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Primary hyperparathyroidism-induced brown tumors caused by parathyroid carcinoma: a case report and literature review

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Abstract

Brown tumors represent a benign disease that is induced by primary or secondary hyperparathyroidism, with the pathological feature of osteitis fibrosa cystica. Primary hyperparathyroidism caused by parathyroid carcinoma resulting in brown tumors is extremely rare. Herein, we report the case of a 60-year-old male patient who was admitted for giant cell tumors of the bone with local pain and limited movement of the left knee joint. With early detection of multifocal osteolytic bone lesions, hyperparathyroidism (parathyroid hormone: 2365.00 pg/mL), and parathyroid cancer, the diagnosis of brown tumors was confirmed without any unnecessary or harmful interventions. Thereafter, he underwent parathyroidectomy, from which postoperative pathology confirmed parathyroid carcinoma, and total knee arthroplasty to restore movement of the knee joint. Seven months after surgery, the left knee joint had good range of movement. This case emphasizes that detecting patients' parathyroid hormone levels should not be neglected when diagnosing multifocal osteolytic bone lesions. A comprehensive analysis combining clinical symptoms, imaging, and laboratory tests is conducive to accurate disease assessments and avoiding unnecessary or even survival-impairing surgery. However, when the tumor involves a large joint or seriously affects joint movement, surgery may be worth considering.

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Introduction

Brown tumors are rare benign and reactive lesions caused by the abnormal bone metabolism in patients with uncontrolled hyperparathyroidism (HPT). The incidence of primary hyperparathyroidism (PHPT) is lower (<2%) than that of secondary hyperparathyroidism (SHPT),[1] while this tumor-like lesion that represents the terminal stage of the bone remodeling process in prolonged HPT is much rarer with an overall incidence of between 2% and 3%.[2] Bone remodeling disorders can occur in any part of the skeleton,[3] mainly in the jaws, ribs, clavicle, extremities, and pelvis, but occasionally in the spine.[4] Brown tumors can be confused with metastatic tumors due to the presence of multifocal osteolytic bone lesions. Clinical manifestations of brown tumors include diffuse skeletal pain, difficulty walking, multiple pathological fractures, and limb deformities; in some cases, the symptoms are only characterized by local pain and swelling. Thus, apart from medical history and clinical manifestations, laboratory results and radiological imaging are indispensable for diagnosing brown tumors, among which extremely high parathyroid hormone (PTH) levels, hypercalcemia, and hypophosphatemia are the distinguishing features. However, it is challenging for surgeons to diagnose brown tumors because PTH is not routinely examined. Additionally, pathological features, usually the gold standard for tumor diagnosis, include mononuclear cells mixed with multinuclear giant cells, hemorrhage, granulation tissue, vascular tissue, and fibrous tissue, which are similar to the features of giant cell tumors (GCTs), possibly leading to an incorrect diagnosis. The key treatment for brown tumors involves partial or complete removal of the parathyroid glands, rather than management of local bone lesions. As PTH levels return to normal, brown tumors will spontaneously recover.[5]

Herein, we report the case of a 60-year-old male patient who was admitted with local pain and limited movement of the left knee joint. With early detection of multifocal osteolytic bone lesions, HPT, and parathyroid cancer, unnecessary and harmful interventions were avoided. The purpose of this report is to highlight the importance of considering HPT in the differential diagnosis of patients with multifocal osteolytic bone lesions and to provide surgeons with a valuable diagnostic experience.

Case presentation

This case report was approved for publication by the Board of Directors of the First Affiliated Hospital of Harbin Medical University, China. The reporting of this study conforms to the CARE guidelines,[6] and written informed consent for treatment and publication of the case was obtained from the patient.

A 60-year-old male patient presented to our hospital due to local pain and limited movement of the left knee joint for 3 months without an apparent trigger.

