diagnosis of non-neuropathic type I Gaucher disease was ultimately confirmed with

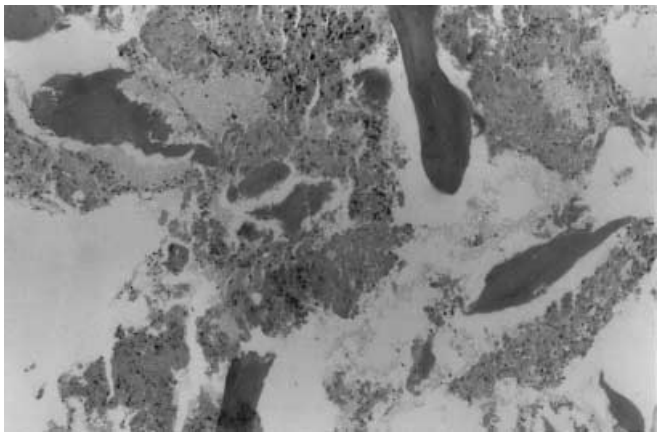

Fig. 3 Distal femoral biopsy demonstrating acute and chronic inflammation, as well as necrotic bone consistent with osteomyelitis (hematoxylin and eosin, ×10)

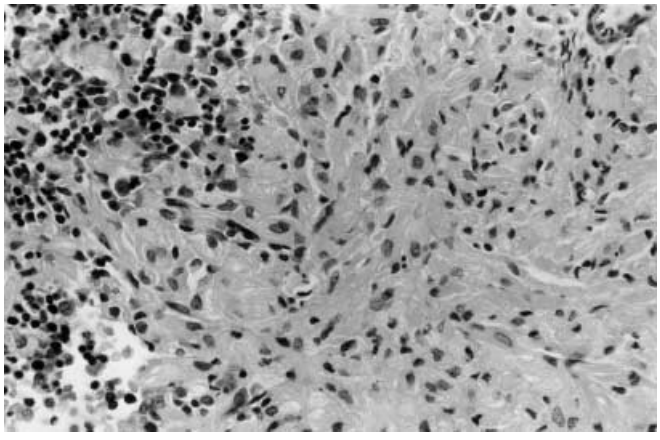

Fig. 4 Bone marrow biopsy demonstrating a pale nodular aggregate of lipid-laden Gaucher cells (hematoxylin and eosin, ×40)

DNA analysis of peripheral blood showing one N370S mutation.

β-Glucocerebrosidase replacement therapy was initiated, and at two and a half years after initial presentation the patient has no distal femoral pain, leg length discrepancy, osteonecrosis, deformity (other than "Erlenmeyer flask"), or functional restriction.

Discussion

The etiology of bone crises in Gaucher disease is uncertain. It has been hypothesized that vascular thrombosis and spasm cause bone infarction and hemorrhage, resulting in periosteal elevation, accumulation of subperiosteal blood, and secondary inflammation [6, 7, 13]. The dramatic relief of pain following decompression is said to be related to alleviation of the high intraosseous pressure generated by the Gaucher cells, although this is disputed [4].

Distinguishing bone pain crisis, or pseudo-osteomyelitis, from infectious osteomyelitis is often a diagnostic challenge, even when the patient is known to have Gaucher disease. Thought to be a condition of growing children [7], bone crises have also been reported in patients older than 40 years [2], most commonly affecting the lower extremity [4, 8]. Both pseudo-osteomyelitis and osteomyelitis can present with the acute onset of fever and severe pain in an extremity accompanied by localized warmth, erythema, and swelling [6, 7]. Some have found an absence of systemic toxicity in bone crises [7], but this is unreliable. Moreover, leukocytosis and elevated sedimentation rates may been seen in either process.

In patients known to have Gaucher disease, the difficulty in distinguishing a crisis from actual osteomyelitis on clinical, laboratory, and radiographic grounds is often superseded by a response to conservative treatment and the failure to culture an organism. Crises can last from days to weeks and patients usually show improvement with symptomatic care, bed rest, and analgesics. Often, when the diagnosis is uncertain, patients are given antibiotics until culture results are obtained and the diagnosis is more certain.

Conventional imaging, including conventional radiographs, technetium scanning, and CT scanning, is of little use in differentiating between bone crisis and osteomyelitis. Sclerosis and periosteal reaction can be seen on plain radiographs at the time of an attack of pseudo-osteomyelitis; however, these findings are nonspecific [7]. Similarly, although technetium bone scanning has been advocated by some authors as a means of diagnosing a bone crisis in Gaucher patients [14], others have reported similar findings in Gaucher [15] and non-Gaucher [16] pediatric patients later proven to have infectious osteomyelitis. CT scanning has been used largely as an adjunct to other radiographic techniques, and has some utility for following disease progression [8, 9] or response to treatment, particularly in the abdominal cavity.

MR imaging, with its excellent ability to delineate bone marrow and soft tissue changes, has emerged as the modality of choice for imaging orthopaedic manifestations of Gaucher disease. Patients tend to exhibit shortened T2 values and heterogeneous signal abnormalities in the affected bone marrow [17]. Both

pseudo-osteomyelitis and osteomyelitis, however, can lead to extensive alteration of soft tissue architecture and signal heterogeneity in the marrow [10, 11]. Nonetheless, a diagnosis of bone crisis is supported whenever a subperiosteal hematoma [7] is visualized. Several investigators [18, 19] have reported that the subperiosteal hematoma is characterized by intermediate to high signal intensity adjacent to bone on T1- and T2-weighted MR images. This contrasts with the typical MR features in osteomyelitis, in which there is loss of fascial planes and usually no hemorrhage [12].

