

Navid Ziran
Suvimol Hill
Mary E. Wright
Joseph Kovacs
Pamela Gehron Robey
Shlomo Wientroub
Michael T. Collins

Ribbing disease: radiographic and biochemical characterization, lack of response to pamidronate

Received: 18 March 2002
Revised: 10 June 2002
Accepted: 11 June 2002
Published online: 15 August 2002
© ISS 2002

N. Ziran
Department of Orthopedic Surgery,
University of Rochester, Rochester,
New York, USA

S. Hill
Department of Radiology,
Warren Grant Magnuson Clinical Center,
National Institutes of Health, Bethesda,
Maryland, USA

M.E. Wright · J. Kovacs
Department of Critical Care Medicine,
Warren Grant Magnuson Clinical Center,
National Institutes of Health, Bethesda,
Maryland, USA

P. Gehron Robey · M.T. Collins (✉)
Craniofacial and Skeletal Diseases Branch,
National Institutes of Dental and
Craniofacial Research, National Institutes
of Health, Bethesda, Maryland, USA
e-mail: mc247k@nih.gov
Fax: +1-301-4020824

M.T. Collins
CSDB/NIDCR/NIH,
Building 30 Room 228, MSC 4320,
Bethesda, MD 20892-4320, USA

S. Wientroub
Department of Pediatric Orthopedic Surgery,
Dana Children's Hospital,
Tel-Aviv Medical Center, Tel-Aviv, Israel

Abstract Ribbing disease is a rare form of sclerosing dysplasia characterized by benign endosteal and periosteal bone growth confined to the diaphyses of the long bones, usually the tibiae and femora. The onset is usually after puberty and the most common presentation is pain that is usually self-limited, but may progress. The etiology and optimal treatment for the disease are unknown. We present the case of a 39-year-old Hispanic man with clinical and radiological manifestations of Ribbing disease. Radiographs and CT imaging demonstrated typical cortical thickening in the mid-diaphyses of the tibiae bilaterally that correlated with intense tracer uptake on ^{99m}Tc -MDP bone scans. MRI demonstrated cortical thickening and abnormal marrow signal consistent with marrow edema. Bone marrow edema may explain the pain frequently associated with the disease. Multiple serum and urine markers of bone metabolism were within normal limits. In an effort to ameliorate pain, the patient was treated with the bisphosphonate, pamidronate. In spite of treatment, pain increased, requiring additional and larger doses

of analgesics. Serial radiographs, CT, bone scans, and MRI all demonstrated disease progression with pamidronate treatment. In this report we present for the first time the finding of bone marrow edema with MRI as well as disease progression during intravenous pamidronate treatment.