He did not experience fever, lethargy, or fatigue. His appetite and weight were stable. The patient had visited a local hospital where a magnetic resonance imaging (MRI) scan was suspected of showing GCT of the left knee. The patient was admitted for GCT of the left lower limb to our hospital. On physical examination, his gait was impaired. A 6×4-cm mass was observed on the lateral femoral midshaft with tenderness, movement worsened the pain, it was hard on palpation, fixed to the tissues underneath, and free from overlying skin. His blood test results revealed the following (normal range): alkaline phosphatase, 577.00 U/L (38–126 U/L); serum calcium, 3.44 mmol/L (2.25–2.75 mmol/L); serum phosphorus, 0.61 mmol/L (0.74–1.39 mmol/L); calcium-to-phosphorous (Ca/P) ratio, 5.64; absolute lymphocyte value, 0.94×10^9/L ($[0.8–4] \times 10^9$/L); absolute monocyte value, 0.20×10^9/L ($[0.12–1] \times 10^9$/L); lymphocyte-to-monocyte ratio (LMR), 4.7; urea nitrogen, 5.23 mmol/L (3.2–7.1 mmol/L); blood creatinine, 73.80 μmol/L (58–110 μmol/L); and uric acid, 378.90 μmol/L (208–506 μmol/L).

After admission, he underwent the following radiological imaging examinations: (1) computed tomography (CT) of bilateral hips, femurs, and knees, which revealed multifocal osteolytic bone lesions in the bilateral ilia, left ischium, right proximal femur, and left femur (Figure 1); (2) X-ray and CT of the chest, which showed multifocal osteolytic bone lesions in bilateral ribs (Figure 2); and (3) MRI of bilateral hips and left shoulder joint, which uncovered multiple irregular-shaped lesions in the right femoral head, right greater trochanter of the femur, left femoral neck, left lesser trochanter of the femur, and left ilium, while the left acetabulum showed slightly

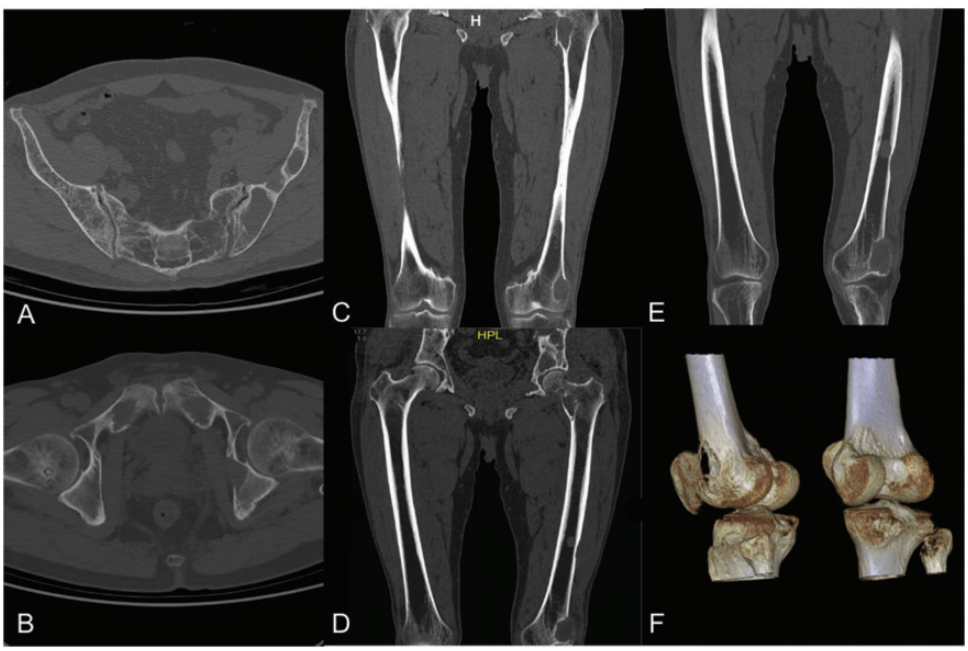

Figure 1. Three-dimensional reconstruction of computed tomography imaging of bilateral hips, femurs, and knees. Axial position (a–b), coronal multiplanar reconstruction (c–e), and volume reconstruction (f) of the bilateral hips, femurs, and knees.

