Diagnosis of a Maxillary Brown Tumor Associated with Hyperparathyroidism Secondary to Chronic Renal Failure – a Case Report

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Summary: Brown tumor associated with hyperparathyroidism secondary to chronic renal failure has been increasingly documented of late. This intraosseous giant cell lesion is indistinguishable from a central giant cell granuloma and is considered as an unusual local complication of renal osteodystrophy. This report presents a case of a maxillary brown tumor in an uremic, non-hemodialysis patient with secondary hyperparathyroidism. The radiographic, biochemical, and histopathological examinations are reported and the possible pathogenesis is also discussed.

Key words: brown tumor, secondary hyperparathyroidism, chronic renal failure

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Brown tumors represent non-neoplastic, giant cell lesions that are histopathologically indistinguishable from giant cell granulomas, and are the result of a bone remodeling process during hyperparathyroidism (HPT). Although these lesions are not uncommon in cases of primary hyperparathyroidism (PHPT), there are also some examples associated with HPT and osteitis fibrosa secondary to renal failure.

Brown tumors are more commonly seen in hemodialysis patients and can be found in any bones such as ribs, clavicles, and pelvis (Som et al, 1983; Weiss et al, 1980). The mandible is frequently affected whereas maxillary involvement is rare (Guney et al, 2001; Morrone et al, 2001; Keyser and Postma, 1996).

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Renal osteodystrophy refers to the skeletal changes resulting from chronic renal disease and is caused by disorders in calcium and phosphorus metabolism, abnormal vitamin D metabolism and increased parathyroid activity (Cohen, 1994; Malluche and Faugere, 1990).

The role of parathormone (PTH) is to control calcium and phosphorus levels in plasma and in extracellular fluid, and this is potentially achieved by modulating the balance between osteoblastic and osteoclastic activities. PHPT results from overproduction of HPT, most commonly caused by adenomas, primary hyperplasia or rarely carcinoma. Secondary hyperparathyroidism (SHPT) results from compensatory hyperplasia, usually of all four glands, most commonly seen in renal insufficiency. Calcium malabsorption and forms of osteomalacia may also rarely lead to SHPT (Malluche and Faugere, 1990; Goshen et al, 2000).

A well-documented case of maxillary brown tumor in a patient with HPT secondary to chronic renal failure, without hemodialysis, is described in our report, and the pathogenic mechanism is also analyzed.

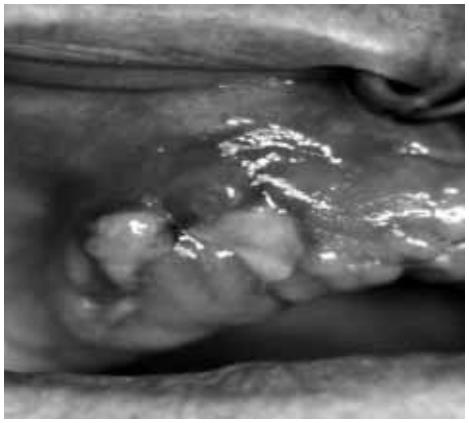

Fig 1 Solid, reddish mass on the labial part of the alveolar ridge of the right maxilla, corresponding to the location of 12–15 teeth, covered by ulcerative mucosa.

CASE REPORT

A 57-year-old man was referred to the Department of Oral Medicine and Maxillofacial Pathology at the Dental School of Aristotle University of Thessaloniki, Greece. The man complained of a slightly painful swelling of the labial part of the edentulous alveolar ridge of the right maxilla. Over a period of two months this lesion progressively resulted in a decreased stability of his upper denture, accompanied by traumatic ulceration of the underlying mucosa. He had a 20-year history of renal dysfunction, without hemodialysis, and increased levels of blood pressure (160 – 100 mmHg).

The clinical examination revealed a 2 X 1.5 cm, solid, reddish, slightly painful mass on the labial part of the alveolar ridge of the right maxilla, corresponding to the location of 12–15 teeth, covered by ulcerative mucosa (Fig 1). No cervical lymphadenopathy or other pathologic findings were found at the physical examination.