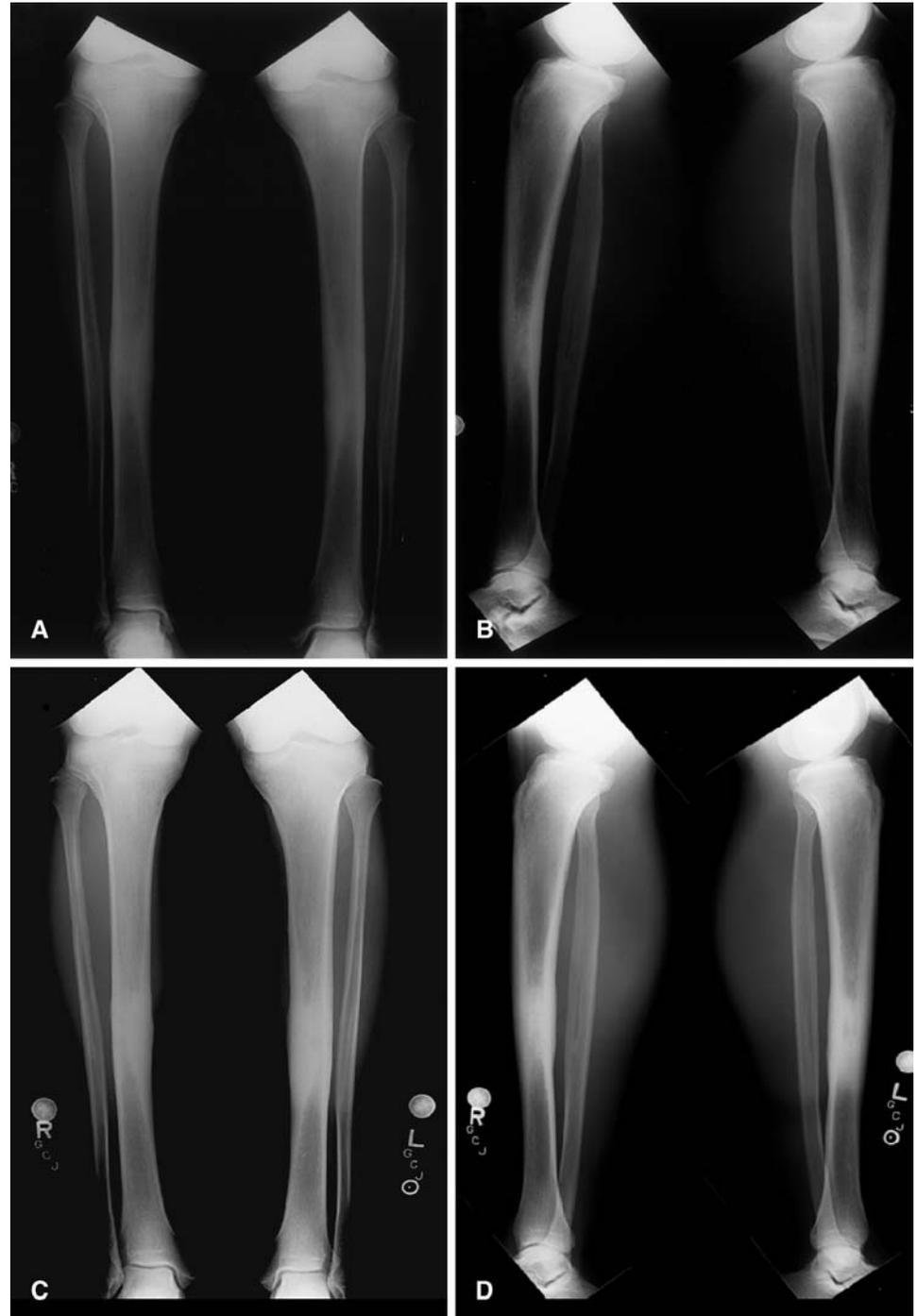
Keywords Diaphyseal dysplasia · Tibiae · Bisphosphonates · Radiographs · CT · MRI

Introduction

Ribbing disease (Online Mendelian Inheritance in Man (OMIM) catalogue # 601477, [<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?601477>]) is a rare form of

sclerosing dysplasia characterized by painful but benign overgrowth of both endosteal and periosteal bone in the diaphyses of certain long bones, especially the tibia and femur [1, 2, 3, 4, 5]. The most common presenting symptom is pain, often unilateral, but frequently becom-

Fig. 1A–D Pre- and post-treatment radiographs of a patient with Ribbing disease. Anterior-posterior and lateral radiographs taken before (**A, B**) and after (**C, D**) treatment with pamidronate demonstrate cortical thickening of the mid-diaphyses of both tibiae, which progressed after treatment