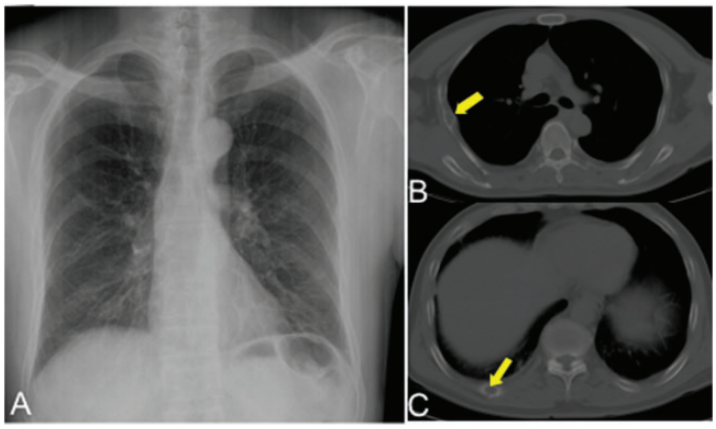

Figure 2. Standard posteroanterior X-ray (a) and computed tomography (b–c) of the chest.

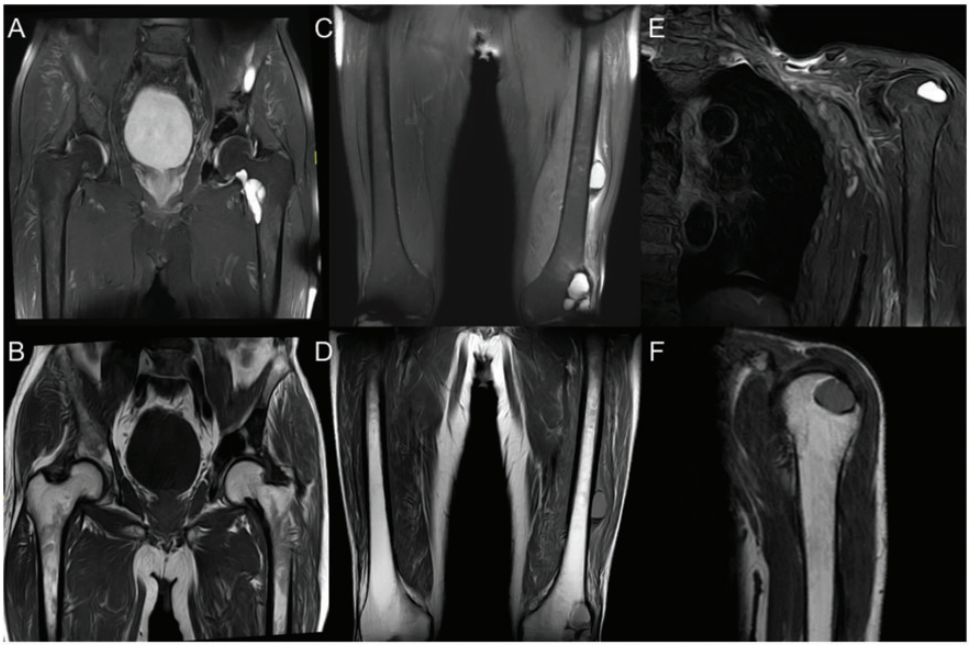

Figure 3. Magnetic resonance imaging of bilateral hips, bilateral femurs, and the left shoulder joint. Coronal T2 weighted image with fat suppression (a), coronal T1 weighted image (b) of bilateral hips. Coronal T2 weighted image with fat suppression (c), coronal T1 weighted image (d) of bilateral femurs. Coronal T2 weighted image with fat suppression (e), sagittal T1 weighted image and (f) of the left shoulder joint.

hyperintense signal on T1 weighted images and hyperintense signal on T2 weighted images with fat suppression. Hypointense signal on T1 weighted images and hyperintense signal on T2 weighted images with fat suppression were observed in the bilateral pubes, left acetabulum, and left ilium (Figure 3a–d). A $2.6 \times 2.2 \times 1.9$-cm mass with slightly hyperintense signal on T1 weighted images, hyperintense signal on

