Synchronous Paget disease of bone and hyperparathyroidism: report of a case with extensive craniofacial involvement

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Paget disease of bone (PDB) and hyperparathyroidism (HPT) are metabolic osseous disorders which affect ≥2% of the population. As these diseases may share clinical, radiographic, biochemical, and histopathologic features, knowledge of their phenotypic overlap may provide diagnostic utility and improve clinical outcome. Scant information is available in the dental literature regarding patients concurrently affected with both pathologies. We present an unusual case report of a 63-year-old woman coaffected with primary HPT, attributed to a functional oxyphilic parathyroid adenoma, and PDB. Bone scintigraphy revealed pagetoid lesions of the skull, humeral head, spine, sacrum, and hemipelvis. Salient craniofacial features noted were bony involvement of the calvarium and midface, resulting in extensive maxillary overgrowth, hearing loss, telecanthus and consequent visual impairment, nasal deformity, and leontiasis ossea. The patient underwent a partial parathyroidectomy and bisphosphonate administration was to be initiated upon extraction of the remaining dentition. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e19-e24)

Paget disease of bone (PDB) and hyperparathyroidism (HPT) are relatively common chronic diseases of bone metabolism. Although the majority of patients affected with these disorders are asymptomatic and often discovered upon routine laboratory studies, each can exert profound impacts on the skeletal system and are capable of promoting a myriad of extraskeletal comorbidities.

PDB is characterized by increased rates of osteoclastic and osteoblastic activity, resulting in haphazard remodeling and weakened deformed bones which are easily prone to pathologic fracture. Complications of PDB include bone pain, nerve compression, hearing loss, osteoarthritis, congestive heart failure, and, rarely, osteosarcoma.1 The incidence of PDB in the USA is ~3%, affecting ≥1.5 million persons, most of which are >50 years of age.5 The etiopathogenesis of PDB has not been clearly established, although it is believed that mutations in the sequestosome-1 (p62) gene exert an integral role in the nuclear factor (NF) κB signaling pathway that governs osteoclastogenesis, implicated in 25%-30% of affected pedigrees and in ~10% of sporadic cases.2 Other identified activators of osteoclastic hypersensitivity involve expression of receptor activator of NF-κB (RANK), RANK ligand, osteoprotegerin, and possibly chronic paramyxoviral infection, namely, the measles virus and the respiratory syncytial virus.2

HPT typically develops as the result of excessive production of parathyroid hormone, most often from a parathyroid adenoma, and less commonly from glandular hyperplasia or carcinoma. Symptomatic patients may demonstrate increased osteolytic bone disease, leading to fracture and pain, impaired renal function, kidney stones, hypertension, peptic ulcer, and, less commonly, cardiac disease.3 Approximately 2% of the population in the USA is affected with HPT.4 Brown tumors, which are considered to be central giant cell neoplasms of HPT, may arise with advanced-stage disease.5 The etiology of HPT is also not well understood, although various factors have been proposed, particularly MEN-1 and cyclin-D1 gene mutations, vitamin D deficiency, and possibly ionizing radiation exposure.5

PDB and HPT generally present with distinct biologic expressions, although considerable physiopathologic overlap may be seen. Conceivably, diagnostic difficulties may arise when a patient is affected with coexisting pathologies. Limited information is available in the dental literature regarding the relevant findings in patients with PDB and HPT. Herein, we present the clinical, laboratory, radiologic, and histopathologic findings in a patient affected with PDB and HPT associated with severe craniofacial involvement.
CASE REPORT

A 63-year-old woman was referred by her attending physician to the University of Maryland Dental School Urgent Care Clinic for evaluation of a “palatal abscess.” For the preceding month, the patient had experienced severe pain of the maxillary right side, creating functional eating problems, and nutritional intake was restricted to liquids. The medical history was relevant for polyostotic PDB, diagnosed in 2000. Initially, the patient had encountered generalized weakness and spinal stenosis, creating walking difficulties. Within 2 years, the patient’s daughter had noticed that her nasal bridge had begun to “deepen” and her “upper jaw was getting bigger.” Progressive cranial enlargement led to increased interorbital width and ensuing visual impairment. Skull radiographs exhibited a generalized “cotton wool” sclerotic appearance (Fig. 1). Tc-99m methylene diphosphonate whole-body bone scintigraphy showed enhanced radionuclide uptake in the calvarium, right humeral head, midthoracic spine, sacrum, and right hemipelvis (Fig. 2).