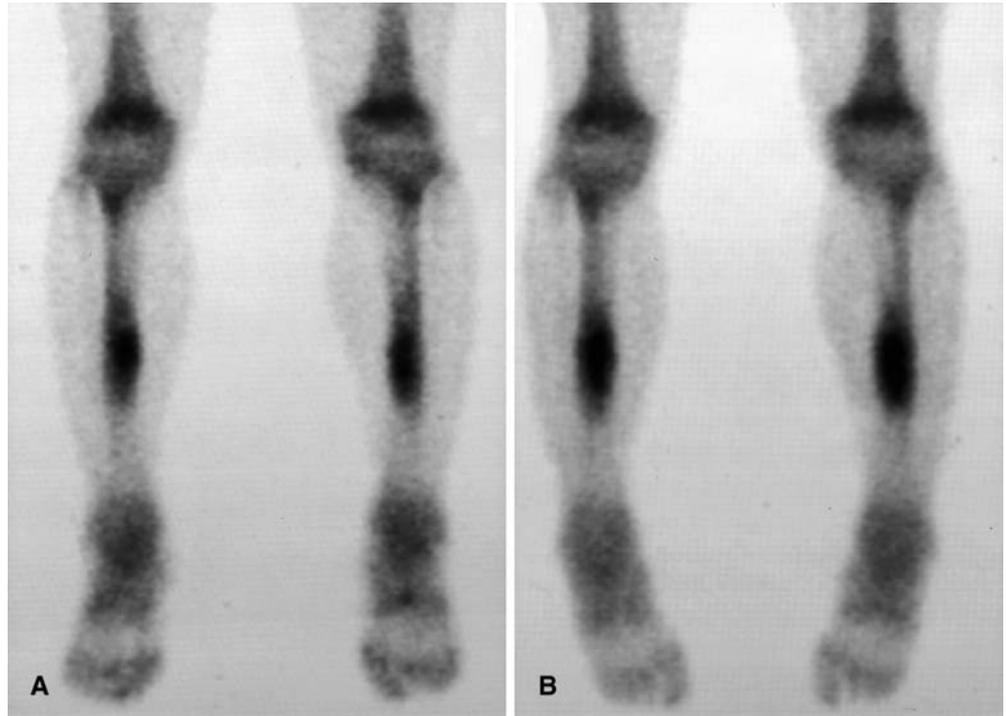


ing bilateral; sometimes it may be associated with mild swelling. The onset is usually after puberty, but there is variability in the natural history, with most cases reported to stabilize with time. Owing to the rarity of the disease (19 cases reported in the English literature), the etiology and genetics of the disease are unclear. Ribbing postulated that the disease was transmitted in an autosomal dominant fashion [1], but others suspect the trans-

mission is autosomal recessive, [6] while yet others believe that Ribbing disease and Camurati-Engelmann disease (progressive diaphyseal dysplasia, OMIM 131300) may represent a phenotypic variation of the same disease [7].

Radiographs reveal cortical thickening with periosteal or endosteal (or both) new bone formation along the diaphysis of the affected bone [3, 5]. Radionuclide bone

Fig. 2A, B Pre- and post-treatment ^{99m}Tc -MDP bone scans of a patient with Ribbing disease. Radionuclide uptake was localized to the mid-diaphyses of both tibiae and increased from before (A) to after pamidronate treatment (B). These were the only areas of abnormal tracer uptake



scans reveal increased tracer uptake in the affected area [3, 5]. In some cases, in which the presentation is unilateral pain, the bone scan will show bilateral disease, and the contralateral side may become painful with time. Computed tomography (CT) scanning shows marrow encroachment or obliteration with endosteal bone formation [5]. Magnetic resonance imaging (MRI) findings have not been previously reported. Alkaline phosphatase is usually reported to be normal.

There are no established medical or surgical treatments for Ribbing disease, although there is a single report of a postmenopausal woman with findings consistent with Ribbing disease and elevated markers of bone turnover who responded favorably to treatment with oral pamidronate [8]. Pamidronate is a second-generation bisphosphonate, which has been shown to be effective in decreasing bone pain in a number of diseases [9, 10, 11]. This report provides the most complete biochemical and radiographic analysis of a patient with Ribbing disease to date, and documents a lack of clinical and biochemical response to treatment with pamidronate.

Case report

A 39-year-old Hispanic man presented in 1999 as a volunteer for a placebo-controlled AIDS vaccine trial. At the initial screening the patient reported mild, but chronic bilateral "knee pain" of approximately 4 years' duration. The pain was worse on the right than the left, and he stated that a previous radiographic evaluation had shown no pathology. He denied previous trauma to this area. He

had seasonal allergies, occasional low back pain, and intermittent depression. His medications were ibuprofen for back pain and an antihistamine. He was adopted and had no knowledge of his biological family's medical history. He was employed as a home health nurse and had no history of substance abuse. At presentation the physical examination was normal.