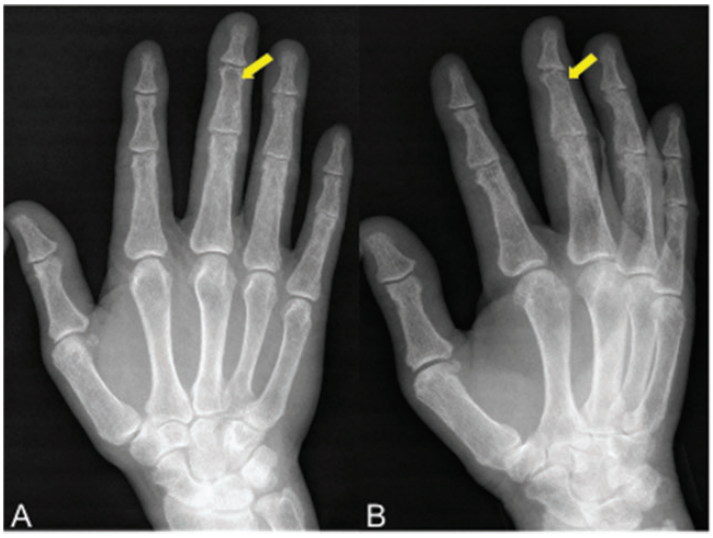

Figure 4. Standard anteroposterior (a) and oblique and (b) X-ray of the right hand.

T2 weighted images with fat suppression, and a clear boundary was observed in the left humeral head (Figure 3 e–f). (4) X-ray of the right hand showed an oval-shaped osteolytic lesion in the distal middle phalanx of the middle finger (Figure 4).

In consideration of the patient's radiological findings and blood test results, HPT was suspected. Thus, the following investigations were performed: (1) ultrasound of the thyroid gland and cervical lymph nodes, which revealed a solid nodule in the right lobe of the thyroid gland with TI-RADS: 3, a cystic nodule in the right lobe of the thyroid gland with TI-RADS: 2, and a cystic nodule in the left lobe of the thyroid gland with TI-RADS: 3; (2) CT of the thyroid gland, which showed a hypodense nodule in the right lobe of the thyroid gland of approximately 1.0 cm in diameter with an unclear boundary and a nodular lesion at the edge of the right lobe of the thyroid gland of approximately 4.0 cm in size (Figure 5). Laboratory results of bone metabolism markers were as follows (normal range): PTH, 2365.00 pg/mL (10–69 pg/mL); N-MID osteocalcin, >300.0 ng/mL (15–46 ng/mL); total type I collagen N-terminal extended peptide, 459.90 ng/mL (17–65 ng/mL); β-collagen special sequence >6.00 ng/mL (0.016–0.584 ng/mL), and 25-hydroxy-vitamin D, 14.53 ng/mL (15–25 ng/mL). The patient's clinical results were suggestive of brown tumors, HPT, a parathyroid mass, and thyroid nodules. Considering the distinct treatments for PHPT and SHPT, the causes of HPT needed to be

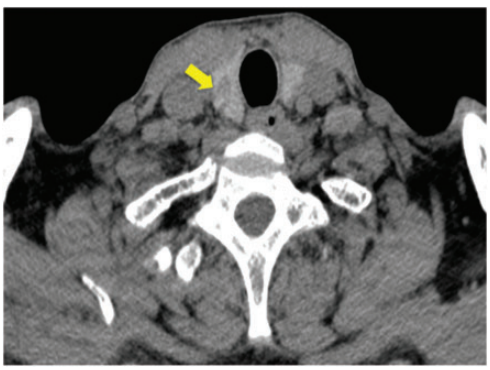

Figure 5. Computed tomography scan of the thyroid gland.

identified. SHPT induced by nephropathy, for which calcium mimetics and vitamin D analogs are the main treatment,[7] was first ruled out because the patient's renal function was normal and there was no evidence of renal calcium deposits or any other nephropathy. Meanwhile, because the diameter of the tumor was 4.0 cm (>2.8 cm) and the patient's LMR was 4.7 (<4.85), PHPT-induced brown tumors caused by parathyroid carcinoma were the most likely diagnosis.[8]