X-ray examination demonstrated a radiolucent, multilocular, cystic lesion in the right maxilla corresponding to 12–15 teeth, containing thin osseous septa between the cystic chambers. Moderate demineralization and disturbance of the trabecular structure of both jaws was also generally observed (Fig 2).

Removal of the lesion and curettage of the bone were performed under local anesthesia. Macroscopically, the specimen consisted of an irregular, solid, oval-shaped mass, covered by a grayish-white surface with foci of hemorrhage (Fig 3).

Microscopically, the maxillary lesion consisted of osteoclast type multinucleated giant cells without strong mitotic activity, varying in both size and shape, unevenly distributed throughout a cellular fibrous stroma. The stroma contained many ovoid or spindle-shaped mononuclear cells (fibroblasts), loosely arranged, and focal areas of moderate osteoblastic metaplasia with depositions of large amounts of newly formed osteoid. There were also many dilated blood vessels, areas of hemorrhage and clusters of hemosiderin. Multinucleated giant cells were located especially besides osteoid trabeculae, adjacent to pools of blood and around the blood vessels (Figs. 4, 5).

Laboratory tests revealed: elevated levels of parathyroid hormone (PTH) 721.00 pg/ml (normal 10–55 pg/ml); serum alkaline phosphatase 328 U/L (normal 100 – 280 U/L); serum calcium 12.4 mg/dl (normal 8.1 – 10.4 mg/dl); and serum phosphorus 5.0 mg/dl (normal 2.5 – 4.5 mg/dl). Renal insufficiency was indicated, supported by: the serum tests of blood Urea nitrogen 130 mg/dl (normal: 10 – 50 mg/dl); and serum creatinine 4.4 mg/dl (normal: 0.6 – 1.0 mg/dl). Furthermore, anemia due to renal failure was also detected (RBC: 3.33 M/μl; HGB: 9.5 g/dl; HCT: 29.3%).

Based on the clinical, radiological and histopathological findings a diagnosis of central giant cell granuloma of the maxilla was suggested. Laboratory tests and medical history of renal dysfunction supported the hypothesis that this giant cell lesion was identical to a brown tumor associated with HPT secondary to chronic renal failure.

DISCUSSION

Brown tumor is a non-neoplastic lesion that only exists in the presence of HPT. It is a local bone destructive phenomenon accounting for rapid osteoclastic bone turnover due to severe HPT (Chew and Huang-Helinger, 1993). The early diagnosis of the PHPT, as a result of the extensive use of biochemical assays over the past two decades, has led to the fact that brown tumor is only a rare manifestation of PHPT (adenoma, primary hyperplasia, or carcinoma) (Mundy et al, 1980, Wang 1971). On the other hand, because of an increasing number of dialysis patients and their increased longevity, brown tumor is seen more often as a result of SHPT: ranging from 1.5% up to more than 13% of patients with chronic renal failure (Keyser and Postma 1996,

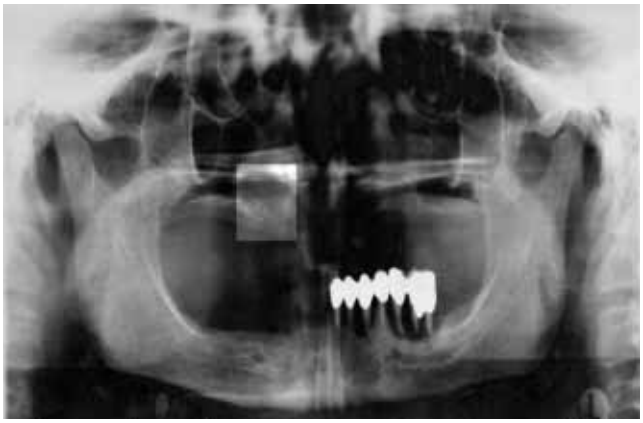

Fig 2 Radiolucent, multilocular, cystic lesion in the right maxilla containing thin osseous septa between the cystic chambers.

