

Silent Swelling of the Tibia in a 43-year-old Man

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History and Physical Examination

A 43-year-old man complaining of right anterior leg pain presented with swelling, minimal redness, and a decrease in hair at the affected site. The pain had been present for 1 year, although he first recognized the swelling 4 months before presentation. There was no history of trauma to the limb.

Physical examination revealed hair loss on the skin over the affected site. The skin was thin and atrophic. There was minimal tenderness at the anterior aspect of the leg. Compared with the contralateral side, the affected leg had an increased circumference of 8 cm, 10 cm below the tibial tuberosity. Serum alkaline phosphatase levels were mildly elevated. Serum calcium and phosphate levels were normal.

Radiography (Fig. 1), computed tomography (CT) (Fig. 2), and MRI (Fig. 3) were performed. To exclude

metastatic involvement, chest and abdominal CT scans were performed, all of which were interpreted as normal.

Based on the history, physical examination, laboratory tests, and imaging studies, what is the differential diagnosis?

Imaging Interpretation

Radiographs of the right tibia showed irregular cortical and trabecular thickening and expansion of the tibia with anterior bowing (Fig. 1). Radiographs also showed blurring of the demarcation between the cortex and medulla with a coarse trabecular pattern. The lesion was localized in the proximal $\frac{2}{3}$ of the tibia, including the proximal metaphysis and diaphysis. CT revealed irregular sclerotic cortical thickening with some lytic component, coarsening of the trabeculae, and expansion of the tibia (Fig. 2). MRI revealed enlargement of the tibia with enhancing cortical thickening and anterior bowing (Fig. 3). Extension into the soft tissues was not detected (Figs. 2, 3).

Differential Diagnosis

Syphilitic osteoperiostitis
Paget's disease
Familial idiopathic hyperphosphatasia (juvenile Paget's disease)
Extensive osteoblastic metastases
Chronic osteomyelitis

To ascertain the diagnosis, needle biopsy of the tibial metaphysodiaphyseal junction was performed (Fig. 4).

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Each author certifies that his or her institution has approved the reporting of this case report and that all investigations were conducted in conformity with ethical principles of research.

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Fig. 1 A radiograph of the right leg shows irregular cortical and trabecular thickening and expansion of the proximal and mid tibia with anterior bowing.



Fig. 3 A coronal T2-weighted MR image shows hypointense-appearing cortical thickening.

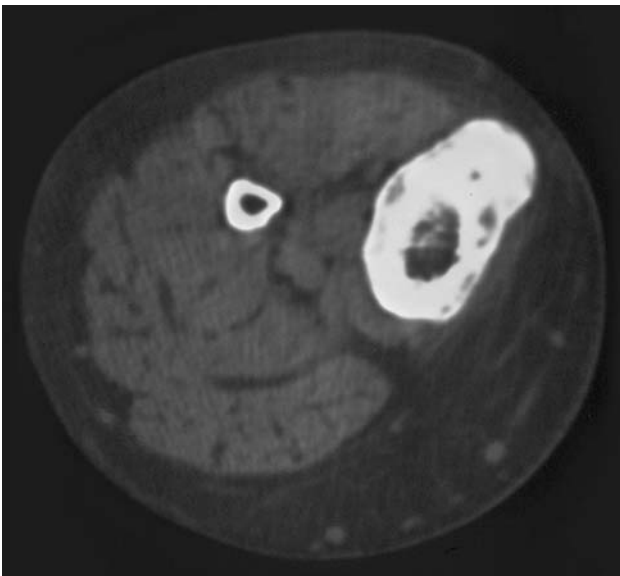


Fig. 2 An axial CT image shows coarse cortical thickening at the mid tibia.

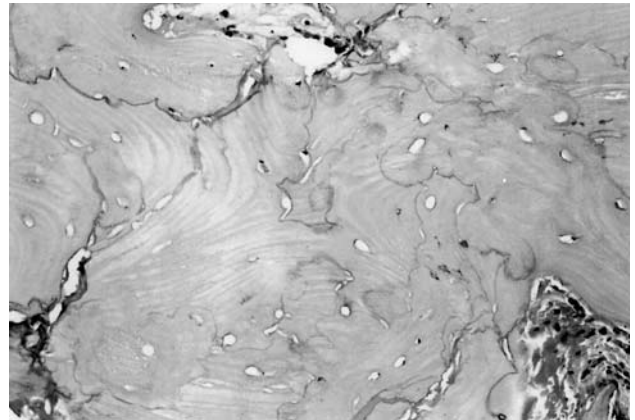


Fig. 4 New bone is woven and has a mosaic pattern, and the medulla is lost. Paratrabeular fibrosis, replacement of marrow with fibrous tissue, and disorganized trabeculae are present (Stain, hematoxylin and eosin; original magnification, $\times 400$).

Based on the history, physical examination, laboratory tests, imaging studies, and histologic picture, what is the diagnosis and how should this patient be treated?

