CHAPTER 34

Paget's Disease of Bone

ROY D. ALTMAN, MD

- Paget's disease affects 1% of the US population over the age of 40 years and is a chronic disorder of adult skeleton characterized by increased resorption and deposition of bone resulting in replacement of the normal matrix with softened and enlarged bone.
- Most adults with Paget's disease are asymptomatic and diagnosis is found on x-ray of the bones.
- Bone pain, fracture, and nerve impingement can occur due to enlarging and poorly constructed bone matrix.
- Potent and generally safe suppressive agents have been developed and have resulted in a more aggressive approach to therapy.

Paget's disease is a chronic disorder of the adult skeleton characterized by increased resorption and deposition of bone resulting in replacement of the normal matrix with a softened and enlarged bone. Initially, there is active resorption by large and increased numbers of osteoclasts containing multiple nuclei, followed by deposition of bone by numerous osteoblasts which most often results in a weakened disorganized bony structure that is interspersed with areas of fibrosis. Although localized to isolated areas of the skeleton, there may be widespread bony distribution.

The bones most commonly affected are the pelvis, femur, skull, tibia, vertebrae, clavicle, and humerus.

Paget's disease of bone is present in approximately 1% of the US population over the age of 40 (1). Prevalence increases with age with almost a 2:1 ratio of men to women. Paget's disease is more common in Europe, particularly the United Kingdom, excluding Scandinavia, and their immigrant descendants of Australia, New Zealand, and the United States. It is rare in Africa and Asia.

The etiology of Paget's disease is unknown. It is more common among relatives of those with Paget's disease, and genetic studies have demonstrated an association to mutation variants of the Sequestrosome 1 gene on the fifth chromosome (2). There is additional evidence suggesting a virus trigger (from the paramyxovirus family) (3). There is man-to-man transmission.

SYMPTOMS

Although Paget's disease is usually asymptomatic, bone pain, bony enlargement, or bony deformity may occur. Bone pain may be deep, aching, occasionally severe, and may worsen at night. The enlarging bones may compress nerves, adding to the pain. Sometimes Paget's disease leads to the development of painful osteoarthritis in contiguous joints (4). Stiff joints and fatigue may develop slowly and subtly.

Symptoms vary, depending on degree of involvement and which bones are affected. The skull may enlarge, resulting in frontal bossing and a larger hat size. Hearing loss may be due to petrous ridge Paget's disease invasion of the cochlea. There may be headaches, dizziness, and bulging scalp veins.

Vertebrae may enlarge, weaken, and fracture, resulting in a loss in body height and a stooped forward (or simian) posturing. Involved vertebrae may compress nerves from the spinal cord, resulting in pain, dysesthesias, weakness, or even lower extremity paraparesis or paraplegia. Long bones become bowed, resulting in reduced function, abnormal gait, and contractures. The involved bone has a tendency to fracture.

There is an association with high output cardiac failure. Sarcomatous degeneration of pagetic lesions occurs in fewer than 1% of patients. Hypercalcemia can occur with/without hyperparathyroidism. The prognosis is most often good, particularly if treated. The unfortunate few who develop pagetic sarcomas have a poor prognosis.

DIAGNOSIS

Paget's disease is often discovered when x-rays or laboratory tests are performed for other reasons. The diagnosis is uncommonly suspected on the basis of symptoms and physical examination. Confirmation of the diagnosis is usually from the characteristic findings

on x-ray. In most patients there will be an increase in the serum alkaline phosphatase. A bone-specific serum alkaline phosphatase can sometimes be of value. The extent of bony involvement can be determined from a pertechnitate radionuclide bone scan. Bone biopsy is only needed when there is concern for malignancy. Other markers of active bone turnover (such as urinary markers of bone turnover) are elevated, but are uncommonly of value in the care of patients with Paget's disease.

THERAPY

The development of potent and generally safe suppressive agents for therapy of Paget's disease has prompted a more aggressive change in therapeutic philosophy. Suppressive therapy for Paget's disease of bone now appears warranted for anyone with evidence of active Paget's disease, including a serum alkaline phosphatase twice the upper limits of the normal range in an asymptomatic patient. Suppressive therapies are not expected to correct existing hearing loss, deformity, or osteoarthritis.

Heel lifts may tend to normalize gait when one lower extremity develops bowing. Bed rest should be avoided, if possible, to prevent hypercalcemia and immobilization osteoporosis. Surgery is often helpful in removing pressure from compressed nerves or to replace a secondary osteoarthritic joint.

Analgesics or nonsteroidal anti-inflammatory drugs may reduce bone pain. Supplemental dietary calcium and vitamin D should be considered.

Bisphosphonates are particularly effective and can be useful before surgery to reduce bleeding from the involved bone during surgery; they are also given to treat pain caused by Paget's disease, to prevent or slow the progression of weakness or paralysis in people who are not surgical candidates, prevent secondary arthritis, progressive hearing loss, or advancing deformity. Oral bisphosphonates should be ingested with a large glass of water (6–8 oz) upon rising in the morning. The patient should remain upright and not eat for at least 30 minutes. Other agents such as parenteral calcitonin and plicamycin are still occasionally of value.

Adverse effects that are common to the bisphosphonates include esophagitis and bone pain. The intravenous bisphosphonates may cause fevers and a flulike syndrome. Mandibular osteonecrosis has been reported with all bisphosphonates, but is particularly uncommon, and is most common with high-dose intravenous bisphosphonates (5).

