Persistent effect of zoledronic acid in Paget’s disease

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Case report

A 60-year-old man presented in the Emergency Department of our clinic due to left kidney colic. He had suffered acute myocardial infarction 11 years before and, shortly afterwards, a coronary artery bypass grafting (CABG) was performed. His treatment included metoprolol, acetylsalicylic acid and atorvastatin. He also reported several episodes of renal colic due to nephrolithiasis.

Physical examination was unremarkable. On admission, laboratory examination was significant for elevated alkaline phosphatase (ALP) levels, 321 IU/L (normal range, 30-125 IU/L). The pelvis-hip-lumbar spine-femur radiography revealed the presence of diffuse osteoblastic lesions, small disseminated lytic regions and trabecular thickness. In addition, cortical bone thickness, enlargement of the diaphysis, bowing deformities and small horizontal pseudofractures on the upper third of the left femur were observed (Fig. 1). Histological examination of a bone specimen obtained from the right ilium showed loss of architectural structure of the osseous trabeculae, mosaic appearance of the osseous lamella, increased osteoclast activity and fibrosis of the marrow spaces were confirmed (Fig. 2).

Typical biochemical, radiological and histological findings established the diagnosis of Paget’s disease. The patient was treated with a single intravenous infusion of 4 mg of zoledronic acid given over a fifteen-minute period. No side effects were observed. Alkaline phosphatase levels normalized with the disease is usually discovered incidentally due to elevated biochemical indices of bone turnover or due to characteristic radiological bone lesions. When symptomatic, the primary manifestations include bone pain, skeletal deformities, fractures and osteoporosis. Malignant transformation to osteosarcoma, fibrosarcoma or chondrosarcoma develops in less than 1% of patients (1, 6).

Treatment aims at the suppression of osteoclast activity and is achieved with bisphosphonates, which represent the treatment of choice for Paget’s disease (1, 7). Zoledronic acid is a novel, more potent compound, which effectively inhibits osteoclast activity without inhibiting osteoid mineralization (8-10). The sustained effect of zoledronic acid in a patient with Paget’s disease is reported.

Introduction

Paget’s bone disease is a disorder in which bone regions with high turnover are replaced by new, vascular, but disorganized and immature bone with excessive fibrosis, high tendency of deformity and diminished mechanical resistance (1, 2). It is quite frequent in Europe being present in 3% of the population above 55 years old (1-3). Its etiology remains unknown; genetic predisposition and environmental factors may contribute to its pathogenesis (2-5). Most patients are asymptomatic and the disease is usually discovered incidentally due to elevated biochemical indices of bone turnover or due to characteristic radiological bone lesions. When symptomatic, the primary manifestations include bone pain, skeletal deformities, fractures and osteoporosis. Malignant transformation to osteosarcoma, fibrosarcoma or chondrosarcoma develops in less than 1% of patients (1, 6).

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phosphatase levels normalized within four months (60 IU/L). At the last follow-up examination, three years after treatment, the patient remains asymptomatic, without significant changes in radiology imaging, and alkaline phosphatase levels are still within the normal range.

Discussion

Paget’s disease is usually asymptomatic at diagnosis. Pain is not a reliable indicator of the extent of the disease, since more than 70% of the lesions is asymptomatic (11). Vertebrae, long bones and skull are the most commonly involved sites. The most characteristic radiological finding is localized bone expansion, which is absent in all other diseases that cause osteosclerosis. Cortical bone thickness and lytic lesions are observed as well. The biopsy findings are pathognomonic of the disease. “Paved” or “mosaic” appearance of the osseous tissue, irregular collagen disposition, hypervascularity and an elevated number of osteoblasts and osteoclasts with multiple nuclei are present (1). Evaluation of disease activity and its response to treatment is based on the determination of alkaline phosphatase, which reflects osteoblast activity (12). Other markers of bone turnover, such as osteocalcin and urinary hydroxyproline, do not appear to be more sensitive than alkaline phosphatase (3, 13). However, recent studies have shown that serum cross-linked C-telopeptides of type I collagen is a sensitive marker of bone resorption in the management of bisphosphonate therapy in Paget’s disease (14).

The primary disorder in Paget’s disease is increased bone resorption. Bisphosphonates increase osteoclasts’ apoptosis, directly suppress their activity and inhibit the proliferation of osteoclasts’ precursors (15). Zoledronic acid is a particularly attractive bisphosphonate, because it increases bone density and restores bone architecture, in contrast to older members of this class, which caused disorders in the osteoid mineralization (5, 10). These favorable characteristics are attributed to the zoledronic acid-induced stimulation of proliferation, differentiation and osteosynthetic capacity of osteoblasts (15).

Administration of zoledronic acid has recently been shown to normalize alkaline phosphatase in 88.6% of patients with Paget’s disease, whereas other bisphosphonates induced complete remissions in only 50-60% of the cases (7, 10, 16). In addition, the same study demonstrated that after a median follow-up time of 190 days, only 1 out of 113 patients who received a single infusion of 5 mg of zoledronic acid had a loss of therapeutic response, in comparison to 21 out of 82 patients treated with risedronate (30 mg per day for 60 days, orally) (16). Our patient received a single dose of zoledronic acid intra-

Fig. 1. Pelvis-hip-lumbar spine-femur radiography showing diffuse osteoblastic lesions, small disseminated lytic regions and trabecular thickness.

Fig. 2. Histological examination of a bone specimen obtained from the right ilium showing mosaic appearance of the osseous lamella (Haematoxylin and eosin, x 400).
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venously and, three years after treat-
ment, alkaline phosphatase levels are
within normal levels, something that
clearly shows the persistence of the
effect of zoledronic acid. In contrast,
older bisphosphonates must be admin-
istered for long periods of time, at least
for six months, in order to achieve and
maintain a response.

Another major disadvantage of cur-
rently used bisphosphonates in Paget’s
disease is that they are administered
orally. This is associated with poor
absorption from the gastrointestinal
tract and the frequent development of
side effects, particularly gastrointestinal
distress and erosive esophagitis (1). In
contrast, zoledronic acid is given intra-
venously, resulting in superior phar-
macokinetic characteristics and has
a favorable safety profile. Moreover,
it is safer and more effective than pa-
midronate, which is the only other bi-
sphosphonate given intravenously for
Paget’s disease (9).

The safety and efficacy of bisphospho-
nates extended the indications of treat-
ment to asymptomatic patients. Thus,
the risk of developing fractures or neu-
rological disorders due to involvement
of the basis of the skull, the vertebral
column or the long bones of lower
extremities make bisphosphonate ad-
ministration imperative (5). Additional
indications for treatment are young pa-
tients and highly active disease. Never-
theless, it has still not been established
if decreasing the rate of bone turnover
also decreases complications. Thus,
treatment indications remain empirical
and should be individualized (6).

Patient follow up is based on alkaline
phosphatase determination every 4-6
months and treatment should be re-
teamed when alkaline phosphatase lev-
els rise above the upper limit of normal
(10). Radiology imaging of the in-
volved bones should also be repeated,
particularly if the skull or the bones of
the lower extremities are involved,
since bisphosphonate administration
might restore bone architecture (1). In
conclusion, zoledronic acid appears to
be safe and effective in Paget’s disease,
and most importantly, able to achieve
significantly prolonged remissions.

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