Tumor-associated Hypercalcemia in a Patient with Paget's Disease

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Paget's disease of the bone, which is characterized by a focal region of highly exaggerated bone remodeling, is very rare in Asia. Most patients with Paget's disease are asymptomatic; they are normocalcemic and show elevated alkaline phosphatase levels. Hypercalcemia in patients with Paget's disease has rarely been reported. We report one Chinese patient with Paget's disease involving the maxilla bone with an initial presentation of facial cellulitis. Asymptomatic hypercalcemia with a low-normal intact parathyroid hormone level developed 9 years later. After clodronate treatment, the level of alkaline phosphatase normalized, but the hypercalcemia did not respond adequately. After analysis of tumor markers and imaging studies, a clinical diagnosis of pancreatic adenocarcinoma with multiple hepatic and lung metastases with pleural effusion was made. We suggest that malignancy-associated hypercalcemia should be considered as one of the causes of hypercalcemia in patients with Paget's disease.

Key Words: hypercalcemia, Paget's disease
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Paget's disease of the bone (osteitis deformans) was first described by Sir James Paget in 1877. It occurs in three phases of the bone forming process. The initial phase of Paget's disease of the bone is characterized by excessive osteoclastic activity and bone resorption in a focal region. This phase is followed by an osteolytic–osteoblastic phase, during which osteoblasts rapidly deposit new bone in a chaotic fashion. In the final phase, the lesions become sclerotic, disorganized and weaker than normal bone [1].

Aside from osteoporosis, Paget's disease is the most common bone disorder in Western countries [2]. The incidence of this disease varies among different ethnicities and areas. In Britain, the overall prevalence was 5% between 1970 and 1977 [3], and declined to 2% between 1993 and 1995 [4]. In Australia, the prevalence in people aged over 55 years was 4% [5]. In Italy, the prevalence is at least 1%, without a trend for a decreasing prevalence [6]. In the Netherlands, the estimated overall prevalence is 3.6% [7]. In the United States, the overall prevalence is 0.71% [8]. However, Paget's disease of the bone is very rare in Africa and Asia.

The majority of patients with Paget's disease are elderly, with an age at diagnosis of usually more than 50 years. It affects both men and women, with a slight predominance in males. Paget's disease most commonly involves the axial skeleton, but it may affect any of the bones. Although most patients with Paget's disease are asymptomatic, 10–30% of patients experience bone pain, skeletal deformities, neurologic symptoms, pathologic fracture, or deafness. Patients may have only one affected bone or have lesions in multiple bones; however, new lesions rarely develop in previously unaffected bones after diagnosis [9]. The most terrible complication of Paget's disease is development of osteosarcoma, with an incidence of about 1%. In addition, Paget's disease may be associated with an increased incidence of primary hyperparathyroidism [10].

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Case Presentation

A 59-year-old female suffered from general weakness in December 1988 and came to our hospital for help. Only elevated levels of alkaline phosphatase (Alk-P) (715 U/L; normal range, 30–110 U/L) were found at that time. Liver function tests and levels of calcium (Ca) and phosphate were within the normal ranges. She was followed-up for 3 years without a definite etiologic diagnosis for the elevated level of Alk-P, and lost to follow-up thereafter.

In June 1995, right facial cellulitis occurred. Skull X-rays showed multiple focal radio-opaque nodular shadows at the maxillary bone and skull bone. Alk-P level was 578 U/L. Complete body bone scan was performed with Tc-99m MDP, which showed intense radioactivity in the skull. Surgical intervention was performed and a biopsy of the right maxilla alveolar bone revealed Paget's disease with local fibrous dysplasia. As diabetes mellitus was also diagnosed, she was referred to our clinic for further treatment.

In May 1998, left facial cellulitis was noted after a dental procedure. Surgical intervention was performed and a biopsy of the left maxilla revealed Paget's disease with focal fibrous dysplasia. The level of Ca was 2.5 mmol/L (normal range, 2.1–2.6 mmol/L) and Alk-P was 818 U/L.

Alk-P levels had fluctuated since 1995, with the highest being 818 U/L in May 1998 and the lowest being 321 U/L in January 2005 (Figure 1). Despite the elevated Alk-P levels, the patient was symptom-free. Ca levels were within the normal range until January 2005, when a high Ca level of 2.9 mmol/L with a low-normal intact parathyroid hormone (iPTH) level of 1.5 pmol/L (normal range, 0.8–7.4 pmol/L) were noted. No evidence of malignancy was found by a survey of hypercalcemia. Clodronate 400 mg twice daily was given for the progressive asymptomatic hypercalcemia. With clodronate therapy, Alk-P levels gradually dropped to 150 U/L, but the level of Ca fluctuated between 2.5 and 2.9 mmol/L.

