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**Kosuke Kita**
Department of Orthopedic Surgery, Osaka International Cancer Institute, Osaka, Japan

**Shigenori Nagata**
Department of Diagnostic Pathology and Cytology, Osaka International Cancer Institute, Osaka, Japan

**Hironari Tamiya**
a) Department of Orthopedic Surgery, Osaka International Cancer Institute, Osaka, Japan
b) Department of Rehabilitation, Osaka International Cancer Institute, Osaka, Japan

**Corresponding Author:**
**Kosuke Kita**
Department of Orthopedic Surgery, Osaka International Cancer Institute, Osaka, Japan

# Osteolytic lesions caused by hyperparathyroidism mimicking multiple bone metastases

**Kosuke Kita, Shigenori Nagata and Hironari Tamiya**

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**Abstract**
Multiple osteolytic lesions in elderly patients are usually metastatic bone tumors, while brown tumor is a rare disease featuring osteolytic lesions associated with hyperparathyroidism. In this report, we present the case of a 62-year-old male with hyperparathyroidism-induced multiple osteolytic lesions that mimicked multiple metastatic bone tumors. At initial presentation, the radiographic images were compatible with metastatic bone tumors; therefore, we performed a needle biopsy on the iliac lytic lesions, which revealed no evidence of malignancy. Furthermore, we performed an operation on the left radial pathological fracture and obtained sufficient sample for histological examination, which again showed no evidence of malignancy. Hence, while investigating for other diseases, we found a tumor in the left thyroid and high levels of intact-parathyroid hormone (PTH), which was a strong clue to the diagnosis of PHPT caused by a parathyroid adenoma. After the resection of the parathyroid adenoma, intact-PTH and calcium levels returned to normal. In conclusion, clinicians including orthopedic specialists should consider the possibility of brown tumors in case of aforementioned clinical features.

**Keywords:** Brown tumor, metastatic bone tumor, hyperparathyroidism, parathyroid adenoma, hypercalcemia

## Introduction
Osteolytic lesions are often observed in conditions such as primary benign and malignant bone tumors, metastatic bone tumors, or metabolic bone disease. Physicians should pay attention to the possibility of metastatic bone tumors in elderly patients because painful bone lesions can occur before the primary site of asymptomatic cancer is identified. Metastatic bone tumors are common among patients with primary cancer of breast, lung, prostate, and thyroid. Furthermore, bone metastases are the most common cause of the bone tumors; however, up to 30% of patients with bone metastases have no evidence of the primary tumor at presentation [1].

Blood tests and images including tumor markers, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography are occasionally unable to detect primary cancer. In such cases, the bone lesions should be examined by needle or open biopsy to obtain a histological diagnosis. However, osteolytic lesions do not necessarily indicate metastatic bone tumors.

Primary hyperparathyroidism (PHPT) is mainly triggered by parathyroid adenoma. The longest natural history study, performed by Rubin *et al.*, with 15 years of follow-up enrolled 121 patients, 86% of whom were asymptomatic [2]. In case of symptomatic patients, typical symptoms of PHPT induced by hypercalcemia include gastrointestinal dysfunction, neurological disturbance, bone disease, and kidney stones.

Bone lesions are one of the symptoms induced by PHPT. Hyperparathyroidism-induced osteolytic lesions, referred as brown tumors, occur in only 1.5%-4.5% of patients with hyperparathyroidism [3]. The name “brown tumor” originated from their gross histological appearance of being a brownish mass, which consists of a combination of recurrent microfractures at various stages of remodeling made up of blood, hemosiderin, and fibrous and connective tissues.

Multiple osteolytic lesions are often present as metastatic bone tumors, particularly in elderly patients. Therefore, for clinicians, brown tumors are sometimes difficult to diagnose.

## Case report
A 62-year-old man visited a hospital with pain and swelling in the left forearm without a history of trauma. A plain digital radiograph in the affected left forearm revealed a lytic

