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Süleyman BALDANE[1]
Süleyman H. İPEKÇİ[1]
Serap BULUT[2]
Emine GÜL BALDANE[3]
Gonca KARA GEDİK[4]
Levent KEBAPCILAR[1]

Case Report

A CASE OF PAGET'S DISEASE OF THE BONE PRESENTED WITH HEARING LOSS AS THE FIRST SYMPTOM

Abstract

A 67-year-old woman presented to the audiology clinic with a complaint of bilateral hearing loss over the past two years. Routine biochemical screening showed an alkaline phosphatase level of 381 U/L, and she was referred to our endocrinology unit. Her vitamin D and parathyroid hormone levels, as well as thyroid, liver and kidney function test results, were within normal ranges. Cranial x-ray radiography showed an increase in the diploe distance and a sclerotic pattern in the calvarium; while whole body bone scintigraphy demonstrated a diffuse increase in radioactive substance involvement of the calvarium. Serum osteocalcin and spot urinary deoxypyridinoline levels were increased. The patient was diagnosed with Paget's disease with hearing loss as the first symptom, and she was started taking zoledronic acid treatment. Three months later, her alkaline phosphatase level had returned to the normal range, and audiologic examination showed a mild improvement in hearing.

Key Words: Osteitis Deformans; Hearing Loss.

Olgu Sunumu

İLK YAKINMASI İŞİTME KAYBI OLAN HASTADA KEMİĞİN PAGET HASTALIĞI TANISI

Öz

Altmış yedi yaşında kadın hasta, her iki kulakta işitme kaybı nedeniyle odyoloji polikliniğine başvurdu. İki yıldır şikayeti olan hastanın rutin serum biyokimya incelemesinde alkalen fosfataz değerinin 381 U/L olması üzerine endokrinoloji ünitemize yönlendirildi. Hastanın vitamin D, parathormon, tiroid fonksiyon testleri, karaciğer fonksiyon testleri, böbrek fonksiyon testleri normal sınırlar içindeydi. Hastanın kranial grafisinde; diploe mesafesinde artış, kalvaryumda sklerotik görünüm ve tüm vücut kemik sintigrafisinde; kalvaryumda diffüz tarzda artmış radyoaktif madde tutulumu izlendi. Serum osteokalsin ve spot idrarda deoksipridinolin düzeyleri yüksek saptandı. İşitme kaybının ilk semptom olarak görüldüğü hastaya mevcut bulgular ile kemiğin paget hastalığı tanısı ile zolendronik asit tedavisi verildi. Tedaviden üç ay sonraki kontrolünde, alkalen fosfataz değerinde normal düzeye gerileme ve odyolojik incelemede hafif düzeyde bir düzelme izlendi.

Anahtar Sözcükler: Kemiğin Paget Hastalığı; İşitme Kaybı.

İletişim ***(Correspondance)***

Süleyman Baldane
Selçuk Üniversitesi Tıp Fakültesi Endokrinoloji ve Metabolizma Bilim Dalı KONYA

Tlf: 033244685
e-posta: baldane42@hotmail.com

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[1] 1Selçuk Üniversitesi Tıp Fakültesi Endokrinoloji ve Metabolizma Bilim Dalı KONYA
[2] Selçuk Üniversitesi Tıp Fakültesi, Kulak Burun Boğaz Hastalıkları Anabilim Dalı KONYA
[3] Konya Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, KONYA
[4] Selçuk Üniversitesi Tıp Fakültesi , Nükleer Tıp Anabilim Dalı KONYA

Introduction

Paget's disease is a chronic progressive metabolic bone disease characterized by increased focal bone turnover, along with an interchange of normal bone structure with disorganized bone tissue (1). The etiology of Paget's disease is not well understood, although environmental factors, paramyxovirus infection, and several genetic factors are thought to be involved (1-3). The axial skeleton is primarily affected but involvement of other regions has been reported, including the pelvis (70%), femur (55%), lumbar vertebrae (53%), skull (42%) and tibia (32%) (1).

The most prominent symptom of Paget's disease involving the skull is hearing loss, which is encountered in approximately half of the patients (1). Hearing loss may be conductive, sensorineural or mixed-type, although its mechanisms have not been determined. In addition to being widespread, hearing loss is an early symptom of Paget's disease, making it useful for early diagnosis (4).