Progressive body weight loss and watery diarrhea developed in March 2006. Abdominal computed tomography revealed a pancreatic tumor with multiple hepatic tumors (Figure 2). Carcinoembryonic antigen level was 30.51 ng/mL (normal, < 3.5 ng/mL) and the level of CA199 was 6,957 U/mL (normal, < 34 U/mL). A Tc-99m MDP whole body bone scan showed no bony metastasis. Pancreatic cancer with multiple hepatic metastases was impressed. Biopsies for pancreatic and hepatic tumors were suggested, but the family requested hospice care and refused invasive procedures. Multiple lung metastases with pleural effusion developed subsequently. Cytology of the pleural effusion showed adenocarcinoma.

Discussion

Although it is a common disease in Western countries, Paget's disease of the bone is very rare in Chinese populations. Wang et al reviewed nine Chinese individuals

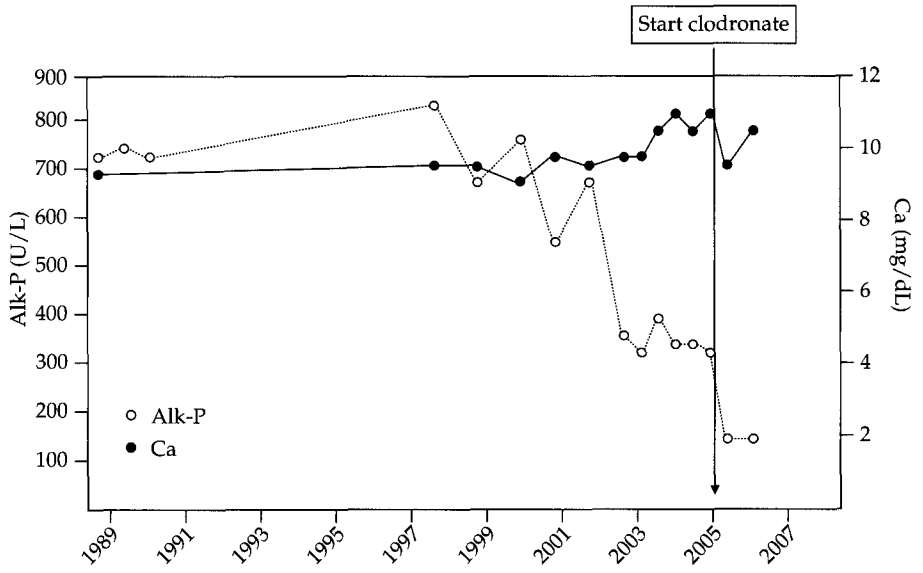

Figure 1. *Relationship between time and levels of alkaline phosphatase (Alk-P) and calcium (Ca).*

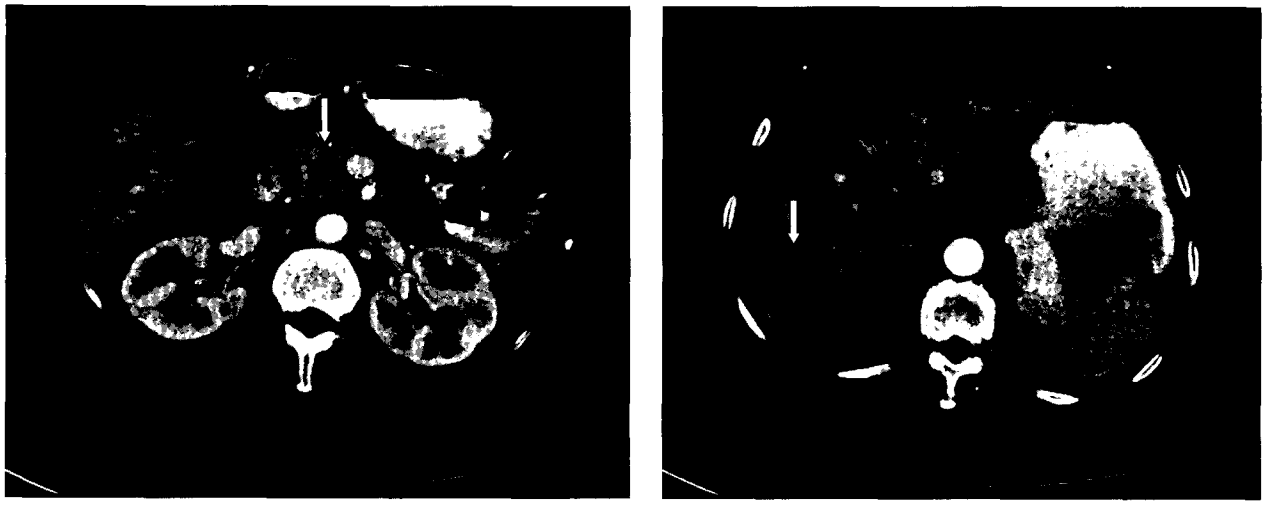

Figure 2. *Abdominal computed tomography with contrast reveals: (A) pancreatic body and tail tumor, 7 cm in size, with (B) multiple hepatic tumors measuring up to 3.5 cm.*

with Paget's disease of the bone reported in the English literature [11]. Compared with Western cases, the Chinese individuals had no familial cases, no malignant transformation, more frequent monostotic involvement (44% *vs.* 17–31%), more frequent skull involvement (44% *vs.* 19%), and a higher frequency of symptomatic cases (78% *vs.* 5–23%). The present case was reported because of the unusual initial presentation of facial cellulitis [12].