After approval by the patient, he underwent right subtotal thyroidectomy and right inferior total parathyroidectomy. Subsequent pathological examination confirmed parathyroid carcinoma and nodular goiter combined with adenoma. Immunohistochemical results of the parathyroid gland showed PTH (+), Tg (−), TTF-1 (−), CD34 (vascular +), and Ki-67 (5%+). Arterial blood gas analysis was performed every 20 minutes during surgery, and the results were 1.90 mmol/L, 1.15 mmol/L, and 1.52 mmol/L. Thus, intraoperative sodium, potassium, magnesium, calcium, and glucose injection (500 mL) plus 2-g calcium gluconate injection was given intravenously to prevent the hungry bone syndrome. One day after surgery, blood tests showed the following results (normal range): serum calcium, 2.65 mmol/L; serum phosphorus, 0.57 mmol/L; serum magnesium, 0.67 mmol/L (0.70–1.07 mmol/L); and serum potassium, 3.50 mmol/L (3.5–5.5 mmol/L). To continue preventing bone starvation syndrome, the patient was immediately given the following treatments: 2 g calcium gluconate injection (intravenous drip), 1.25 g magnesium sulfate injection (intravenous drip), Calcitriol Soft Capsules *via* oral administration, calcium carbonate and vitamin D3 tablets *via* oral administration, and potassium citrate *via* oral administration. His PTH level dropped to 1.72 pg/mL within 1 week after surgery. His serum calcium and phosphorus levels were 2.65 mmol/L and 0.57 mmol/L, respectively. Owing to the severe bone destruction of the patient's left knee that limited movement, the patient agreed to undergo total knee arthroplasty to restore movement of the knee joint and improve quality of life (Figure 6). Hematoxylin and eosin staining confirmed the diagnosis of parathyroid carcinoma (Figure 7a–b) and brown tumors (Figure 7c–d). Immunohistochemical results indicated the following: P63 (−), CD68 (partial +), SATB2 (+/−), KI67 (5%+), SMA (several +), CD34 (vascular +), MDM2 (−), and H3.3G34W (+/−). Improved postoperative knee movement without pain or discomfort was obtained. After discussing the remaining multifocal osteolytic bone lesions, the patient decided to let them recover spontaneously as the PTH levels returned to normal. Seven months after discharge, blood investigations (PTH, 55.87 pg/mL; serum calcium, 2.29 mmol/L; serum phosphorus, 1.23 mmol/L; and Ca/P ratio, 1.86), survival status, movement of the left knee, and recovery of the remaining lesions were satisfactory.

Discussion

Brown tumors are pathological lesions caused by abnormal PTH levels in patients with HPT. PHPT is less common than SHPT, with incidence rates of 1.5% and 11%, respectively.[9] The main causes of PHPT include solitary adenoma (80%–85%), parathyroid hyperplasia (10%–15%), multiple adenomas (5%), and parathyroid carcinoma (1%–5% or less).[10] In this case, PHPT was caused by right parathyroid carcinoma and had a great impact on serum calcium and phosphate levels, resulting in a bone metabolism disorder. The radiological characteristics of brown tumors present multifocal osteolytic bone lesions with clear boundaries, which is similar to aneurysmal bone cysts, GCTs, bone metastases, multiple myeloma, and malignant fibrous histiocytoma.

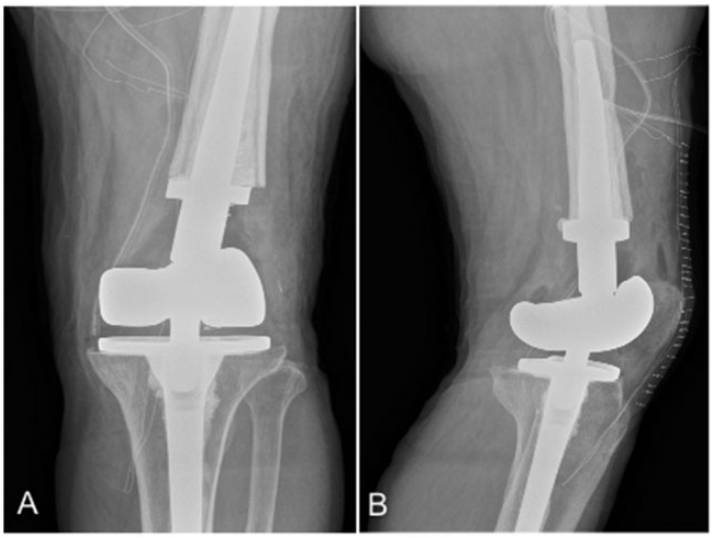

Figure 6. Standard anteroposterior (a) and lateral and (b) X-ray of the postoperative left knee.

