



## Primary Hyperparathyroidism with Extensive Brown Tumors and Multiple Fractures in a 20-Year-Old Woman

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A brown tumor is a benign fibrotic, erosive bony lesion caused by localized, rapid osteoclastic turnover, resulting from hyperparathyroidism. Although brown tumors are one of the most pathognomonic signs of primary hyperparathyroidism, they are rarely seen in clinical practice. In this report, we present a case of 20-year-old woman with recurrent fractures and bone pain. Plain digital radiographs of the affected bones revealed multiple erosive bone tumors, which were finally diagnosed as brown tumors associated with primary hyperparathyroidism due to a parathyroid adenoma. This case shows that multiple, and clinically severe form of brown tumors can even occur in young patients.

**Keywords:** Brown tumor; Hyperparathyroidism; Parathyroid neoplasms

### INTRODUCTION

Primary hyperparathyroidism is a disorder in which excess parathyroid hormone (PTH) is secreted from one or more of the parathyroid glands. The inappropriately increased secretion of PTH usually affects calcium and phosphate levels, and bone metabolism, resulting in hypercalcemia and hypophosphatemia. However, clinical manifestations of primary hyperparathyroidism are variable in terms of etiology and serum PTH levels. Approximately 70% to 80% of patients with primary hyperparathyroidism are asymptomatic; these patients are often identified following screening of calcium levels during other investigations [1]. The remaining 20% to 30% of patients often present with recurrent nephrolithiasis, osteoporosis, proximal muscle weakness, and psychiatric symptoms [2].

A brown tumor is a focal, benign bony lesion caused by localized, rapid osteoclastic turnover of bone, resulting from direct effects of PTH. Brown tumors are one of the most pathognomonic signs of primary hyperparathyroidism; however, they are rarely seen in clinical practice. Brown tumors have been reported occur in 1.5% to 4.5% of patients with primary or secondary hyperparathyroidism [3]. Clinically, brown tumors often cause swelling, pathological fracture, and bone pain.

There have been reports of brown tumors associated with primary hyperparathyroidism, but most of them present a focal brown tumor usually localized to the jaw and maxilla [4,5]. Here, we report a case of extensive brown tumors and multiple fractures caused by a parathyroid adenoma in a 20-year-old woman.