Histology Interpretation

Hematoxylin and eosin-stained specimens revealed the normal compact density of the cortex was lost owing to excessive osteoclastic resorptive activity, which led to increased bone turnover (Fig. 4). The osteoclasts were multinucleated with intranuclear inclusions, and their number and size were increased. The cortex was widened by the formation of new bone on its outer and inner surfaces. The new bone was woven and had a mosaic pattern, and the medulla was lost. Paratrabecular fibrosis, replacement of marrow with fibrous tissue, and disorganized trabeculae were present.

Diagnosis

Paget's disease of the tibia.

Discussion and Treatment

Paget's disease of bone is a slowly progressive disorder of unknown etiology, which causes solitary (monostotic) or widespread (polyostotic) lesions and pain in the human skeleton [11]. It is also known as osteitis deformans and was first described by Sir James Paget in 1877 [14]. The disease is characterized by excessive bone resorption in focal areas followed by abundant new bone formation, with eventual replacement of the normal bone marrow by vascular and fibrous tissue [17]. Sarcomatous transformation is heralded by findings of masslike replacement of the marrow space, cortical destruction, and an associated soft tissue mass on CT and MR images [19].

Syphilitic infection of bone is a combination of osteitis and periostitis. Of the long bones, the tibia is most commonly affected. In congenital syphilis, characteristically, the lesions are widespread and symmetric. Destructive changes are usually seen in the metaphysis at the junction with the growth plate. At later stages, involvement of the tibia results in a characteristic anterior bowing known as "saber-shin" deformity. Occasionally, the predominant change is bone destruction without new bone formation. The bone lesions usually respond well to intensive antisyphilitic therapy [1]. Familial idiopathic hyperphosphatasia (juvenile Paget's disease) affects mostly young children within their first 18 months. It is associated with progressive bone deformities and characterized by painful bowing of the limbs, muscular weakness and abnormal gait, pathologic fractures, spinal deformities, loss of vision and hearing, elevation of serum alkaline phosphatase, and an increase in leucine aminopeptidase. Increased turnover of bone seen by radionuclide bone scan is characteristic in

juvenile Paget's disease. Although the disorder has no relationship to classic Paget's disease, it exhibits similar radiographic features. However, unlike Paget's disease, the epiphyses are usually not affected [5]. Metastatic carcinomas may resemble Paget's disease, but bony expansion is lacking and cortical destruction is more frequent. In any site, if destruction of bone, extracortical extension, or a possible soft tissue mass is present, neoplasia must be ruled out, especially if pain is increasing [15]. Chronic osteomyelitis is nearly always a sequel to antecedent acute osteomyelitis, so the patient will have a history of infection. It is common in the long bones and often confined to one end of the bone, but it may affect the whole length. The bone is thickened and generally denser than normal, although often honeycombed with granulation tissue, fibrous tissue, or pus. Often, a sinus track leads to the skin surface. On radiographic examination, the bone is thickened and shows irregular and patchy sclerosis, which may give a honeycombed appearance. If a sequestrum is present, it is seen as a dense loose fragment with irregular but sharply demarcated edges, lying within a cavity in the bone [1].

Paget's disease is an age-related condition, and the majority of the patients are elderly, with an average age at the time of diagnosis of more than 40 years. There is a slight male predominance.

The cause of Paget's disease remains uncertain. However, a viral cause is suggested by osteoclasts with intranuclear inclusion bodies (resembling paramyxoviridae) [4, 12]. There is a certain genetic predisposition to Paget's disease, including one involving the RANKL/OPG/RANK/NF- κ B signaling pathway [23].

The pathogenesis of the disease is characterized by excessive and abnormal remodeling of bone with active and quiescent phases [19]. Three phases of the disease have been described. The initial phase, which is called the lytic phase (incipient active), is characterized by excessive bone resorption in a focal region. Subsequently, the mixed phase (intermediate active) shows markedly increased bone formation attributable to newly appearing osteoblastic activity that lacks the original lamellar character of the bone and is referred to as a mosaic or jigsaw pattern [19]. Thus, the new bone is disorganized, which eventually results in bowing of the bones [8]. Finally, the disease progresses to the blastic phase (late inactive), in which osteoblastic activity gradually declines.

Most often, Paget's disease has an asymptomatic course and patients are incidentally recognized during radiographic examinations. However, 10% to 30% of patients have pain, skeletal deformity, neurologic symptoms, or pathologic fractures [10]. The most serious and feared complication of Paget's disease is sarcomatous transformation to osteosarcoma in the pagetic bone, which occurs in less than 1% of patients [7, 17].

In blood serum analysis, elevated alkaline phosphatase levels related to increased rate of bone formation are found particularly in the mixed and blastic phases. Increased serum and urine levels of hydroxyproline related to increased rate of bone resorption are found in the lytic phase.

The sites most commonly affected by Paget's disease are in the axial skeleton. The pelvis is the most commonly affected site (30%–75%), followed by the skull (25%–65%) [2, 3, 16, 19].