Case

A 67-year-old woman presented to the audiology clinic with bilateral hearing loss. Routine biochemical screening revealed an alkaline phosphatase (ALP) concentration of 381 U/L (normal limits: 40-150 U/L), and she was referred to our endocrinology unit. Systemic investigation revealed no other complaints than hearing loss. A detailed medical history revealed that the patient had experienced hearing loss for approximately two years. On previous hospital visits, she was told that the hearing loss was due to age and that she needed to use a hearing aid.

Physical examination revealed no pathologic findings. Apart from her high ALP levels, the patient's vitamin D and parathyroid hormone (PTH) levels, as well as thyroid, liver, and kidney function test results, were within normal limits (Table 1). ALP isoenzyme electrophoresis showed her rate of bone ALP was 95% (normal limits:23-75%). The patient's cranial x-ray radiography demonstrated an increase in diploe distance and a sclerotic pattern in the calvarium (Figure 1). Whole-body bone scintigraphy following administration of 20 mCi teknetium-99m methylene diphosphonate (Tc-99m MDP) demonstrated a diffuse increase in radioactive substance involvement of the calvarium (Figure 2). Her serum osteocalcin concentration was 110.5 ng/mL (normal limits: 15-45 ng/mL) and her spot urinary deoxypyridinoline (DPD) level was 29.3 nM/mM creatine (normal limits: 5-20 nM/mM creatine).

Table 1— Laboratory Test Results.

Parameter	Result	Normal Range
Alkaline phosphatase (ALP) (U/L)	381	40-150
Bone ALP (%)	95 (361 U/L)	23-75
Parathyroid hormone (PTH) (pg/mL)	45	12-65
25(OH) Vitamin D (ng/mL)	32	30-150
Thyroid stimulating hormone (μU/L)	2.59	0.56-5.57
Uric acid (mg/dL)	3,5	2.6-6.0
Aspartate aminotransferase (U/L)	16	5-34
Alanine aminotransferase (U/L)	9	0-55
Gamma-glutamyl transferase (U/L)	11	9-36
Direct bilirubin (mg/dL)	0.1	0-0.5
Total bilirubin (mg/dL)	0.3	0.2-1.2
Urea (mg/dL)	34	21-43
Creatinine (mg/dL)	0.6	0.4-1
Hemoglobin (g/dL)	13.2	12.3-15.3
Erythrocyte sedimentation rate (mm/hour)	12	0-20

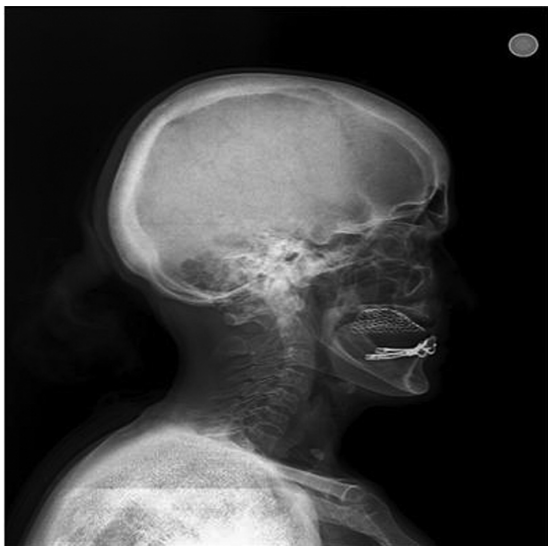

Figure 1— Increased diploe distance and a sclerotic image in the calvarium from the lateral cranial x-ray radiography.