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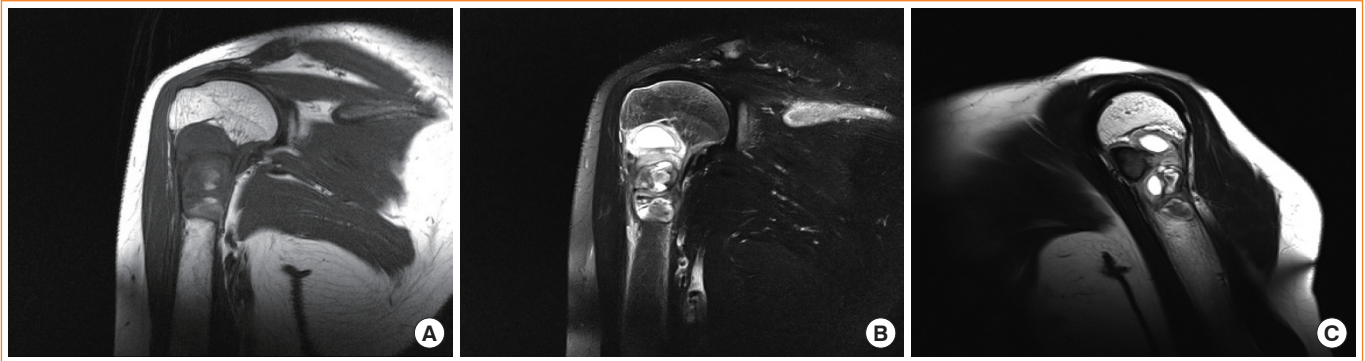
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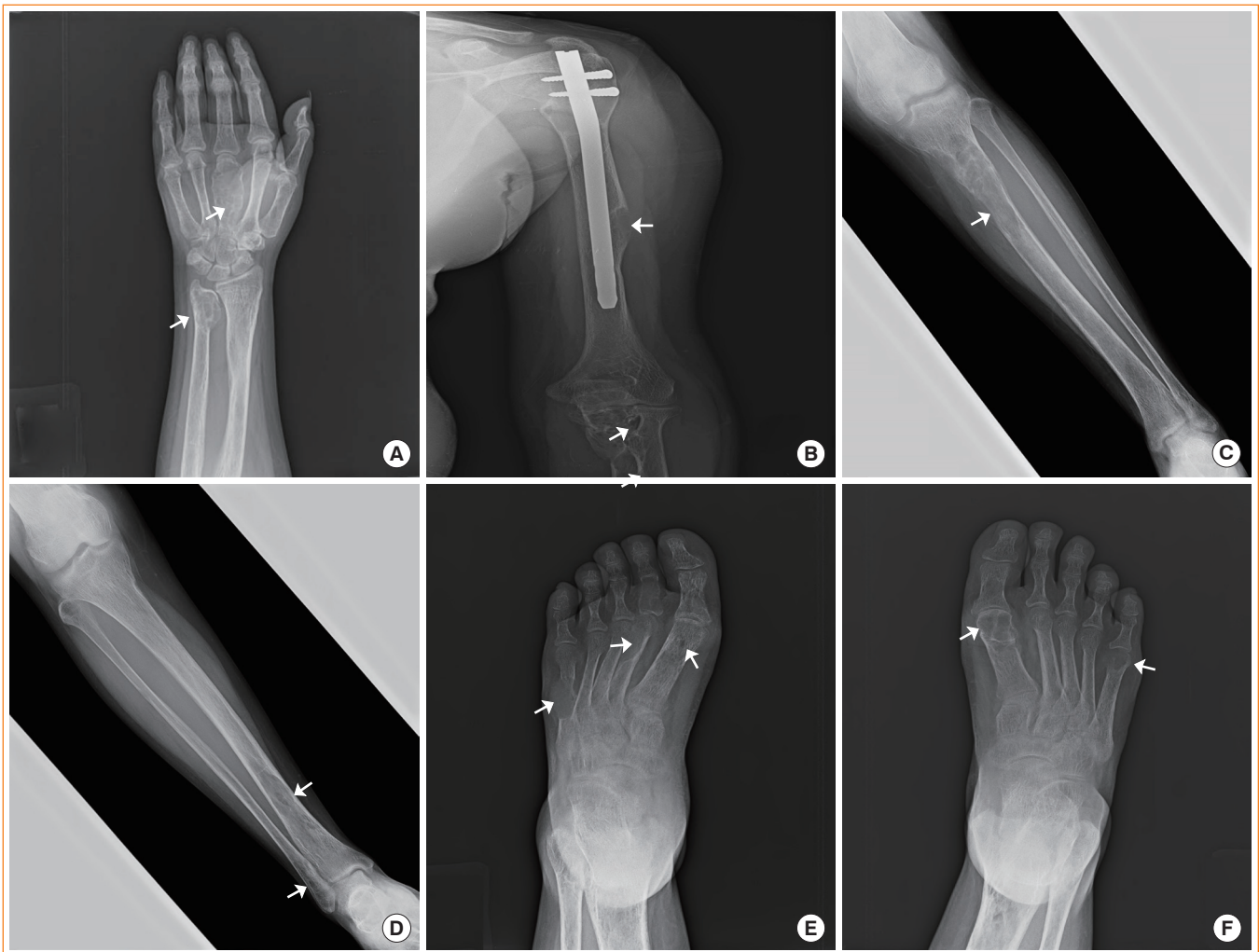
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**Fig. 1.** Mongolian magnetic resonance imaging of the affected shoulder (A, T1 coronal; B, T2 coronal FS; C, T2 sagittal view) showed 5 cm-sized expansile tumorous lesion with heterogeneous signal intensity on right humerus metaphysis, with internal cystic change containing fluid level inside.



**Fig. 2.** Plain digital radiograph of the affected left wrist and hand (A), humerus (B), both tibia (C, left tibia; D, right tibia) and foot (E, left foot; F, right foot) revealed multiple bony osteolytic expansile lesions (arrows) with cortical thinning, diffuse osteoporosis and subperiosteal bone resorption, without definite evidence of pathological fractures in both tibia and fibula, metatarsal bones, left proximal ulna and humerus, left distal ulnar and 3rd metacarpal bone. These findings are thought to be compatible with brown tumors of hyperparathyroidism and not like malignancy.

## CASE REPORT

A 20-year-old Mongolian woman was referred to our endocrinology department for further evaluation of recurrent fractures and bone tumors. She had been experiencing bone pain and recurrent bone fractures of the limb over 2 years following minor trauma. Three months previously, she had undergone surgery of the left humerus in a Mongolian tertiary care center. She was also evaluated for a tumorous lesion associated with the fracture site (Fig. 1). The biopsy report of the tumorous lesion identified that it was composed of multiple giant cells and some fibroblasts suggestive of a brown tumor or giant-cell tumor. However, there had not been any further evaluations of the tumor or the fractures.