In 2006, a mildly elevated serum calcium of 11.1 mg/dL (normal range 8.4-10.2 mg/dL) was noted, despite some degree of ambulation, and a parathyroid hormone assay indicated a marked elevation of 307.0 pg/mL (normal range 12.0-65.0 pg/mL). Other significant elevations were serum alkaline phosphatase (ALP) at 2,629 U/L (normal range 38-126 U/L) and urinary hydroxyproline at 679 mg/24 h (normal range 15-45 mg/24 h). By this time, the patient had also developed hypertension, anemia, and severe bilateral hearing loss. In 2008, the ALP had increased to 3,103 U/L. Further elevations in calcium and parathormone values, coincident with persistent activity on a parathyroid scan, prompted the need for a partial parathyroidectomy. Within 1 day after surgery, the serum calcium and parathyroid hormone levels had returned to normal.

On gross examination, the surgical specimen consisted of a 1.8 × 1.0 cm ovoid nodular mass of reddish brown soft tissue with a glistening capsular surface and weighing 1.0 g. The cut surface exhibited a glistening brown tan appearance. Histopathologic assessment revealed a well circumscribed oxyphilic cell adenoma, which served to establish the diagnosis of primary HPT (Fig. 3).

At present, the craniofacial characteristics were significant for an enlarged calvarium, frontal bossing, exophthalmos, and telecanthus. A moderate degree of midface deformity was also evident, resulting in an abnormal nose with unequal sizes of the nares and a broad flattened nasal bridge, pronounced and broadened nasolabial folds, asymmetric enlargement of the malar bones, prominence of the philtrum, and an asymmetric upper lip (Fig. 4). The intraoral examination was remarkable for generalized severe overgrowth in height and width of the maxillary ridges, which were hard and nontender. Numerous retained root tips and grossly carious teeth were seen in both jaws. Conspicuous mildly tortuous venules were evident along the maxillary left alveolus (Fig. 5). An indentation was seen in the alveolar ridge of the maxillary left canine area, attributed to impingement of the opposing canine. Current medications were clonidine and lisinopril for hypertension management.

A panographic survey revealed extensive bilateral expansion of the maxilla extending to the tuberosities; the bone had a diffuse “ground glass” radiodensity. The skull base had a “cotton wool” pattern and the maxillary sinuses exhibited bilateral obliteration (Fig. 6). The mandible did not seem to display any pagetoid changes, although several periapical radiolucencies were apparent, likely attributed to pulpal necrosis.

The patient was then referred to the Department of Oral and Maxillofacial Surgery for removal of the remaining non-
restorable dentition. After the extraction of one of the maxillary right root tips, harvested bone from the socket was submitted for histopathologic review. Microscopically, dense viable bone was evident with active osteoblastic and osteoclastic activity; multiple reversal lines were also seen (Fig. 7). The root fragment displayed prominent hypercementosis (Fig. 8). These findings were consistent with PDB. The institution of bisphosphonate therapy was to commence upon successful completion of intraoral healing, due to persistent

Fig. 2. Tc-99m methylene diphosphonate bone scan. Increased radionuclide uptake in the calvarium, right humeral head, midthoracic spine, sacrum, and right hemipelvis.

Fig. 3. Parathyroid adenoma with a complete delicate capsule composed of uniform polygonal oxyphilic cells (hematoxylin and eosin, ×50); inset: nests of oxyphilic adenoma cells, showing bland nuclei and abundant oxyphilic cytoplasm set in vascular background; inset ×200).

Fig. 4. Craniofacial overgrowth resulting in frontal bossing, telecanthus, nasal deformity, prominent nasolabial folds, and asymmetric upper lip.

Fig. 5. Massive enlargement of the maxillary alveolus with prominently engorged venules along the left side.
symptomatology concomitant with the extreme elevation of ALP. There were no plans as yet to perform maxillary reduction surgery.

DISCUSSION

Diagnostic difficulties may arise when patients are affected with PDB and HPT as these disorders share some phenotypic expression. The clinical manifestations often seen with pagetoid bone are expansion and deformity. Skull involvement is observed in 8.5%-44.1% of PDB-affected patients, principally in the calvarium, with fewer cases primarily arising in the jaws. When gnathic involvement is discerned, it is typically bilateral and with a 2:1 predilection for the maxilla. Isolated cases of unilateral involvement of the maxilla and mandible have been reported. Midface hypertrophy of the facial and cranial bones, as seen in the present patient, is referred to as leontiasis ossea (lionlike facies). This dysmorphologic feature has been reported with PDB, secondary HPT, fibrous dysplasia, chronic renal insufficiency, and reactive inflammatory bone disease.

Although 13% of patients with primary HPT have radiographic evidence of jaw disease, usually affecting the mandible, expansion is not a common clinical feature and is generally attributed to brown tumor proliferation. Brown tumors of the jaws are occasionally seen in secondary HPT (associated with chronic renal disease) and are capable of marked unilateral overgrowth. Rarely, bilateral maxillary expansion has been reported with secondary HPT. Michiwaki et al. described a 42-year-old man with secondary HPT with excessive clinical and radiographical enlargement of the maxilla; the bony deformities were not ameliorated post-parathyroidectomy, as seen in our affected patient.