Hearing loss was evaluated by high resolution computed tomography (HRCT) imaging of the temporal bone and audiological analysis. HRCT showed bilateral external auditory canals, middle ear and mastoid air cells and a cochlear structure; the ossicular chain was intact (Figure 3). Audiological

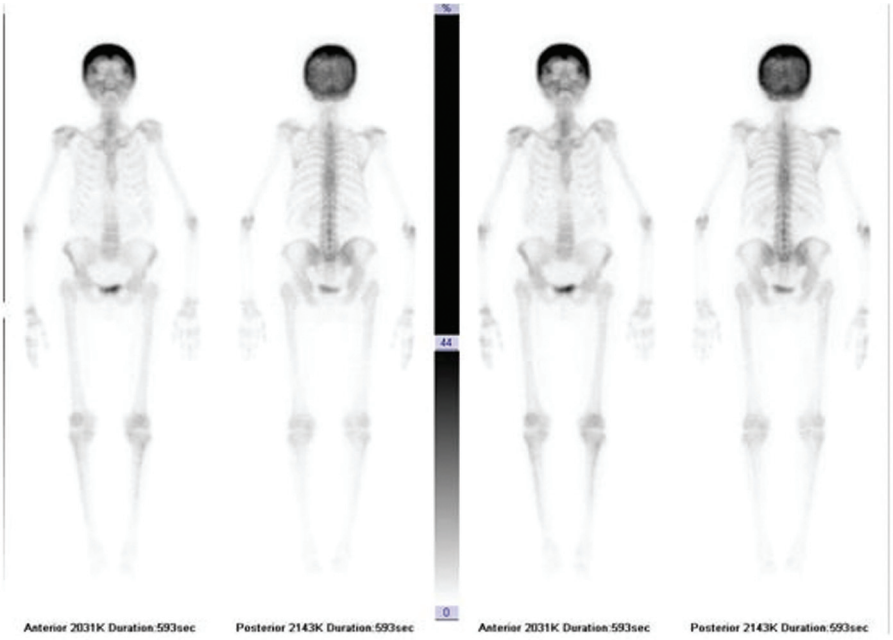

Figure 2— Diffused increase in radioactive substance involvement of the calvarium upon whole-body Tc-99m MDP bone scintigraphy.

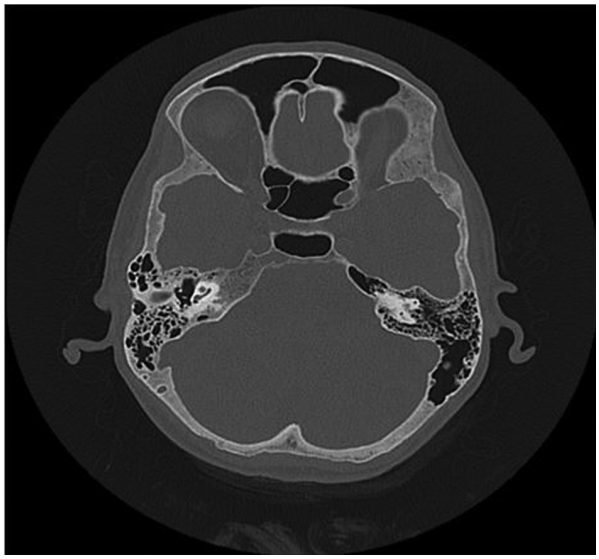

Figure 3— Temporal bone HRCT image: Intact ossicular chain, normal cochlear structure.

examination at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz revealed moderate (35 decibel) bilateral sensorineural hearing loss. A bilateral type-A tympanogram was obtained. Acoustic reflexes could be obtained in both ears, with no associated tinnitus or vestibular dysfunction.

The patient was diagnosed with Paget's disease with hearing loss as a first symptom. She was started on treatment with zoledronic acid (5 mg single dose, intravenous). At a three month follow-up visit, her ALP level (109 U/L) had returned to within the normal range, her serum osteocalcin concentration was 32 ng/mL, and her spot urinary DPD value was 12.2 nM/mM creatine. Audiologic examination showed a mild improvement in hearing, of about 5-decibels.

Discussion

Paget's disease is the second most commonly encountered metabolic bone disease after osteoporosis. Its incidence increases with age, affecting about 1-2% of older white men (>55 years). The prevalence of the disease varies with ethnicity and geographic location. Although relatively common in the United Kingdom, the United States of America and New Zealand, few cases have been reported in the Scandinavian countries, in Asia and on the Indian subcontinent (1).

Genetic predisposition may be the most important factor in disease etiology, with about 15% of patients having a family history of disease. Paget's disease demonstrates an autosomal dominant inheritance in most families, with increased penetrance during the sixth and seventh decades of life (2).