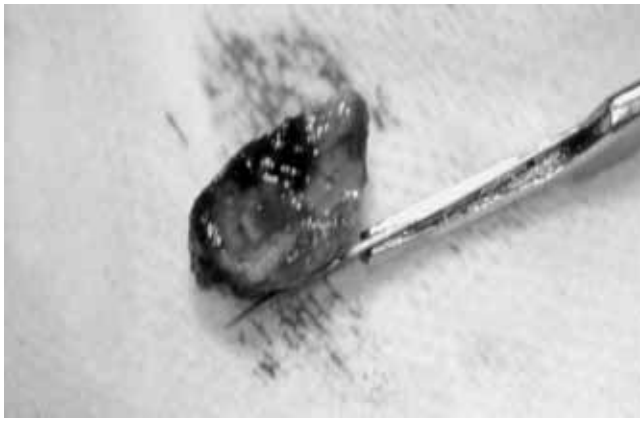

Fig 3 Irregular, solid, oval-shaped mass, covered by a grayish-white surface with foci of hemorrhage.

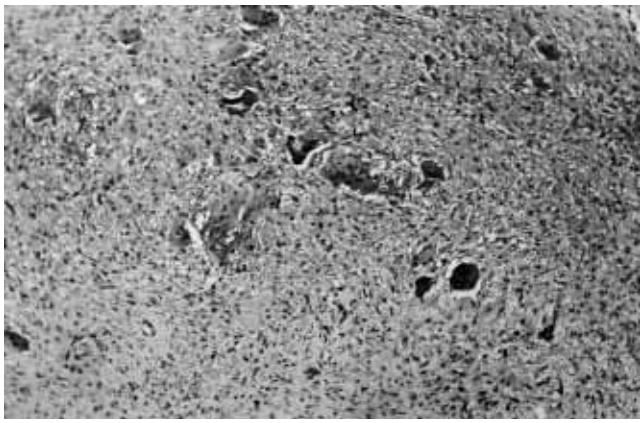

Fig 4

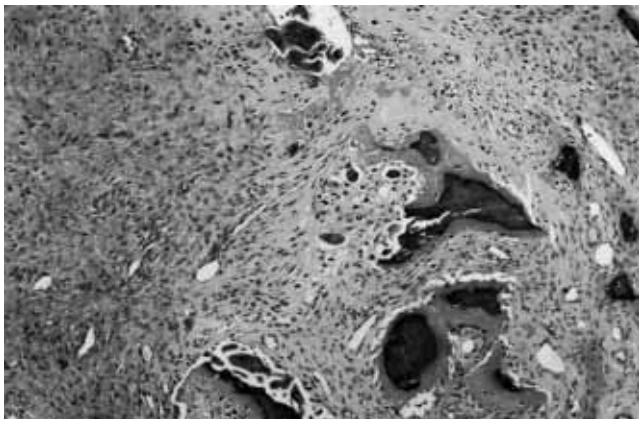

Fig 5

Figs 4 and 5 Osteoclast type multinucleated giant cells, cellular fibrous stroma containing ovoid or spindle-shaped mononuclear cells (fibroblasts), depositions of newly formed osteoid, dilated blood vessels, areas of hemorrhage and clusters of hemosiderin.

Griffiths et al, 1977). Rarely, SHPT may also occur in cases of calcium malabsorption and osteomalakia (Shang et al, 2003).

Partially as a result of phosphate accumulation, the circulated concentrations of ionized calcium and calcitriol decrease in patients with advanced renal failure (Fukagawa and Kurokawa, 1997). Furthermore, uremic toxins and phosphate may block the interaction of calcitriol-receptor complex in parathyroid cells (Hsu et al, 1994, Brown et al, 1993). Both of these abnormalities inhibit the direct suppression of PTH by calcitriol (Coburn and Llach, 1994), stimulate secretion of PTH, and perhaps lead to a progressive resistance to calcitriol resulting in SHPT (Akizawa et al, 1993).