At the first visit to our clinic, she complained of pain and tenderness of her left lower leg and left knee joint. But, she did not complain of any neuropsychiatric or gastrointestinal symptoms. She also did not have another past medical history including urinary stones. Plain digital radiographs of the affected bones (both tibia and fibula, metatarsal bones, left proximal ulna and humerus, left distal ulnar and third metacarpal bone) revealed multiple bony osteolytic expansile lesions with cortical thinning, diffuse osteoporosis, and subperiosteal bone resorption compatible with brown tumors (Fig. 2). Additionally, a radiograph of her skull showed a granular “salt and pepper” appearance, typical finding of primary hyperparathyroidism

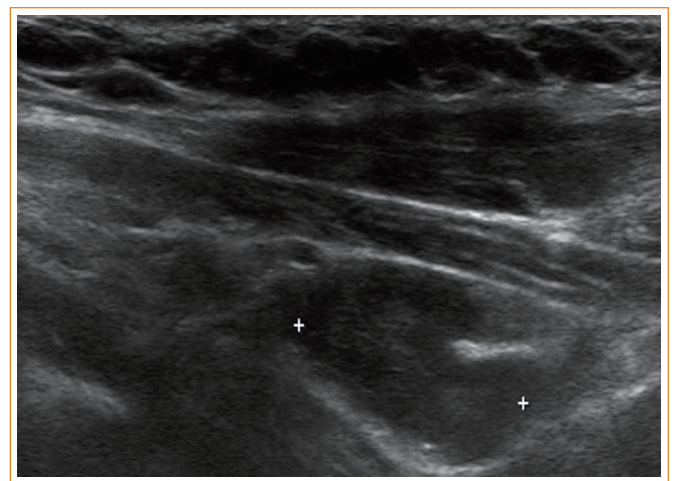


**Fig. 3.** Skull X-ray showed a granular “salt and pepper” appearance, which is thought to be a typical finding of primary hyperparathyroidism. It also showed enlargement of the sella turcica, which can be commonly seen in cases of pituitary tumors.

(Fig. 3).

Initial laboratory tests indicated elevated serum calcium levels of 10.3 mg/dL (normal range, 8.8 to 10.0), ionized calcium levels of 6.01 mg/dL (normal range, 4.4 to 4.9), and low phosphorus levels of 1.3 mg/dL (normal range, 2.5 to 4.5). Serum alkaline phosphatase levels were elevated at 2,032 IU/L (normal range, 30 to 120), and serum intact PTH levels were markedly increased to 978.4 pg/mL (normal range, 8 to 76). Twenty-four-hour urinary calcium was also elevated at 555.4 mg/day (normal range, 100 to 300). Further laboratory tests including serum PTH-related peptide, albumin, and creatinine were within normal limits. A parathyroid imaging work-up with neck ultrasonography and a parathyroid scan (technetium-99m sestamibi) revealed an approximately 2 cm mass in the inferior aspect of the left thyroid gland, suggestive of a solitary parathyroid adenoma (Figs. 4, 5). Additional evaluations for hyperparathyroidism-associated conditions were also performed. Dual-energy X-ray absorptiometry identified osteoporosis; the Z-score for the left femur neck was  $-5.5$  ( $0.21 \text{ g/cm}^2$  as bone mineral density [BMD]), and for the spine was  $-3.6$  ( $0.59 \text{ g/cm}^2$  as BMD). Further tests for multiple endocrine neoplasm type 1, including pituitary hormones, revealed no additional abnormal findings.

Following management of bone pain and fracture sites, a left-side parathyroidectomy was performed. A  $2.6 \times 2.1 \times 2.1$  cm, multi-lobulated, grayish-brown, soft mass was excised. Postoperative histopathological examination revealed features