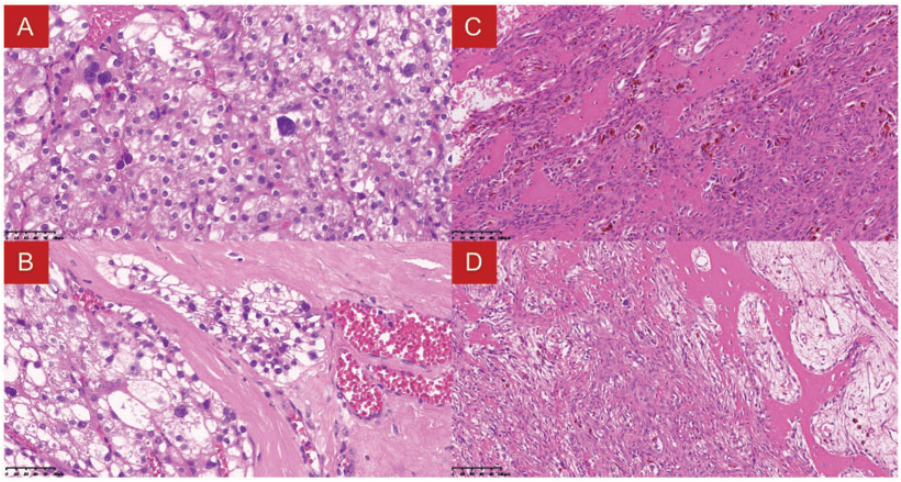

Figure 7. Hematoxylin and eosin staining of parathyroid carcinoma (a–b, magnification: 400×) and brown tumor (c–d, magnification: 200×) samples.

The clinical symptoms of the patient in this case were atypical with only pain and limited movement of the left knee joint. MRI findings showed that a cystic lesion was observed in the left knee joint, indicating a misdiagnosis of GCTs. The nonspecific signs and symptoms, lack of experience by clinicians, and insufficient examinations increase the rate of misdiagnosis, leading to inappropriate treatments of local lesions without management of HPT. These situations lead to limited surgical efficacy, risk of fracture malunion, or internal fixation breakage.

Although it has been reported that the rate of musculoskeletal manifestations in

patients with HPT can reach 54.7%,[11] the multifocal osteolytic bone lesions and nonspecific symptoms add to the difficulty of diagnosing brown tumors. Apart from total knee arthroplasty to restore knee movement and relieve pain, no other surgery was performed to treat the osteolytic lesions in this case. However, when reviewing the literature, there were misdiagnoses in several cases. Zhong et al.[12] reported the case of a 44-year-old Asian male patient with pain in the left shoulder joint for 2 months who was diagnosed with aneurysmal bone cysts after several multinucleated giant cells were observed without atypia *via* an ultrasound-guided puncture biopsy. Postoperative pathology revealed the tumor was a brown tumor caused by PHPT. Panagopoulos et al.[13] presented the case of a 53-year-old white male who was initially misdiagnosed with GCTs and underwent unnecessary surgery, although it was ultimately diagnosed as brown tumors by electrolyte examination and elevated PTH levels. Brown tumors, GCTs, and aneurysmal bone cysts cannot be distinguished by histology alone due all three presenting similar pathological features, with multinucleated giant cells and tough vascular fibrotic matrix. Thus, it is crucial to combine clinical data and laboratory tests when pathologists make the diagnosis. Additionally, the age and imaging features of aneurysmal bone cysts can be evidence to distinguish from brown tumors. Aneurysmal bone cysts usually affect patients in their teens and 20s and shows fluid levels on MRI. GCT and HPT are usually not encountered at the same time.[14] The exception is that Ouzaa et al.[15] described the case of a 66-year-old woman with osteolytic lesions in the distal radius and PHPT; thus, she was diagnosed with brown tumors. After 1-year follow-up, her osteolytic lesions had not recovered but rather gotten worse, of which the biopsy was suggestive of GCT. The effect was remarkable after surgery. Therefore, when diagnosing such cases, monism should not be the only idea considered. Combined with the patient's clinical manifestations, laboratory tests, radiological imaging, and biopsy, clinicians should be aware that sometimes GCT and HPT exist at the same time.

