Skeletal Lesions in Primary Hyperparathyroidism

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Abstract: *Background:* Osteitis fibrosa cystica (OFC), a relatively rare skeletal disorder caused by excess parathyroid hormone, is often misdiagnosed as a neoplasm. A summary of the diagnostic procedures and treatment protocols, especially the indications for orthopedic surgery, is helpful to avoid overtreatment. *Methods:* Eight patients from the Orthopedic Department of Qilu Hospital of Shandong University diagnosed with OFC caused by primary hyperparathyroidism were treated, and the clinical manifestations, biochemical and radiography examination findings, surgeries and prognoses were recorded. *Results:* All cases (5 female and 3 male) were admitted to our department with the complaint of bone pain (5/8) or fracture after mild trauma (3/8). Biochemical screening revealed hypercalcemia and high parathyroid hormone of varying levels. Two cases were misdiagnosed as primary bone lesion and metastasis. All cases were treated with parathyroidectomy and experienced spontaneous and progressive regression of the boney disease. Four cases underwent orthopedic surgery. Bone biopsies were necessary to exclude malignant tumors, especially with orthopedic procedures. *Conclusions:* OFC can easily be misdiagnosed in orthopedic patients because of a lack of radiological and histologic specificity. Reaching the correct diagnosis requires a combination of clinical manifestations, routine biochemical screenings, radiographic examinations of bone and parathyroid and bone biopsy. It is generally acknowledged that parathyroidectomy is effective, but orthopedic surgery is sometimes necessary after a correct diagnosis and parathyroidectomy. However, the indications for orthopedic surgery must be strictly controlled to avoid overtreatment.

Key Indexing Terms: Osteitis fibrosa cystica; Brown tumor; Primary hyperparathyroidism. **[Am J Med Sci 2015;349(4):321–327.]**

Osteitis fibrosa cystica (OFC) is a skeletal disorder that occurs secondary to hyperparathyroidism and is caused by long-term stimulation by excess parathyroid hormone (PTH). The overactivity and proliferation of osteoclasts stimulated by PTH breaks down bone and leads to replacement of bone matrix and thinning of the cortex. The cystic defects can be filled with brown hemosiderin deposits, leading to the term, "brown tumors."[1] This process is not neoplastic but rather a reparative cellular process.[2] Brown tumor most commonly presents as a slowly enlarging painful mass that can be locally aggressive, without metastatic potential.[3]

Primary hyperparathyroidism (PHPT) is most often caused by parathyroid adenoma (80%–85%) with parathyroid carcinoma occurring in less than 0.5% to 4% of cases. Women are more often affected than men, especially postmenopausal women of age 50 to 60 years. The estimated incidence is 2 to 3 cases per 1,000 women and 1 case per 1,000 men, approximately a 3:1 ratio.[4] Secondary hyperparathyroidism is caused mainly by chronic kidney disease; hereditary disease is rare and presents mainly in adolescents.[5]

Asymptomatic hypercalcemia is the most common clinical manifestation of PHPT, occurring in approximately 80% of cases.[6] With now common routine biochemical screening, the incidence of the severe form of the skeletal manifestations has decreased in developed countries in recent decades.[7] However, because of a delay in seeking medical attention and lack of routine biochemical screening, OFC remains the primary presentation of PHPT in many developing countries.[8]

OFC is characterized by the presence of subperiosteal resorption in the digits, skull and long bones, diffuse osteopenia and brown tumors.[6] In patients with PHPT whose chief complaint is bone pain, the incidence of misdiagnosis is relatively high and results in ineffective therapy.[8,9] Surgical overtreatment is unnecessary and causes additional patient trauma. There is no doubt that parathyroidectomy is the first choice in OFC management; however, there is debate about whether orthopedic intervention is also necessary.[10–12] The ideal diagnostic and orthopedic therapeutic approach requires further research.

The authors describe 8 patients suffering from OFC caused by PHPT in the orthopaedic department. The authors discuss the clinical manifestations, diagnosis, treatment and prognosis.

PATIENTS

Eight patients were initially admitted to the orthopaedic department because they presented with bone pain or fracture, and bone diseases were assumed. No family history of parathyroid or thyroid disease and no calcium deficiencies were found in these patients. Patient information included clinical manifestations, preoperative biochemical screening, radiographic evaluations of bone and parathyroid, histologic findings, surgeries and prognosis.

Biochemical examinations comprised serum calcium and phosphorus, serum alkaline phosphatase, serum creatinine, serum urea nitrogen and intact PTH. Radiological surveys for bone diseases included plain film radiography, computed tomography (CT), magnetic resonance imaging (MRI) and emission computed tomography (ECT). Plain film radiography or ultrasound of the abdomen was performed to identify kidney or ureteral calculi. Parathyroid radiography consisted of CT, ultrasound or ECT. Bone mineral density (BMD) was not measured because of limited availability. Bone biopsy was performed to exclude malignant tumors.

The 8 patients underwent parathyroidectomy. One of the patients was misdiagnosed as having a bone cyst, another 3 patients presented with pathological fracture after minor trauma and 1 was misdiagnosed with a simple fracture. Histologic examinations were performed after parathyroidectomy and orthopedic surgery or biopsies. Changes in the concentrations of serum calcium and PTH were followed after

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Submitted October 3, 2013; accepted in revised form September 11, 2014.

The authors have no financial or other conflicts of interest to disclose.