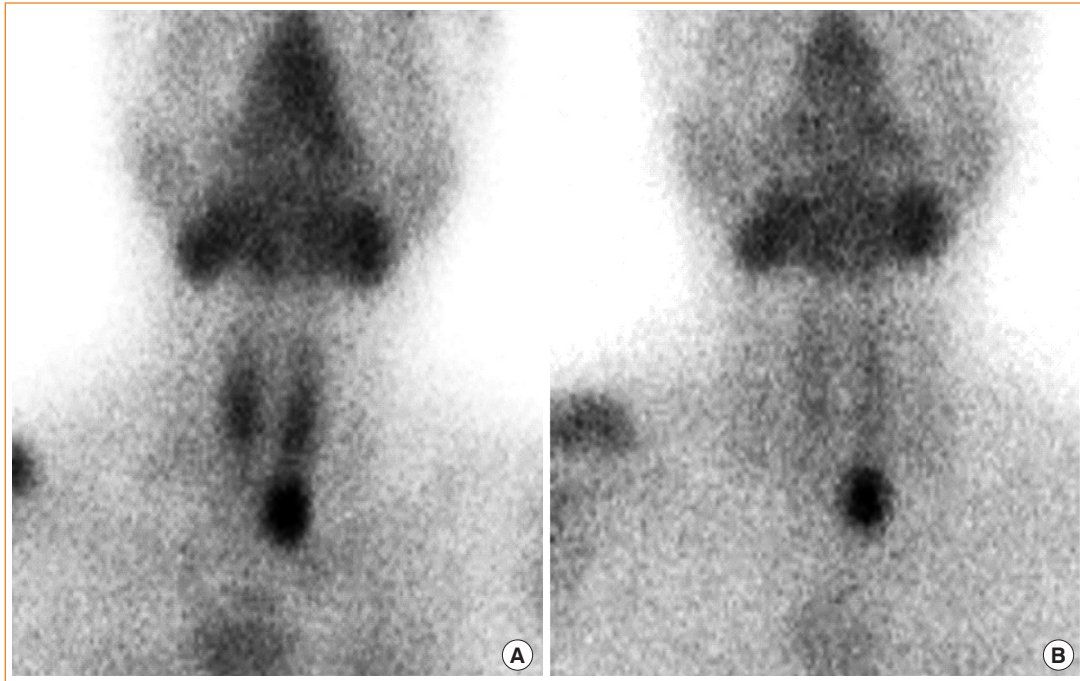
**Fig. 4.** Ultrasound of neck revealed several nodules which were thought to be parathyroid; well-defined hypoechoic nodules sized 0.85 cm, 0.75×0.74 cm, maximum size is 1.83 cm, and there was no other significant lymphadenopathy.



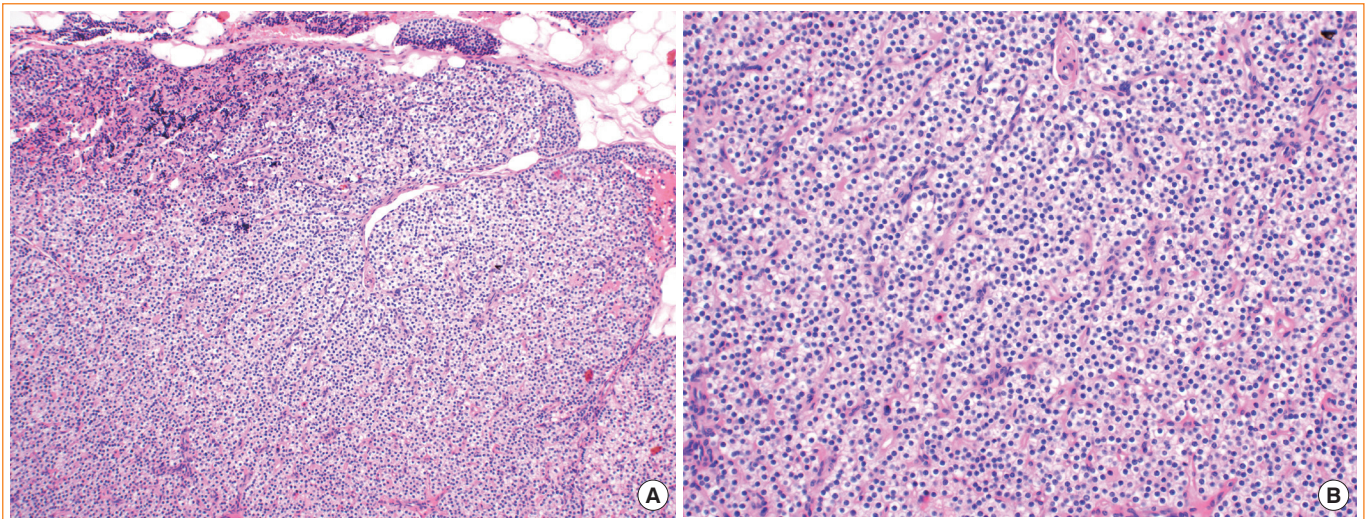
of a parathyroid adenoma (Fig. 6); the lesion was distinguishable from the rim of compressed normal gland that contains abundant stromal fat. Within the adenoma, tumor cells were arranged in cords and solid sheets, and mainly composed of chief

cells, which have centrally placed hyperchromatic nuclei and pale eosinophilic cytoplasm.