Brown tumors can also occur in some rare sites including the spine, especially involvement of the cervical spine. Alfawareh et al.[4] reported the case of a 26-year-old female college student who was admitted due to pain in the cervical spine for 2 months. X-ray and MRI detected the osteolytic bone lesion in the second cervical vertebra, while another was found in the mandible. Parathyroid mass, high PTH levels, and systemic findings from the bone scan raised the possibility of brown tumors of the bone. Three months after parathyroidectomy, a CT scan revealed a good level of calcification and filling of the lesions. This case provides clinicians the possibility that when osteolytic changes occur in the spine, apart from bone metastases, brown tumors should be taken into consideration. Notably, bone metastases are mostly seen in middle-aged or elderly patients and with primary tumors, which can easily be distinguished from brown tumors.

PHPT diagnoses on the basis of serum calcium and PTH are not completely accurate due to the presence of normocalcemic PHPT, normohormonal PHPT, and non-PHPT-related hypophosphatemia. Considering that calcium and phosphorus homeostasis are directly interrelated *via* several hormones and that their serum concentration is approximately inversely related even in PHPT, Madeo et al.[16,17] proposed the Ca/P ratio, which was shown to be a highly accurate indicator for diagnosing PHPT in single and multicenter studies, with cutoff values of 2.71 and 2.55 mmol/L, respectively. The Ca/P ratio of the patient in this report before surgery was

5.64 (much higher than 2.71), but after systemic therapy, the Ca/P ratio dropped to 1.86, which validated the findings of Madeo et al. Additionally, Ohkuwa et al.[8] demonstrated that patients with tumor diameters greater than 28 mm and LMR less than 4.85 had a higher probability of parathyroid carcinoma. In this case, the tumor diameter was 4.0 cm and LMR was 4.7; postoperative pathology confirmed parathyroid carcinoma. This suggested that preoperative assessment of inflammatory markers and the Ca/P ratio makes sense when diagnosing PHPT to distinguish between benign and malignant parathyroid tumors.

Regarding treatment, brown tumors generally spontaneously regress after parathyroidectomy. Thus, it is not advised to select a therapy only on the basis of Mirel's score, unless the tumor limits the movement of a joint or elicits pathological fractures, wherein surgery is indispensable.[12] In this case, although the parathyroid carcinoma had been removed, the patient still underwent total knee arthroplasty to restore knee movement, which improved the patient's quality of life. Previously, Zhong et al.[12] reported a case in which lesions of the proximal left humerus were resected because the brown tumor in that case was very large and could easily cause pathologic fractures. Hu et al.[18] reported the case of a 50-year-old woman with left elbow and thoracodorsal pain who was later diagnosed with multifocal brown tumors. Conservative treatment to raise serum calcium levels and surgical interventions to remove the parathyroid adenoma were efficient therapies. At her 1-year follow-up, the bone lesions had completely disappeared.

In conclusion, this case report emphasizes that diagnoses for multifocal osteolytic bone lesions are not limited to metastatic tumors or multiple myeloma and that emission computed tomography and serum protein electrophoresis can easily distinguish the possible diseases.[19] PHPT-induced brown tumors also need to be included in the differential diagnosis of osteolytic lesions to avoid unnecessary surgery and improve prognosis. Clinical and histopathological diagnosis is not enough for brown tumors. A comprehensive analysis that combines clinical symptoms, imaging, and laboratory tests is also required. Thus, surgeons, pathologists, and radiologists need to keep in close communication and not be limited by monism when diagnosing multifocal osteolytic bone lesions.

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Author contributions

All authors contributed to the study conception and data collection. Data and literature analyses were performed by Zhongkai Zhou, Ying Shi, Chao Li, and Wei Wang. The first draft of the manuscript was written by Zhongkai Zhou, Ying Shi, and Chao Li. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author on request (Contact Wei Wang, 1391082196@qq.com).

Declaration of conflicting interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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