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parathyroidectomy in all patients. Postoperative hypocalcemia was managed by administering oral calcium and 1,25-dihydroxyvitamin D (calcitriol) in addition to calcium gluconate infusion. The mean postoperative follow-up duration was 46.6 months (range, 4–96 months). The postoperative evolution of brown tumors was mainly evaluated by radiography.

RESULTS

The 8 cases included 5 (62.5%) women and 3 (37.5%) men with a mean age of 42 years (range, 28–55 years). All cases were admitted to our department with a chief complaint of bone pain or fracture in different sites, and we divided the cases into 2 groups: fracture and nonfracture (Table 1).

Five cases (62.5%) were diagnosed with malaise with local bone pain. The average visual analog scale pain score was 5.6 (range, 4–8) preoperatively. One patient was misdiagnosed as having a bone cyst and underwent tumor curettage and allograft bone padding. Recurrence occurred 3 years later when the diagnosis was confirmed, and a parathyroid adenoma was resected. Three cases (37.5%) sought medical attention for pathological bone fracture; all fracture sites were in the lower limbs. Before pathological fracture, all patients reported feeling either no pain or mild discomfort only. One patient was treated as a simple bone fracture and underwent external fixation surgery (1/3), with severe bone pain recurring in the same leg 1 year later. The other 2 cases were treated with open reduction and internal fixation. We identified nephrolithiasis in 5 cases by abdominal plain film radiography (62.5%) with 1 patient also having a severe peptic ulcer and no improvement with proton pump inhibitors.

Routine biochemical screening was carried out in all patients (100%) (Table 2). Serum calcium was elevated to varying degrees with a mean concentration of 3.26 mmol/L (range, 2.66–3.72 mmol/L). All cases presented with high alkaline phosphatase levels of 401 to 2,537 U/L with a mean value of 1,002 U/L. The mean PTH value was 1,058 g/mL (range, 99–2,261 g/mL).

All patients initially underwent plain film radiography, with additional CT or MRI after hospital admission (Figures 1A–D). Radiological evaluation demonstrated lytic lesions in not only cortical bone such as the femoral and humeral shaft but also in the cancellous bone such as the pelvic ring, femoral head and vertebrae. The final radiological diagnoses were subjective and included brown tumor (3/8, 37.5%), bone cyst (1/8, 12.5%), giant cell tumor (1/8, 12.5%) or multiple bone metastases (1/8, 12.5%); another 2 cases showed osteolytic lesions without clear results (2/8, 25%). Eight cases (100%) had cervical CT imaging examination (Figure 1E), ultrasound or parathyroid ECT (Figure 2A), which identified the character of the space-occupying lesions in the parathyroid gland area. Six patients (75%) accepted ECT examination of the entire skeleton, showing diffuse increased radioactive nuclide concentration (Figure 2B).

Parathyroidectomy was performed after clear diagnosis in all 8 cases (100%) (Table 3). Intraoperative exploration accurately estimated the tumor size, location and states of invasion, and all tumors were located in the lower thyroid lobes (100%). Intraoperative fast-frozen pathology and routine postoperative pathology of the parathyroid tumors revealed predominantly parathyroid adenoma (Figure 2C) (87.5%), and only 1 case was diagnosed as parathyroid carcinoma (12.5%). Recurrence was observed in 1 patient after the first parathyroidectomy because of residual tumor, and a second surgery was curative. Two patients underwent bone biopsy and 4 patients underwent orthopedic surgery, including 3 pathological fracture cases. All 6 histopathological results after bone processing showed giant cell tissue.

After parathyroidectomy, clinical evaluation of brown tumors demonstrated spontaneous regression in all cases but with different regression response patterns. Six months postoperatively, all 5 patients who had suffered from bone pain on admission had their pain resolve after parathyroidectomy. Serum calcium and PTH were monitored after parathyroidectomy. Hypocalcemia commonly persisted and was managed by oral calcium carbonate and calcitriol.

Successful diagnosis followed by parathyroidectomy was curative. Four cases underwent orthopedic surgeries; however, 2 cases (50%) were misdiagnosed, delaying the cure of the primary causes by 1 year in 1 case and 3 years in the other.

DISCUSSION

OFC is a nonneoplastic lesion caused by chronic stimulation by excess PTH. The over secretion of PTH results in not only the overactivity of osteoclasts but more importantly, an increased proliferation and number of osteoclasts, termed osteoclast cytosis. Normal bone stroma is then replaced by fibrous tissue, hemorrhage, hemosiderin deposition and cystic areas. The hemorrhage and hemosiderin deposition give the tumor a brownish color and thus the term brown tumor.[1]

PHPT is the most common reason for excess PTH. Parathyroid adenoma predominates and was diagnosed in 87.5% of our patients with only 1 case (12.5%) of parathyroid carcinoma. The reason that women are more often affected is not clear; however, a higher sensitivity to PTH in women, especially menopausal women, may partly explain why more

TABLE 1. Basic information and clinical manifestations

Case	Gender	Age (yr)	Malaise	Bone pain	VAS score	Fracture	Nephrolithiasis
1	F	55	Present	Present	5	Absent	Absent
2	F	41	Present	Present	6	Absent	Present
3	F	28	Present	Present	5	Absent	Present
4	F	54	Present	Present	4	Absent	Absent
5	M	37	Present	Present	8	Absent	Present
6	F	53	Absent	Absent	0	Present	Present
7	M	30	Absent	Absent	0	Present	Absent
8	M	36	Absent	Absent	0	Present	Present

F, female; M, male; PHPT, primary hyperparathyroidism.

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