Two Cases of Monostotic Paget’s Disease: Effects of Bisphosphonate

MADOKA HOSHIRO, TAKESHI HARADA, HIROSHI IWAI, TOSHIYUKI MIYATAKE, AKIYOSHI NISHIMURA, YASUHIRO OHNO AND NORIHIKO AOKI

Department of Endocrinology, Metabolism and Diabetes Mellitus, Kinki University School of Medicine, Osaka-Sayama 589-8511, Japan

Abstract. We report two cases of monostotic Paget’s disease which were effectively treated with bisphosphonate. Case 1 was a 60-year-old female. Medical examination revealed high alkaline phosphatase (ALP) levels making her visit our clinic. Hematological examination showed high levels of ALP isozyme 3 and bone metabolism markers, and bone scintigraphy demonstrated strong accumulation of $^{99m}$Tc on the skull. With the diagnosis of monostotic Paget’s disease of the skull, treatment with bisphosphonate (etidronate) was started. The response to etidronate was good and after 12 weeks of treatment, the ALP levels decreased to about 26% of the levels before treatment, without the appearance of any symptoms or lesion development. One year and three months later, ALP increased again, and etidronate administration was resumed. However, four years after the diagnosis of the disease, etidronate became ineffective and oral administration of alendronate, a stronger bisphosphonate, was started at 5 mg/day. The patient responded favorably to the bisphosphonate and is still under observation. Case 2 was a 71-year-old female. High ALP levels were found during the follow-up of type 2 diabetes, and the case was diagnosed as monostotic Paget’s disease of the pelvis based on bone metabolism markers and bone scintigraphy. Etidronate treatment at 200 mg/day resulted in the improvement of bone metabolism markers and bone scintigraphy findings. When she died of colon cancer twelve months later, with no marked progress of the Paget’s disease of bone observed clinically.

Key words: Paget’s disease of bone, Bone turnover markers, Bisphosphonate

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PAGET’S disease of bone was reported for the first time in the UK in 1877. It is a chronic, progressive disease with bone thickening and deformity caused by an abnormally activated turnover of bone (both bone resorption and formation). The cause is still unknown. However, slow viral infection including paramyxovirus infection has been suggested recently as a cause. The morbidity rate differs among races, and it is high in Western countries and low in Japan. It is prevalent in those aged 45 to 65, especially in middle-aged or older males, and often occurs in the same family. At the early stage and in cases of the monostotic type, it is sometimes asymptomatic. However, pain gradually appears and the disease progresses with repeated remissions and relapse, and eventually results in deformity, fracture, and symptoms of nerve compression.

Recently, the development of bisphosphonate, which is a bone resorption inhibitor, has dramatically improved the treatment strategy for the disease and the drug is supposed to be useful in the long-term control of the disease. However, because Paget’s sarcoma appears in 0.1 to 1.0% of the Paget’s disease cases, it is necessary to pay attention to the deterioration of the symptoms as well as the elevation of bone metabolism markers during follow-up.

We have recently experienced 2 cases of monostotic Paget’s disease which were treated with bisphosphonate. As the disease is rather rare in this country, it seems of value to report here our cases with the special reference to the treatment.
Case Reports

Case 1

A 60-year-old female was referred to our clinic due to the high serum alkaline phosphatase (ALP) value, which showed an elevation in her standard laboratory tests. In December 1997, the ALP value was 2624 IU/l. The high ALP value persisted in further tests without any show of symptoms or identifiable cause during examination with various other tests. She was admitted to our hospital in January 1998.

She was 152 cm in height and 60.2 kg in weight. Her blood pressure was 136/76 mmHg, pulse rate was 80 beats per minutes, and body temperature was 36.5 °C. There were no abnormal findings upon the chest, abdomen and in neurological examinations.

Laboratory data

Blood cell counts were normal. Her blood chemistry revealed high values of ALP (2604 IU/l), total cholesterol (234 mg/dl), GOT (45 IU/l), and GPT (61 IU/l), indicating hypercholesterolemia and mild liver dysfunction. In terms of the ALP isozymes, ALP\textsubscript{3} accounted for 100%, implying a high value of bone-derived ALP. None of her other blood chemistry including other biliary tract enzymes were abnormal.