During the course of the protocol, he received 4 doses of vaccine versus placebo without incident. At approximately week 9 of the study he complained of increased knee pain as well as pain in the area of the right tibia for which he had begun taking celecoxib. The pain continued to increase, requiring hydrocodone for relief. By week 32, bilateral shin pain was the dominant complaint. Physical examination revealed slight prominence bilaterally overlying the medial anterior diaphyseal region, which was warm to the touch. Biochemical evaluation at that time included tests for erythrocyte sedimentation rate, serum rheumatoid factor, anti-DNA antibodies and antinuclear antibody, all of which were normal or negative. Radiographs showed symmetrical focal cortical thickening in the medial mid-diaphyses of both tibiae (Fig. 1A, B). ^{99m}Tc -MDP bone scan showed increased tracer uptake in the mid-tibiae bilaterally (Fig. 2A). A CT scan demonstrated thickening of the posterior medial cortices of both tibiae (Fig. 3A). MRI showed both periosteal and endosteal thickening associated with bone marrow signal abnormality consistent with marrow edema (Figs. 4A, C). Taken together, the medical history and findings, with the radiographic images, established the diagnosis of hereditary multiple diaphyseal sclerosis, or Ribbing disease. Serum alkaline phosphatase, osteocalcin, parathyroid hormone, ionized calcium, phosphorus, 1,25- and 25-vitamin D, testosterone, gonadotropins, and urinary N-telopeptide, pyridinoline and deoxypyridinoline were normal. Because the patient might have received an experimental vaccine, the study was unmasked prematurely, and it was revealed that he had received placebo.

In an effort to relieve the pain, which was requiring increasing amounts of narcotic analgesic to control, and based on the case report of a patient responding to oral pamidronate therapy, the patient received 2 doses of intravenous pamidronate (90 mg/dose) at

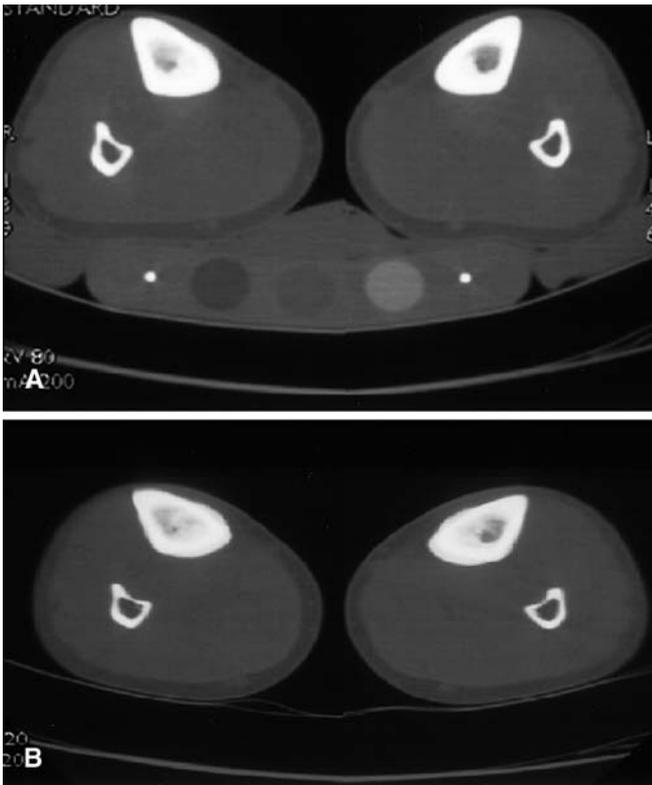


Fig. 3A, B Pre- and post-treatment CT scan images of a patient with Ribbing disease. Axial images obtained before (A) and after (B) pamidronate treatment show thickening of the posterior medial cortices of both tibiae with marrow ablation that progressed with treatment

3-month intervals. Two weeks after the first infusion, he complained of increased pain at night but within 2 weeks it had reverted to his pre-pamidronate baseline. When he returned 3 months later for the second treatment, he reported a slight decrease in pain.