The relationship between Paget's disease and the onset of hypercalcemia has rarely been delineated in the literature. Hypercalcemia in Paget's disease is rare, occurring primarily with active, polyostotic disease and immobilization or dehydration [13]. However, an increased prevalence of primary hyperparathyroidism was found [10]. The overall prevalence range of primary hyperparathyroidism in Paget's disease is 2.2–6.0%, with a mean of 4.4% [14]. No Chinese individual with both Paget's disease and primary hyperparathyroidism has previously been reported. In the report of 11 cases of concurrent Paget's disease and primary hyperparathyroidism without surgery, the levels of iPTH varied within a wide range from 5.6 to 596 pmol/L, and the corrected plasma Ca levels were between 2.65 and 3.19 mmol/L [14]. Of 19 surgical cases of Paget's with primary hyperparathyroidism, the levels of iPTH ranged from 2.9 to more than 500 pmol/L, and the corrected plasma Ca levels ranged from 2.57 to 3.72 mmol/L [14]. The range of iPTH levels varied widely, even in the high-normal range, in patients with Paget's disease and primary hyperparathyroidism.

Our patient was active in her daily activities at the initial presence of hypercalcemia (when Ca level was 2.9 mmol/L and iPTH level was 1.49 pmol/L) and remained ambulatory during most of the follow-up period. Hypercalcemia in this case was not attributed to immobilization. The levels of Alk-P kept decreasing in the presence of hypercalcemia. As the levels of Alk-P reflected the disease activity of Paget's disease of the bone, the hypercalcemia in this case was apparently not related to Paget's disease of the bone. The low-normal value of iPTH and Alk-P levels were not compatible with the possibility of primary hyperparathyroidism. As no etiology was identified, only treatment for hypercalcemia was given. After follow-up for 14 months, symptoms of progressive body weight loss and watery diarrhea appeared, and a pancreatic tumor with multiple hepatic tumors was found. Finally, we considered that the etiology was tumor-associated hypercalcemia.

Patients with longstanding Paget's disease should be followed-up indefinitely because of the increased risk of malignant transformation. A tumor can arise in pagetic bone and may present with soft tissue swelling, increased pain or a rapidly increasing Alk-P. Although malignant transformation was not found in the reported Chinese individuals, the follow-up durations were mostly not available, and the longest one reported was 16 months [11]. After a period of 10 years of follow-up in the present case, malignancy-associated hypercalcemia, rather than malignant transformation of bone lesion, developed. Because of the patient's condition

and the family's request, no pathologic tissue was obtained to confirm the etiologic diagnosis. From the analysis of tumor markers and imaging studies, all attending physicians and consultants reached an agreement in the clinical diagnosis of pancreatic adenocarcinoma with multiple hepatic and lung metastases with pleural effusion. Although parathyroid hormone-related peptide was not checked in the present case, we considered that malignancy-associated hypercalcemia was the etiology of the hypercalcemia based on the low-normal value of iPTH and the above-mentioned differential diagnosis.

In conclusion, although Paget's disease of the bone may be associated with an increased incidence of primary hyperparathyroidism, the appearance of hypercalcemia in patients with Paget's disease without high disease activity warrants careful evaluation for the possibility of malignancy-associated hypercalcemia or primary hyperparathyroidism.

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Paget 氏病合併腫瘤相關之高血鈣症

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Paget 氏病的特色是骨頭局部不正常的快速吸收並增生，通常沒有症狀或是只發現異常高的鹼性磷酸酶。它在西方國家並不少見，但在亞洲及非洲則相當罕見。我們報告一位七十六歲女性的 **Paget** 氏病人以臉部蜂窩性組織炎表現，在九年長期追蹤後發生無症狀的高血鈣症，副甲狀腺素濃度並不高，鹼性磷酸酶濃度顯示疾病活性也不高，其他並無明顯造成高血鈣的原因。使用雙磷酸鹽治療後，鹼性磷酸酶濃度恢復正常，但無症狀之高血鈣症持續。經腫瘤指標及影像學檢查，臨床診斷發現胰臟腫瘤併多發性肝臟與肺臟轉移。**Paget** 氏病合併高血鈣症應考慮惡性腫瘤的可能性。

關鍵詞：高血鈣症，**Paget** 氏病

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