Radiographic evaluation is the mainstay of diagnosis in uncomplicated Paget's disease [19]. In the lytic phase, osteolysis begins as a subchondral area of lucency in long bones. In the tibia, the initial lesion is diaphyseal rather than a subchondral localization [21]. Cortical thickening and coarse trabeculation of the cancellous bone as a result of new bone formation and remodeling characterize the mixed stage. The blastic phase is the stage of diffuse increase in bone density and enlargement and widening of the long bones. Bone scintigraphy is a sensitive but not specific examination for detecting osteoblastic activity seen in Paget's disease [20]. The disorganized pattern of trabecular thickening seen pathologically is better observed on CT and MRI scans than on radiographs.

The aim of the treatment in Paget's disease is to control the pain and prevent complications, rather than to cure the disease. Calcitonin has been used alone or in combination with other medications for a long time [6, 13]. Although calcitonin can induce remission in patients with Paget's disease, more than 50% of patients treated more than 6 months have calcitonin antibodies develop and 10% to 20% become resistant to calcitonin [17].

With the introduction of etidronate for clinical use in 1971, oral bisphosphonates, which block osteoclast formation and induce osteoclast apoptosis, became the treatment of choice for Paget's disease. Complications associated with long-term etidronate treatment, such as increased risk of fractures including vertebral collapse attributable to focal osteomalacia, limit its use. Alternative bisphosphonates, such as alendronate and risedronate, are commonly used in combination with calcitonin. Although many authors advocate daily doses of 40 mg alendronate sodium for Paget's disease, the gastrointestinal side effects caused by such high doses often necessitate discontinuation of the therapy. Wendlova et al. [22] treated patients with 10 mg alendronate sodium per day for 6 months in combination with calcitonin and calcium carbonate and obtained normalization of the bone turnover, reduction of the number of osteoplastic foci on radiographs of the vertebrae and pelvis, regression of the vertebrogenic pain syndrome, and improved patient mobility.

After effective treatment methods, biopsies of the bone affected with Paget's disease reveal normal lamellar deposition at sites of new bone formation and remodeling

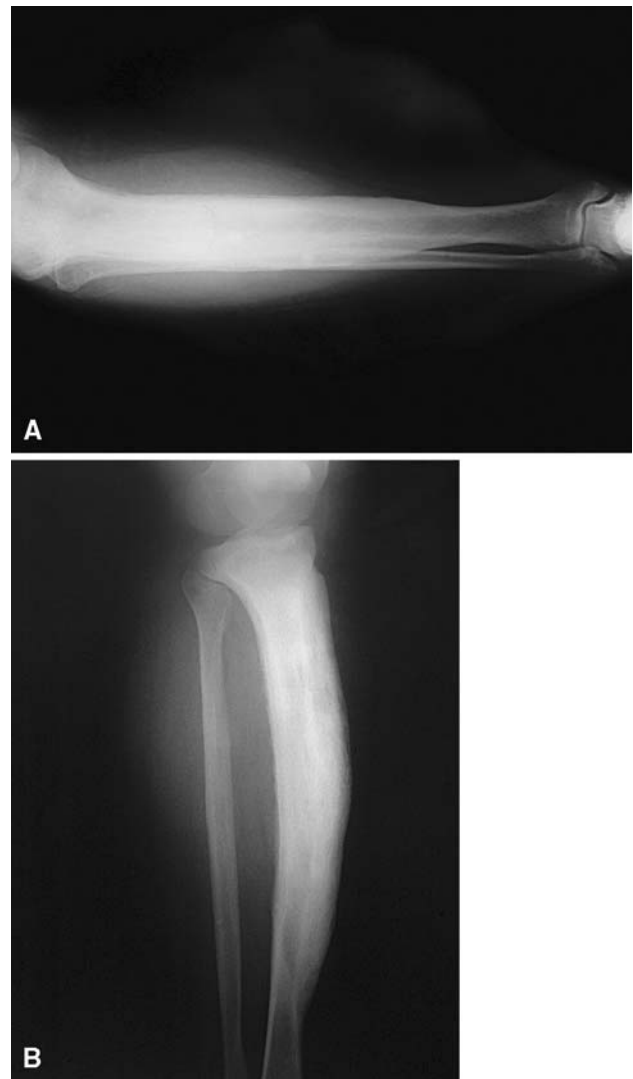


Fig. 5A–B Final followup (A) anteroposterior and (B) lateral radiographs of the right leg show the tibial diameter had decreased 3 cm, but bowing persisted.

[9]. Therefore, treating Paget's disease even in an asymptomatic patient is recommended if the process is active at sites where disease progression over time is likely to put the patient at risk of complications [18].

We treated the patient with 40 mg alendronate sodium per day combined with synthetic salmon calcitonin. The patient's pain was relieved within the first month. The treatment continued for 6 months. At the end of treatment, circumference of the right tibia decreased 1 cm. There were no morphologic changes on radiographs. At the 1-year followup, the patient was pain-free even with full weightbearing. At 3 years followup, the circumference had decreased 3 cm. Bone mineral density was increased and the patient denied pain in the affected leg. The patient was clinically well. However, bowing of the tibia persisted on the radiographs (Fig. 5).

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