Our patient's MR findings were initially interpreted as being consistent with florid osteomyelitis, which was supported by gross and histopathologic findings at the time of surgery, as well as by the culture of coagulase-negative *Staphylococcus* and response to antibiotic treatment. However, the retrospective MR findings of intermediate to increased signal on T1-weighted and gradient echo images (Fig. 2A, B), combined with the lack of gadolinium uptake (Fig. 2C) in the posterior fluid collection, suggest the presence of a subperiosteal hematoma consistent with pseudo-osteomyelitis, not osteomyelitis.

In patients without a previous diagnosis of Gaucher disease, it is unknown what percentage have a bone crisis at initial evaluation. Most studies are retrospective and do not detail the manner of presentation [8, 14]. According to the international Gaucher Registry, 33% of patients reported at least one bone crisis; however, it is difficult to ascertain whether this complication preceded the diagnosis of Gaucher disease [20]. Goldblatt et al. [2] reported pseudo-osteomyelitis as a mode of presentation in three of 35 patients, while Yossipovitch et al. [7] reported it in seven patients, one of whom had no prior diagnosis of Gaucher disease. Although no Gaucher cells were seen on review of our patient's initial biopsy, the development of pancytopenia prompted further investigation which led to the diagnosis of Gaucher disease. The lack of appreciation of both mild Erlenmeyer flask changes on conventional radiographs and a subperiosteal hematoma on MR imaging, as well as the growth of an organism most often thought to be a contaminant, resulted in a delay in making the correct diagnosis.

This case illustrates the importance of considering the diagnosis of pseudo-osteomyelitis in any pediatric patient, even those without known predisposing risk factors for Gaucher disease or evident hematologic abnormality. Although our patient has done very well, the orthopaedic implications of prolonged delay in the diagnosis of Gaucher disease may be serious, since the skeletal response to enzyme replacement therapy is sub-optimal once bone ischemia and infarction occur [3].

References

1. Charrow J, Esplin, JA, Gribble TJ, et al. Gaucher disease: recommendations on diagnosis, evaluation, and monitoring. Arch Intern Med 1998; 158:1754–1760.
2. Goldblatt J, Sacks S, Beighton P. The orthopedic aspects of Gaucher disease. Clin Orthop 1978; 137:208–214.
3. Pastores GM, Hermann G, Norton KI, et al. Regression of skeletal changes in type 1 Gaucher disease with enzyme replacement therapy. Skeletal Radiol 1996; 25:485–488.
4. Stowens DW, Teitelbaum SL, Kahn AJ, et al. Skeletal complications of Gaucher disease. Medicine (Baltimore) 1985; 64:310–322.
5. Sacks S. Osteitis in Gaucher's disease. S Afr J Surg 1971; 9:161–166.
6. Noyes FR, Smith WS. Bone crises and chronic osteomyelitis in Gaucher's disease. Clin Orthop 1971; 79:132–140.
7. Yossipovitch ZH, Herman G, Makin M. Aseptic osteomyelitis in Gaucher's disease. Israel J Med Sci 1965; 1:531–536.
8. Bell RS, Mankin HJ, Doppelt SH. Osteomyelitis in Gaucher's disease. J Bone Joint Surg Am 1986; 68:1380–1388.
9. Hermann G, Pastores GM, Abdelwahab IF, Loberboym AM. Gaucher disease: assessment of skeletal involvement and therapeutic responses to enzyme replacement. Skeletal Radiol 1997; 26:687–696.
10. Cremin BJ, Davey H, Goldblatt J. Skeletal complications of type I Gaucher disease: the magnetic resonance features. Clin Radiol 1990; 41:244–247.
11. Fletcher BD, Scoles PV, Nelson AD. Osteomyelitis in children: detection by magnetic resonance. Radiology 1984; 150:57–60.
12. Lanir A, Hadar H, Cohen I, et al. Gaucher disease: assessment with MR imaging. Radiology 1986; 161:239–244.
13. Schubiner H, Letourneau M, Murray DL. Pyogenic osteomyelitis versus pseudo-osteomyelitis in Gaucher's disease: report of a case and review of the literature. Clin Pediatr 1981; 20:667–669.
14. Katz K, Mechlis-Frish S, Cohen IJ, Horev G, Zaizov R, Lubin E. Bone scans in the diagnosis of bone crisis in patients who have Gaucher disease. J Bone Joint Surg Am 1991; 73:513–517.
15. Sziklas JJ, Negrin JA, Rosshirt W, Rosenberg RJ, Spencer RP. Diagnosing osteomyelitis in Gaucher's disease: observations on two cases. Clin Nucl Med 1991; 16:487–489.
16. Howie DW, Savage JP, Wilson TG, Paterson D. The technetium phosphate bone scan in the diagnosis of osteomyelitis in childhood. J Bone Joint Surg Am 1983; 65:431–437.
17. Rosenthal DI, Scott JA, Barranger J, et al. Evaluation of Gaucher disease using magnetic resonance imaging. J Bone Joint Surg Am 1986; 68:802–808.
18. Horev G, Konreich L, Hadan H, Katz K. Hemorrhage associated with "bone crisis" in Gaucher's disease identified by magnetic resonance imaging. Skeletal Radiol 1991; 20:479–482.
19. Singleton EB. Film panel case. Pediatr Radiol 1990; 20:373.
20. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. Arch Intern Med 2000; 160:2835–2843.