The most important genetic alterations associated with the development of Paget's disease are mutations in the Sequestosome 1 (SQSTM1) gene, which has been reported in both familial and sporadic cases of Paget's disease (3).

Most patients with Paget's disease are asymptomatic and may remain asymptomatic throughout their lifetimes. Some patients are incidentally diagnosed when assessed for other health conditions, by, for example, the discovery of an increased serum ALP or abnormal radiography findings. In contrast, many other patients may remain asymptomatic for many years, delaying the diagnosis of the disease. The average time from the appearance of first symptoms to diagnosis has been reported to range from four to nine years (5).

Large population studies have demonstrated that Paget's disease is associated with back pain, osteoarthritis, hip arthroplasty, knee arthroplasty, fracture(s), and an increased risk of hearing loss (6). Since some of these symptoms, such as back pain, osteoarthritis, and hearing loss are frequently observed in older individuals, Paget's disease may be overlooked. Our patient was not diagnosed with Paget's disease until two years after her first complaints of hearing loss and after several visits to other hospitals. A proper diagnosis of Paget's disease was delayed in this patient, because her hearing loss was associated with older age.

About 30% of patients with Paget's disease are symptomatic, with bone pain the most common complaint. Pain typically occurs at rest and increases at night. Other common complaints due to complications of this disease include pain associated with secondary osteoarthritis, pathologic fractures, bone deformities and hearing loss. Less frequently reported complications include hypercalcemia (together with immobilization), heart failure, osteosarcoma, and paraplegia (1).

Hearing loss has been reported in approximately half of Paget's disease patients with skull involvement (1). Hearing loss may appear as conductive, sensorineural or mixed-type, with mixed-type bilateral hearing loss most frequently associated with Paget's disease. Hearing loss is accompanied by vertigo in 25% of patients and by tinnitus in 20% (4). Although several abnormalities of the external, middle and inner ear have been described in patients with hearing loss, the mechanism of hearing loss is not well understood, and its cause cannot be described in most patients (7). The bilateral sensorineural hearing loss in patient was not accompanied by any pathological finding in the HRCT of the temporal bone.

Bone pain is the most frequent indication for treatment of patients with Paget's disease, with other indications including hearing loss, spinal cord compression, skull involvement and hypercalcemia. Bisphosphonate therapy, the treatment of choice, rapidly inhibits the process of Paget's disease development and maintains long-term disease control. Bisphosphonates have been found to reduce bone turnover and improve histology, suggesting that these agents may prevent the complications of the Paget's disease (5).

Bisphosphonate therapy has been reported to induce rapid regression of symptoms in patients with spinal stenosis associated with Paget's involvement. Bisphosphonates, however, are expected to have little effect on complications such as hearing loss (7). Improvements in hearing and decreased progression of hearing loss have previously been reported in patients treated with bisphosphonates, both in case reports and retrospective studies. However, a recent prospective non-controlled study found that bisphosphonate treatments did not significantly improve hearing loss (8).

The oral bisphosphonates alendronate and risedronate, and the intravenous agents, pamidronate and zoledronate, were recently approved for the treatment of Paget's disease. The use of oral bisphosphonates is very limited, due to low response rates to treatment, the absence of sustained remission and the frequently encountered gastrointestinal side effects. Zoledronic acid is the treatment of choice due its early reduction of bone turnover, a sustained response for up to 24 months, and lower rates of gastrointestinal side effects (9). Intravenous zoledronic acid (5 mg single dose) was deemed preferable in our patient due to her two-year history of the disease. Although an auditory test after 3 months showed mild improvement in hearing, the difference was not statistically significant.

In conclusion, most patients with Paget's disease are diagnosed late in the course of disease, after many years of asymptomatic disease. Paget's disease should be considered in patients presenting with hearing loss as the solitary symptom, without other symptoms such as bone pain, bone deformity and pathologic fractures. Paget's disease should be suspected in older patients who present with hearing loss. ALP analysis and CT scanning of the skull may contribute to the early diagnosis of Paget's disease. Furthermore, bisphosphonate treatment may result in improved hearing loss in patients with Paget's disease.

Conflict of Interest

The authors declare that they have no conflict of interests.

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