Endocrinological data

Serum Ca and P levels were normal. Intact PTH (22 pg/ml) and 1,25(OH)\textsubscript{2}D\textsubscript{3} (40.2 pg/ml) were also normal. Bone Gla protein (BGP) level was elevated to 12.9 ng/ml (normal 3.1–12.7) and the urinary hydroxyproline value elevated to 1319 \(\mu\)mol/day (normal 83–330). In addition, the acid phosphatase level elevated to 27.9 IU/l (normal 7.2–14.1). Thyroid hormones showed normal values.

Radiologic findings

Ultrasonography and abdominal computed tomography (CT) showed no abnormal findings. Because the bone-derived ALP isozyme accounted for 100% and the markers of bone formation and absorption were increased, bone lesions were suspected and bone scintigraphy was performed (Fig. 1). Irregular and strong accumulation was observed on the skull, and a skull X-ray showed bone thickening and patchy consolidation, which created a cotton-wool appearance (Fig. 2). In addition, a skull CT revealed severe deformity of the entire skull. A cranial MRI revealed that the skull was apparently thickened with multiple low signals produced by T1 intensifying images and irregular high
signals produced by T2 intensifying images (Fig. 3).

Taken together, in addition to the remarkably high values of ALP, the elevated levels of ALP isozyme 3 and urinary hydroxyproline, a marker of bone resorption, normal thyroid and parathyroid function as well as the characteristic X-ray images led to the diagnosis of Paget’s disease. In addition, a fatty liver was diagnosed due to her hypercholesterolemia and mild liver dysfunction and the predominance of abnormal GPT in serum.
Clinical course (Fig. 4)

Etidronate at 400 mg/day was started in February 1998 to treat the patient’s Paget’s disease of bone. Several months later, all the ALP, ALP₃, and BGP values showed a tendency to decrease. Etidronate was stopped in September 1998. In February 1999, bone scintigraphy demonstrated no change in accumulation in the skull. However, the patient’s ALP and BGP levels became elevated in May 1999 and etidronate was resumed at 400 mg/day in July. The ALP and BGP values decreased without the appearance of symptoms. Four months later, administration of etidronate was stopped. The patient did not visit our clinic from February 2000 through October 2000. In November 2000, she visited our cardiology department complaining of chest pains. Electrocardiography and cardiac ultrasonography showed no abnormal findings. However, since her ALP level had elevated to 811 IU/l, etidronate at 200 mg/day was resumed. Because the second administration of etidronate at 400 mg/day in 1999 led to the development of skin eruptions, the dose was reduced to 200 mg/day in 2000. At this point, bone scintigraphy showed no remarkable changes as compared with the previous result. The drug was administered for 10 months, but the ALP levels did not decrease. In October 2001, the drug was replaced with alendronate at 5 mg/day. ALP levels decreased after several months of treatment, and her ALP and ALP isozyme 3 values became 476 IU/l and 314 IU/l, respectively, without any symptoms in July 2002.

Case 2

A 71-year-old female was referred to our clinic with high ALP levels. She had been treated for type 2 diabetes at a local clinic since 1989. In January 2000, her ALP levels increased and she was referred to our clinic. She had a past history of appendicitis at age 40 and a cataract when she was 70 years old. Her family history included her father’s diabetes and hypertension, and her elder brother’s rectal cancer.

She was 153 cm in height and 60 kg in weight. Her blood pressure was 144/80 mmHg, pulse rate was 72 beats per minutes, and body temperature was 35.4 °C. There were no abnormal findings upon the chest and abdomen and in neurological examinations.

Laboratory data

Blood cell counts were normal. Blood chemistry revealed high values of ALP (958 IU/l). In terms of ALP subtypes, ALP₃ accounted for 100%, indicating a high value of bone-derived ALP. None of her other blood chemistry including other biliary tract enzymes such as γ-GTP and LAP were abnormal.

Endocrinological data

Serum Ca and P levels were normal. Intact PTH (15 pg/ml) and 1,25(OH)₂D₃ (60 pg/ml) were also normal. The BGP level was within the normal range at 4.1 ng/ml (normal, 3.1–12.7), while her urinary hydroxyproline value was slightly elevated at 334 μmol/day (normal, 83–330). Thyroid hormone levels were at normal values.