Alendronate (Fosamax, Merck) is a potent nitrogen-containing bisphosphonate administered orally as 40 mg/day for 6 months (6). Alendronate can be administered for 3 months if the alkaline phosphatase has normalized. Alendronate is well tolerated with esophageal and gastric ulceration as the major adverse effect.

Disodium etidronate (Didronel® Procter & Gamble) was the first of the bisphosphonates to be used in Paget's disease (7). The duration of response correlates inversely with the pretreatment level of serum alkaline phosphatase. The response to repeat therapy with disodium etidronate is variable and there is increasing resistance to repeated retreatments. Non-union fractures tend to calcify their callus following disodium etidronate therapy. The dose of disodium etidronate is 5 mg/kg per day or 400 mg daily for a 40-kg (88 lb) to 80-kg (176 lb) patient. Adverse reactions to disodium etidronate include abdominal cramps, diarrhea, hyperphosphatemia, increasing bone pain, and a possible increase in fractures. Hyperphosphatemia appears to be due to a direct renal effect of disodium etidronate. Esophagitis is uncommon.

Pamidronate (APD, Aredia® Novartis Pharmaceuticals) is 100 times more potent than disodium etidronate in its effect on osteoclasts. Pamidronate produces rapid and dramatic biochemical responses in Paget's disease (8). Pamidronate should be administered as 60 to 90 mg intravenous infusions with normal saline or dextrose/water. A variety of regimens have been used effectively, including daily infusions for 3 to 5 days, once weekly for 3 to 5 weeks, once with re-evaluation monthly, etc. Progressive resistance often occurs with re-treatments. Adverse reactions to pamidronate include transient fever (usually <39.2°C), transient lymphopenia, mild and transient nausea, and uveitis.

Risedronate (Actonel® Procter & Gamble/sanofi-aventis) is a potent tertiary nitrogen containing bisphosphonate administered orally as 30 mg/day for 2 months (9). Prolonged remissions have been reported. There are reports of esophagitis and other nonspecific gastrointestinal complaints.

Tiludronate (Skelid® Sanofi Winthrop Industrie) is a nitrogen-containing bisphosphonate administered orally as 400 mg/day for 3 months (10). The major adverse event is esophagitis.

Zoledronate (Zometa® Novartis Pharmaceuticals) is a potent bisphosphonate administrated as a 4-mg intravenous 15-minute infusion. Responses are longer than risedronate (11). Renal failure, fever, flulike syndrome, and bone pain have been reported.

Synthetic salmon calcitonin (Miacalcin) is administered as 100 (MRC) units or 0.5 mL of salmon calcitonin subcutaneously or intramuscularly daily for the first month (12). The dose can be decreased or the interval between doses increased depending on the response to therapy. Primary and secondary resistance to calcitonin can occur. Most patients will have chemical exacerbation within 6 months of calcitonin discontinuation.

Salmon calcitonin is supplied as 400 units per 2-mL vial and should be refrigerated. Adverse reactions

include gastrointestinal, vascular, and local reactions at the injection site. Most occur within several minutes of injection and last about 1 hour.

Plicamycin (Mithramycin) is used only in severely affected patients because of multiple associated adverse effects.

Despite the fact that Paget's disease is uncommon, interest into its pathogenesis and therapy continue. Much understanding about bone metabolism and bone disease in general has been generated by research into Paget's disease. With our present state of knowledge, it is most often rewarding to care for patients with Paget's disease of bone—for both the physician and patient.

REFERENCES

1. Altman RD, Bloch DA, Hochberg MC, Murphy WA. Prevalence of pelvic Paget's disease of bone in the United States. J Bone Miner Res 2000;15:461–465.
2. Michou L, Collet C, Laplanche JL, Orcel P, Cornelis F. Genetics of Paget's disease of bone. Joint Bone Spine 2006;73:243–248.
3. Kurihara N, Zhou H, Reddy SV, et al. Expression of measles virus nucleocapsid protein in Osteoclasts induces Paget's disease-like bone lesions in mice. J Bone Miner Res 2006;21:446–455.
4. Altman RD. Musculoskeletal manifestations of Paget's disease of bone. Arthritis Rheum 1980;23:1121–1127.
5. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaw. Ann Intern Med 2006;144:753–761.
6. Walsh JP, Ward LC, Stewart GO, et al. A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. Bone 2004;34:747–754.
7. Altman RD, Johnston CC, Khairi MRA, Wellman H, Serafini AN, Sankey RR. Influence of disodium etidronate on clinical and laboratory manifestations of Paget's disease of bone (osteitis deformans). N Engl J Med 1973;289:1379–1384.
8. Vasireddy S. Talwalkar A, Miller H, Mehan R, Swinson DR. Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. Clin Rheumatol 2003;22:376–380.
9. Crandall C. Risedronate: a clinical review. Arch Intern Med 2001;161:353–360.
10. Morales-Piga A. Tiludronate. A new treatment for an old ailment: Paget's disease of bone. Expert Opin Pharmacother 1999;1:157–170.
11. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005;353:898–908.
12. Martin TJ. Treatment of Paget's disease with calcitonins. Aust N Z J Med 1979;9:36–43.