Two weeks after the second cycle of pamidronate lower extremity pain increased and transdermal fentanyl, acupuncture and a nonsteroidal analgesic were added to the oxycodone regimen. By the time he returned for a third cycle of pamidronate, the pain persisted but was controlled with analgesics. Imaging studies performed prior to the third infusion (Figs. 1C, D, 2B, 3B, 4B, D) suggested worsening of the disease process, and treatment with pamidronate was discontinued. Thirty months after the first treatment with pamidronate, he now reports almost complete resolution of pain and an increase in function. Pain is only occasional and is usually controlled with non-narcotic analgesics.

Discussion

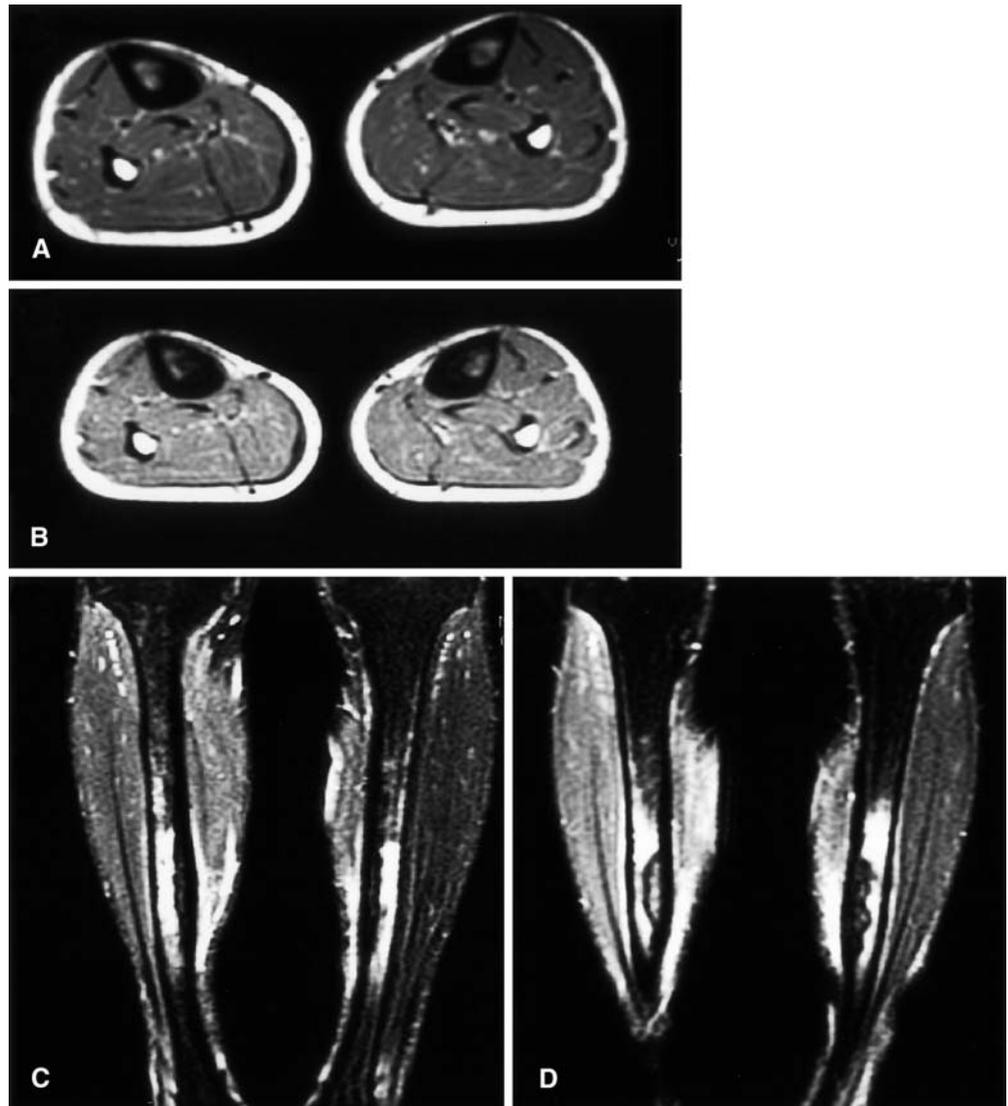
In this report we present the radiographic and biochemical characterization of a case of Ribbing disease, and document the ineffectiveness of intravenous pamidronate in preventing disease progression or relieving pain. We present here for the first time the MRI appearance of Ribbing disease, which demonstrated marrow edema at the affected sites (Fig. 4A, B). Recent studies have