Radiologic findings

Because the ALP isozyme 3 value accounted for 958 IU/l and markers of bone formation and resorption were elevated, bone lesions were suspected and bone scintigraphy was performed (Fig. 5). Heavy accumulation was observed on the right iliac bone, the ischial bone, and the pubic bone in bone scintigraphy, and pelvic X-ray showed bone consolidation at these sites.

Taken together, the elevated levels of bone-type ALP (ALP isozyme 3) and urinary hydroxyproline, a

Fig. 5. Bone scintigraphy before treatment showing increased uptake in the pelvis and spine.
marker of bone resorption, normal thyroid and parathyroid function, and the characteristic X-ray image led to the diagnosis of Paget’s disease.

**Clinical course (Fig. 6)**

Etidronate at 200 mg/day was started in March 2000 for Paget’s disease of bone. About four weeks later urinary hydroxyproline levels tended to decrease, and at eight weeks they were reduced to about 50% of the initial levels. ALP and ALP$_3$ values also tended to decrease gradually. In October 2000, the ALP levels had decreased to 357 IU/l, and the etidronate administration was stopped in November 2000. In December, bone scintigraphy demonstrated no change in accumulation as compared with the last result. In February 2001, ALP isozyme 3 was decreased to normal level (108 IU/l) and urinary hydroxyproline decreased to 46 µmol/day. However, rectal cancer with liver metastasis was newly diagnosed in April 2001. At that time, bone scintigraphy demonstrated an improved accumulation on the pelvis. Her ALP level was 278 IU/l which was normal, and she was transferred to the department of surgery for the treatment of her rectal cancer. When she died of rectal cancer in 2001, her ALP levels kept within the normal range and x-ray examinations showed no further deterioration of the systemic bone. So we assumed that no progression of Paget’s disease of bone had occurred in the patient.

**Discussion**

Paget’s disease is prevalent in European countries. For instance, the disease is observed in 5% of those aged 50 or older in the UK. On the other hand, it is a rare disease for Africans and Asians, and it is estimated that the number of patients in Japan is less than 200 [3, 5]. According to the latest reports, a genetic predisposition to Paget’s disease has been reported and up to 14% of patients have a family history of the disease [12].

Excessive bone resorption occurs first, followed by the secondary excessive bone formation. Although the etiology has not been identified, late-onset paramyxovirus infection in addition to genetic factors is suspected to trigger the onset of the disease [3, 4, 6, 12].

X-ray images of Paget’s disease of bone were classified as: stage I, predominant osteolytic change; stage II, a combination of osteolytic change and bone con-
which would occur if one were to wear a hat too small to cause a headache, which has been likened to that of skull thickening, compressed vessels and nerves may only 5% of the disease are symptomatic. In cases with causes of the presence of marked bone consolidation. In the present cases, no other members of the families had the disease, and the skull and the pelvic bone were affected in a monostotic way, respectively. Case 1 was considered as being at stage II due to the cotton-wool appearance and Case 2, at stage III because of the presence of marked bone consolidation.

Most of Paget’s disease cases are asymptomatic and only 5% of the disease are symptomatic. In cases with skull thickening, compressed vessels and nerves may cause a headache, which has been likened to that which would occur if one were to wear a hat too small for the head, difficulty in hearing, and symptoms based on the ischemia of verteobasilar arteries. Loss of auditory acuity occurs in approximately 50% of patients with skull involvement [3, 13]. Bone sarcoma occurs in a maximum of 1% of the patients and the rate increases in the long-term follow-up [5, 14]. In Case 1, although the skull thickening was remarkable, no other symptoms than a large head had developed at five years after diagnosed, and in Case 2 there were no symptoms at all.