PTH increases the urinary excretion of phosphates, decreases urine calcium excretion and augments the release of calcium from bone. This hormone modulates the balance between osteoblastic and osteoclastic activity. In cases of secondary HPT, lamellar bone is constantly resorbed while woven bone is laid down to replace it. Furthermore, soft tissue may proliferate to replace the lost bone. The most frequently observed changes involve the skeletal system and can appear before, or during treatment with hemodialysis.

These changes include: bone remodeling; osteomalacia; generalized osteoporosis; subperiosteal bone resorption of phalangeal tufts and the clavicle; absence of lamina dura around the teeth roots;

mottling of the skull, and a 'salt and pepper' radiologic appearance of the skull; erosion of the distal clavicle and margins of the symphysis pubis; rib fractures; necrosis of the femoral head; and osteitis fibrosa cystica which is osteitis with fibrous degeneration and cystic spaces (Som et al, 1983; Keyser and Postma, 1996; Cohen, 1994; Kar et al, 2001; Neville et al, 2002; Shang, 2003).

Brown tumor is considered as a localized form of fibrous cystic osteitis. A case of PTH-induced rapid bone resorption results in the replacement of normal marrow content by hemorrhage and reparative granulation tissue containing giant multinucleated cells (Chew and Huang-Hellinger, 1993; Bekeret et al, 2000; Shah et al, 1994). It is histologically identical to the central giant cell granuloma and the differential diagnosis includes other giant cell lesions such as true giant cell tumor, reparative giant cell granuloma and cherubism (Dusunsel et al, 2000; Yamazakiet al, 2003). It usually affects the clavicle, ribs, pelvis and femur (Orejas et al, 1993; Okada et al, 2000; Krause et al, 2000). The mandible is occasionally involved, and maxillary lesions have been increasingly reported in recent years (Balon, 1998; Phelps et al, 1994).

Histological findings include dilated blood vessels, hemorrhage and deposits of hemosiderin form the 'brown' appearance of this tumor. Other findings are: a combination of osteoblatic/osteoclastic activity; focal areas of osteoblastic metaplasia that result in large amounts of unmineralized osteoid in the stroma; cyst formation; great numbers of mononuclear stromal cells and multinucleated giant cells; hemosiderin-laden macrophages; and proliferating plump fibroblasts (Neville et al, 2002). Giant cells appear to be ultastructurally, similar to osteoclasts except for the ruffled cell border and mononuclear spindle cells with many cytoplasmic microfilaments having enlarged processes that enfold the giant cells (Okada 2000). As compared to the giant cell tumor, giant cells of giant cell granuloma are smaller and fewer in number, and contain fewer nuclei (Franklin et al, 1979).

Immunohistochemical studies suggested a common mesenchymal origin of many giant cells and mononuclear stromal cells based on their immunoreactivity for vimentin and lysozyme (Okada et al, 2000). Most of the giant cells showed strong immunoreactivity for CD68 and all were negative for proliferating cell nuclear antigen, a1-antitrypsin, a1-antichymotrypsin, CD34, or S-100 protein. Only a small population of mononuclear cells was positive to CD68 but most of them showed Ki67 positive staining. These results may suggest that central giant cell granulomas (and obviously brown tumors) are primarily fibroblastic granulomatous inflammatory lesions and that the multinucleated giant cells are derived from macrophages (Okada et al, 2000; O' Malley et al, 1997; Regezi et al, 1987).

Clinically, brown tumors of jaws most commonly appear as slowly growing, painful, hard, clearly visible and palpable swellings that mimic malignant lesions, which may deform the affected bone, leading to masticatory dysfunction (Tarell et al, 1996). Radiographically, they appear as oval radiolucent regions resembling cystic lesions (Cawson et al, 2001). Computer tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy can also be useful in clinical practice (Morrone et al, 2001).

In conclusion, the diagnosis of a central giant cell granuloma may alert us to a possible coexistence of systemic metabolic abnormality such as HPT and/or chronic renal failure. Also, because of the moderate frequency rates of asymptomatic brown tumors, and the high incidence of HPT secondary to renal insufficiency (Massry, 1978), the diagnosis of brown tumor should be always suspected in uremic patients on the basis of laboratory findings such as intact PTH and alkaline phosphatase.

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