demonstrated that marrow edema is often associated with, and may be responsible for, at least in part, the pain associated with osteoarthritis [12]. The MRI appearance and the prominent finding of pain in this disease may be useful in helping to differentiate Ribbing disease from intramedullary osteosclerosis [13], another diaphyseal dysplasia disease which bears perhaps the greatest clinical and radiographic similarity to Ribbing disease. It does not appear that the MRI finding of marrow edema is characteristic of intramedullary osteosclerosis [13]. This finding lends support to what has been reported as a potential treatment for Ribbing disease, the creation of a wide surgical “window” at the site of pain [14]. Present in the post-treatment MRI are areas of high signal intensity demarcated by a serpentine margin of low signal intensity (Fig. 4D). These are highly suggestive of medullary bone infarcts, which would both be consistent with and explain the increase in pain the patient was experiencing at the time. This could represent the effect of pamidronate, but would more likely represent the natural history of the disease. One may also consider the diagnosis of painful transient tibial edema [15], which clinically resembles the presentation here. However, in that condition the radiographs are usually normal.

Consistent with previous reports, the bone formation marker alkaline phosphatase was not elevated. In addition, the more specific markers of bone metabolism, including osteocalcin, which is a marker of bone formation, and the markers of bone resorption, N-telopeptide, pyridinoline and deoxypyridinoline cross-links, were also normal. Together these measures of bone metabolism would suggest that Ribbing disease is not a “high turnover” bone state, a finding which may help to differentiate it from Camurati-Engelmann disease [16]. This seems to be at odds with the increased tracer uptake on ^{99m}Tc -MDP bone scan and the increase in bone in the diaphyses. In most bone diseases, where there is increased tracer uptake on bone scan the markers of bone turnover are usually increased [17]. The lack of elevation in bone turnover markers may be explained by the limited amount of the skeleton involved as reflected by the focality of the uptake. That is, the area of involved bone may have been too small to affect the overall turnover markers. However, this is not necessarily inconsistent with the limited literature that is available about Ribbing disease at the histological level, which fails to identify a pattern suggestive of either a preponderance of osteoblastic or osteoclastic activity [5].

Given the effectiveness of bisphosphonates in relieving pain in a number of skeletal diseases [18, 19, 20] and a previous report of the efficacy of oral pamidronate in treating a patient with Ribbing disease [8], we treated this patient with pamidronate. It was both clinically and radiographically ineffective and the disease progressed under treatment. This is consistent with a recent report

Fig. 4A–D Pre- and post-treatment MRI images of patient with Ribbing disease. Pre-treatment axial (A) T1-weighted (1.5 T, SE 400/9; TR/TE) and coronal (C) STIR (5866/38/150; TR/TE/TI) MR images demonstrate focal cortical thickening and abnormal marrow signal in both tibiae (diminished on the T1-weighted scans, increased on the STIR scans) consistent with bone marrow edema. Post-treatment scans (B, D) demonstrate progression of changes in the interim and narrowing of the marrow cavities as well as thickening of the cortices by both endosteal and periosteal bone deposition



which demonstrated that pamidronate was ineffective in treating the similar condition, Camurati-Engelmann disease [16]. The effectiveness of corticosteroids in the latter case suggests that they may also be effective in Ribbing disease. Thus, while it was disappointing that pamidronate was not effective, it was not surprising. Whether the disease progression that was observed over the course of treatment represents the natural history of the disease or exacerbation by pamidronate is not clear, but we feel that it suggests that bisphosphonates should be used cautiously if at all to treat this condition in other patients.