In terms of bone metabolism markers which are considered to be good indicators for diagnosis and treatment of Paget’s disease, elevated levels of total serum ALP, bone-specific ALP, and osteocalcin (BGP) indicate accelerated bone formation, although BGP is not closely associated with the disease activity [1]. The reasons for these observations are still unknown. The lack of correlation between serum BGP and ALP levels may be attributable to the expression of these markers at different stages of osteoblast development [1]. BGP, produced by osteoblasts or released during degradation of bone matrix by osteoclasts, may indicate either the formation of the bone when resorption and formation are coupled, or the turnover of the bone when they are uncoupled. The total alkaline phosphatase in serum is also a sensitive marker of Paget’s disease and is usually utilized for therapeutic monitoring of Paget’s disease because of cost effectiveness [17]. Bone resorption can be indicated by increased urinary hydroxyproline (urinary HOP) or type I collagen cross-linked N-telopeptide (NTx). Since urinary HOP is greatly influenced by food intake, it is often difficult to correctly measure the level without fasting. NTx is reliable because it is only slightly influenced by food intake. It is necessary to adopt suitable metabolism markers to match the disease stage. The decrease of bone resorption markers in serum occurs within the first few days after starting bisphosphonate therapy, while the decrease in bone formation markers occurs a few weeks later [7]. The effect of bisphosphonate for bone formation appears a little behind the effect for bone resorption [4]. This indicates that bone resorption markers can be better than bone formation markers for judging the early response the bone to short term treatments with bisphosphonates [16]. In this study, the total ALP values were considered as a marker for the disease activity and its recurrence, while NTx and urinary HOP were used to judge the early response to the drugs.

Numerous clinical studies have proven the effectiveness of bisphosphonate for Paget’s disease [8, 9, 10]. Bisphosphonates are now available and the first choice drugs for the treatment of Paget’s disease. After the development of the first-generation bisphosphonate (etidronate), the second- and third-generation bisphosphonates (tiludronate, pamidronate, alendronate and resedronate) were developed. However, medical insurance in Japan covers only treatment with etidronate for Paget’s disease. It has been reported that etidronate given orally at 5 mg/kg was effective in more than 80% cases studied [21]. The amount of bisphosphonate required increases as the disease activity gets higher, and when resistance to the bisphosphonate appears, it is necessary to increase the dosage or to replace it with a stronger bisphosphonate. In Case 2, the administration of etidronate at 200 mg/day seemed to improve both metabolic markers and bone scintigraphy findings, but this limited short-term observation was not enough to predict any further effects.

Alendronate can be given orally and intravenously. Oral administration is solely available for the treatment of Paget’s disease in the United States, Australia
and Canada. The standard way of alendronate administration recommended by the manufacturer is 40 mg/day for six months [19]. On this regimen, alendronate decreased serum ALP values by about 79% (vs. 44% on etidronate at 400 mg/day) and urinary deoxypyridinoline by 75% (vs. 51% on etidronate at 400 mg/day). The response rates at 18 and 30 months have been reported to be 82% and 66%, respectively. Alendronate appears to be a highly effective treatment for Paget’s disease of bone and offers an important therapeutic advance over etidronate [15, 20].

In a comparative study of the effects of two oral doses of alendronate (20 mg/day for 6 months vs. 40 mg/day for 6 months) in the treatment of Paget’s disease [22], the decrease in serum ALP was significantly more pronounced in the patients treated with 40 mg (50 ± 10% of initial value) than in those with 20 mg (76 ± 9%). The changes in serum ALP usually attained the bottom at the 4th month after the initiation of treatment. It has been reported that a dose of 20 mg/day of alendronate is insufficient and cannot be compensated by a longer duration of the treatment. In this study, since the total ALP values did not decrease, intermittent etidronate administration was replaced with alendronate. As the administration of alendronate for Paget’s disease of bone is not covered by medical insurance in Japan, the administration of 5 mg of alendronate, a recommended dosage for osteoporosis, was continued in this case, making the levels of total ALP and urinary HOP decrease.

In Japan, Paget’s disease of bone which had been resistant to the treatment with etidronate was reported to be successfully treated with an intravenous administration of 10 mg of alendronate [18]. The oral administration of alendronate at 5 mg/day turned out to be effective as shown here, which is supposed to be the first case in our knowledge hence worth of reporting.

Actually, in case 1, ALP fell to 58% of pretreatment values and the urinary HOP reduced to 65% of the initial levels at the 7th month after the initiation of treatment with the oral administration of alendronate of 5 mg/day, although they did not fall into the normal ranges.

Since the suppression of biochemical indices of bone turnover is associated with the duration of remission, the purpose of the treatment with bisphosphonate is to reduce of the biochemical indices to the normal range [4]. In this context, the oral administration of alendronate at 5 mg/day may be insufficient in case 1. However, because none of the side effects of alendronate occurred, the oral administration of 5 mg/day has been continued. It is not obvious at this moment whether the bone metabolic markers will fall further or re-elevate in future. When a bone metabolism marker re-elevates in future, a higher dose of the drug should be considered.

References