Radiographic changes are a hallmark of PDB, a manifestation of active bone biology, whereas only 20% of patients with HPT exhibit any radiologic bony abnormalities. The radiologic changes of PDB and HPT are not pathognomonic, particularly regarding jaw involvement. As a reflection of the osteolytic activity of either disorder, marked reduction in bone trabeculation may be observed and described as having a “ground glass” or granular texture. Additionally, the lamina dura may become less pronounced around 1 or more teeth. Affected patients with fibrous dysplasia may also manifest “ground glass” osseous lesions, occasionally with moderately elevated ALP values. With disease pro-
gression, osteoblastic changes associated with PDB are delineated by clusters of radiopaque patches, referred to as a “cotton wool” appearance. Furthermore, the presence of hypercementosis is commonly recognized with PDB but is absent with HPT. It was believed that the maxillary involvement in the present patient represented pagetoid changes, which was corroborated by histopathologic osseous findings and the presence of the hypercementosis.

Routine laboratory studies of PDB and HPT often feature distinctive bone biomarker profiles, although biochemical overlap may occur. PDB is typically noted for significant elevations of serum ALP, with normal parathormone and calcium levels, whereas HPT is associated with marked increases of parathormone, hypercalcemia, hypercalcuiuria, and moderate to severe increases of serum ALP. Interestingly, ~15% of symptomatic patients with PDB present with normal ALP values19 and 12%-18% of pagetoid patients exhibit superimposed increases in parathormone levels.20 Recently, normocalcemia has been described in a subpopulation of patients with HPT.21 Our patient demonstrated hypercalcemia antecedent to the discovery of the parathyroid tumor, with a return to normocalcemia immediately after surgery. ALP levels typically fall by 6%-83% in post-parathyroidectomy patients with PDB.22 Similarly, our patient had a 62% decrease of serum ALP to 1,604 U/L after partial parathyroidectomy.

Other causes of hypercalcemia may be attributed to excessive intake of vitamin A or D, theophylline, or aspirin; therapeutic doses of diuretics or lithium; immobilization; thyrotoxicosis; Addison disease; milk-alkali syndrome; inflammatory disorders; sarcoidosis; rhabdomyolysis; acquired immunodeficiency syndrome; and various malignancies, such as parathyroid carcinoma, head and neck squamous cell carcinoma, breast carcinoma, lung carcinoma, pancreatic adenocarcinoma, and multiple myeloma.23-26 It is important to identify the underlying etiology of hypercalcemia as delay can lead to gastrointestinal, cardiac, and psychiatric disorders, kidney stones, hypotonia, coarse tremor, and coma.27,28 Clinicians should be suspicious when hypercalcemia suddenly arises in a patient previously diagnosed with PDB as it may be indicative of the onset of some additional pathologic process, as seen in the present case.

The histopathologic findings of pagetoid and HPT-affected bone are not regarded as pathognomonic and the definitive diagnosis should be established with the synthesis of the supportive clinical, radiographic, and laboratory studies. Both disorders feature abnormal bone resorption with a “mosaic” or “woven” architecture and are associated with multinucleated osteoclasts set in a vascular and fibrous connective background. PDB can further be characterized by the presence of osteoblastic activity and reversal lines, and affected teeth may display increased cementum formation. The differential diagnosis should also include florid cemento-osseous dysplasia, fibrous dysplasia, and osteosarcoma.

Although there are isolated reports and limited case series of patients coaffected with PDB and HPT, the causal relationship of these 2 disorders has been controversial. Posen et al.29 identified an increased prevalence of HPT in a PDB-affected subgroup and proposed that their coexistence may be attributed to hypersecretion of parathormone by some unspecified skeletal metabolite. Parfitt30 argued that the diagnosis of both of these diseases simply might be a chance finding as a result of a comprehensive medical workup of either disorder. Other investigators have noted that the coexistence of HPT in PDB-affected subgroups is similar to the prevalence of HPT in the general population, and they have suggested that their association may be aleatory in nature.

Siris et al.20 postulated that increased parathyroid hormone production is a homeostatic response to increased calcium demands consequent to increased bone turnover, as seen with metabolically active pagetoid bone formation. In addition, they remarked that hypersecretion of parathyroid hormone may arise in an older subpopulation who are otherwise inclined to manifest impaired calcium absorption in the gastrointestinal tract and reduced dietary calcium intake, similar to the age group of individuals with PDB.20 The present affected patient developed HPT after the onset of extreme PDB activity, perhaps lending support to this compensatory pathophysiologic relationship. Nevertheless, clinicians should be aware of the diverse presentations of PDB and HPT and that timely diagnosis may render therapeutic application.

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REFERENCES