The resolution of pain with time, in the absence of any further specific treatment, likely represents the natural history of the disease. It appears that the natural history is one of waxing and waning of symptoms independent of treatment.

In conclusion, this report expands our understanding of Ribbing disease by demonstrating that marrow edema, as visualized on MRI scanning, is associated with the disease and may be the cause of the pain, that both markers of bone formation and resorption are normal, and that bisphosphonates are an ineffective treatment.

Acknowledgement The authors are indebted to April Powers and Grace Kelly for their essential participation in the study and meticulous care of the patient.

References

1. Ribbing S. Hereditary, multiple diaphyseal sclerosis. *Acta Radiol* 1949; 31:522-536.
2. Paul LW. Hereditary multiple diaphyseal sclerosis (Ribbing). *Radiology* 1953; 60:412-416.
3. Shier CK, Krasicky GA, Ellis BI, Kottamasu SR. Ribbing's disease: radiographic-scintigraphic correlation and comparative analysis with Engelmann's disease. *J Nucl Med* 1987; 28:244-248.
4. Furia JP, Schwartz HS. Hereditary multiple diaphyseal sclerosis: a tumor simulator. *Orthopedics* 1990; 13:1267-1274.
5. Seeger LL, Hewel KC, Yao L, et al. Ribbing disease (multiple diaphyseal sclerosis): imaging and differential diagnosis. *AJR Am J Roentgenol* 1996; 167:689-694.
6. Hurdley JD, Wilson FC. Progressive diaphyseal dysplasia: review of the literature and report of seven cases in one family. *J Bone Joint Surg Am* 1973; 55:461-474.
7. Makita Y, Nishimura G, Ikegawa S, Ishii T, Ito Y, Okuno A. Intrafamilial phenotypic variability in Engelmann disease (ED): are ED and Ribbing disease the same entity? *Am J Med Genet* 2000; 91:153-156.
8. de Rubin ZS, Ghiringhelli G, Mansur JL. [Clinical, humoral and scintigraphic assessment of a bisphosphonate as potential treatment of diaphyseal dysplasia: Ribbing and Camurati-Engelmann diseases]. *Medicina (B Aires)* 1997; 57:56-60.
9. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *J Bone Miner Res* 1997; 12:1746-1752.
10. Wimalawansa SJ, Gunasekera RD. Pamidronate is effective for Paget's disease of bone refractory to conventional therapy. *Calcif Tissue Int* 1993; 53:237-241.
11. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; 88:1082-1090.
12. Felson DT, Chaisson CE, Hill CL, et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 2001; 134:541-549.
13. Chanchairujira K, Chung CB, Lai YM, Haghighi P, Resnick D. Intramedullary osteosclerosis: imaging features in nine patients. *Radiology* 2001; 220:225-230.
14. Bettini G, Bonvi V. Etiopathogenetic, clinical, and radiographic considerations on Ribbing's disease: report of 2 cases of familial nature. *Arch Putti* 1962; 16:58-72.
15. Reinus WR, Fischer KC, Ritter JH. Painful transient tibial edema. *Radiology* 1994; 192:195-199.
16. Inaoka T, Shuke N, Sato J, et al. Scintigraphic evaluation of pamidronate and corticosteroid therapy in a patient with progressive diaphyseal dysplasia (Camurati-Engelmann disease). *Clin Nucl Med* 2001; 26:680-682.
17. Mari C, Catafau A, Carrio I. Bone scintigraphy and metabolic disorders. *Q J Nucl Med* 1999; 43:259-267.
18. Chapurlat RD, Meunier PJ. Fibrous dysplasia of bone. *Baillieres Best Pract Res Clin Rheumatol* 2000; 14:385-398.
19. Lyles KW, Siris ES, Singer FR, Meunier PJ. A clinical approach to diagnosis and management of Paget's disease of bone. *J Bone Miner Res* 2001; 16:1379-1387.
20. Paterson AH. The potential role of bisphosphonates as adjuvant therapy in the prevention of bone metastases. *Cancer* 2000; 88:3038-3046.