Two days postoperatively, the patient experienced transient hypocalcemia (7.3 mg/dL), but recovered with calcium carbon-



**Fig. 5.** To further assess the parathyroid gland, technetium-99m (Tc-99m) sestamibi parathyroid scan was carried out, showing normal uptake pattern in both Tc-99m per technetate and focally increased residual uptake at the lower pole region of left thyroid lobe in the Tl-Tc per technetate subtraction image (A, early phase; B, delayed phase). This result showed “parathyroid adenoma” close to the left lower pole of left thyroid.



**Fig. 6.** Histopathological report showed features of parathyroid adenoma as above (H&E stain, A,  $\times 100$ ; B,  $\times 200$ ). In figure (A) and (B), within the adenoma, tumor cells are arranged in cords and solid sheets. The tumor cells are mainly composed of chief cells, which have centrally placed hyperchromatic nuclei and pale eosinophilic cytoplasm.

ate supplementation. Four days postoperatively, serum intact PTH level was decreased to 17.3 pg/mL. Three days afterwards, she was discharged free of symptoms, and returned to Mongolia.

## DISCUSSION

Primary hyperparathyroidism is a disorder in which excess PTH is secreted from one or more of the parathyroid glands. The prevalent routine serum chemistry screening of calcium brought early detection of primary hyperparathyroidism, which led to a decrease in classical form with renal stones or bone manifestations. The incidence of primary hyperparathyroidism is reported as approximately 22 per 100,000 persons per year. Primary hyperparathyroidism is more common in woman than man, and peak incidence occurs in the 6th to 7th decade of life. [1,6].

A brown tumor is a bone lesion that results from bony resorption by excess osteoclastic activity, and replacement by fibrous tissue and giant cells. Brown tumor is an uncommon pathognomonic sign of hyperparathyroidism. However, there have been reports of cases from various regions worldwide. Most of the reports presented a solitary lesion, generally localized to the facial bones [7,8], and more frequently associated with secondary hyperparathyroidism than primary hyperparathyroidism [9,10].

Our case is unique in several aspects; the patient presented with multiple, extensive brown tumors, mainly involving bones of the limbs, and related fractures. Several reports have presented cases of multiple brown tumors associated with primary hyperparathyroidism [11-13]. However, in those reports, the tumors usually affected the maxilla, pelvis, and ribs, other than long bones. There have been also similar reports with multiple brown tumors involved in bones of limbs in Korea, the young woman in our case experienced recurrent fractures, which has not been observed in other cases, implying a clinically overt form of brown tumors [14,15]. Another notable finding from our case is that the patient was a 20-year-old woman. Considering that the first occurrence of fracture was approximately 2 years prior to diagnosis, we assume that hyperparathyroidism was present for a considerable length of time before that first fracture. We only identified one other case of an adolescent female with multiple brown tumors in Turkey [16].

Because the presentation of our case was atypically severe, and developed in a young woman, we could have considered another possible diagnosis, including giant-cell tumor, or metastatic bone lesions. The main differential diagnosis was giant-

cell tumor, which is a highly vascular lesion usually found in the metaphysis or epiphysis of a limb bone, in the pelvis, or in the spine [17]. A large case series of 195 patients showed that the peak incidence of giant-cell tumor was in the third decade of life, and usually involved the distal part of major tubular bones in the extremities, a description which resembles our case [18]. The radiological appearance and histology of giant-cell tumors may closely mimic those of brown tumors; therefore, the clinical manifestation and laboratory tests play an important role in the differential diagnosis. In this case, a biochemical assay and subsequent parathyroid imaging definitively confirmed a diagnosis of primary hyperparathyroidism; therefore, we could follow the standard treatment protocol without confusion.

The patient had to return to Mongolia following treatment; therefore, we could not perform our usual clinical follow-up after the parathyroidectomy. Most of the previous reports showed slow regression of bone lesions and improvement of BMD following the operations [11-13].

In summary, we have presented a case of a young woman with multiple brown tumors and related fractures associated with primary hyperparathyroidism. Although very rare, this case showed that multiple, and clinically severe, brown tumors can even occur in young patients.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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