expansile lesion with a fracture in the left radial shaft (Figure 1A and B). The patient was diagnosed with a metastatic bone tumor and referred to our institution for specialized treatment. We also suspected a metastatic bone tumor based on his age (>60 years) with a pathological fracture and a lytic mass. MRI, CT, and blood tests were performed to locate other osteolytic lesions and the primary cancer site. The CT revealed osteolytic lesions in the right ilium and right pubis (Figure 1C and D) and a low-density area in the thyroid left lobe and lytic bone lesions in both pelvic bones and the right clavicle (Figure 2A). Whole-body MRI (diffusion-weighted whole-body imaging with background body signal suppression) showed foci of low signal intensity within the fifth thoracic vertebra, fourth lumbar vertebra, pelvic bones, and right clavicle (data not shown). The diffusion-weighted MRI revealed a mass in the left thyroid lobe (Figure 2B). Laboratory blood analysis showed an extremely high serum calcium (Ca) level (14.7 mg/dL; normal range, 8.4–10.7 mg/dL); additionally, serum alkaline phosphatase (ALP) level was elevated (862 IU/L; normal range, 50–240 IU/L). Among tumor markers, serum prostate-specific antigen and cytokeratin-19 fragments level was 6.620 ng/mL (normal level ≤ 4 ng/mL) and 3.5 ng/mL (normal level ≤ 2.8 ng/mL), respectively. The levels of other tumor markers including those for thyroid cancer were within normal ranges (Carcinoembryonic antigen (CEA): 1.7 ng/ml (normal level ≤ 5 ng/mL), thyroglobulin: 10.3 (normal level ≤ 33.7 ng/mL). The possible primary site of malignancy was thought to be thyroid, prostate, or of a hematopoietic origin (as seen in multiple myeloma).

To detect the origin of the suspected bone metastases, CT-guided needle biopsy was performed on osteolytic lesion in the left ilium. The biopsy revealed only fibrotic marrow with hemosiderin deposition and no evidence of malignancy (Figure 3A).

An open reduction and internal plate fixation and open biopsy were performed and again, there was no evidence of malignancy (Figure 3B). Hence, this case with osteolytic lesions seemed not to be of bone metastasis but of another disease including hyperparathyroidism. Consequently, an additional laboratory test was conducted. We found that serum intact-PTH level was 1070 pg/mL (normal range, 10-65 pg/mL). Thus, we strongly suspected PHPT and consulted an otolaryngologist who suspected parathyroid adenoma rather than carcinoma from the result of sestamibi scan (data not shown). A single adenoma was found at the surgery and parathyroidectomy was then performed. Afterwards intact-PTH levels went down to normal (Table 1) and Ca and ALP levels also decreased. We histopathologically confirmed the condition as parathyroid adenoma, which was an encapsulated nodule without any invasive features or vascular permeation (Figure 3C). Currently, pain from the multiple osteolytic lesions have completely alleviated and no breakage of the fixed plate on the right radial fracture has been observed (Figure 4A and B). New bone formation/bony union of the left proximal fracture is also in progress (Figure 4C-E).

## Discussion

In the present case report, we presented a brown tumor in 62-year-old male patient that mimicked multiple bone metastases. We initially suspected bone metastases although hypercalcemia and low-density area in the thyroid left lobe were found. When we reviewed this case, there were two key points that misled us.

First, age is an important factor to diagnose osteolytic lesions. We often experience multiple bone metastases from various types of cancer, particularly in elder patients. A previous paper suggested that the most frequent diagnoses of bone tumor and tumor-like lesion in patients between 40 and 60 years-old were plasmacytoma/myeloma (19.4%), giant cell tumor (14.1%) and metastases (12.3%). In patients older than 60 years, prevalence was metastases (37.2%), plasmocytoma/myeloma (11.8%) and malignant fibrous histiocytoma (6.7%) [4]. This means that age is strongly related to diagnosis for bone tumor and tumor-like lesion and the most frequent diagnosis is metastasis in elderly patients.

Another reason is characteristics of brown tumors. When it comes to tumor location, there is a difference in the preferred location; the mandible, ribs, clavicle, and pelvis are more likely, and the spine is not a common location for brown tumors [5]. In contrast, the spine is a common site for metastatic bone tumors. Furthermore, brown tumors affect more women than men and are most common in individuals aged between 20 and 50 years old. Rarity of brown tumors (prevalence: 1.5%-4.5% of hyperparathyroidism cases) is another trait [3].

In our case, CT revealed a low-density area in the left thyroid lobe and osteolytic lesions in both pelvic bones and the right clavicle; therefore, we suspected multiple metastases of cancer from the thyroid. However, cases of bone metastases from thyroid carcinomas are rare, and the prevalence is 3.8%-4.2% [5]. Considering the low occurrence of bone metastases from thyroid carcinoma, we should have suspected other diseases including brown tumors.

Brown tumors occurs due to hyperparathyroidism in which Ca level tends to be high, and the measurement of PTH level is essential for diagnosis. In our case, considering high Ca level, hyperparathyroidism should have been deemed as a diagnosis. We recommend examination of the serum PTH level in such cases.

For treatment of brown tumors, parathyroidectomy is essential. Aslan *et al*. reported a case in which Ca and PTH levels got back to normal and the size of brown tumors shrinked after parathyroidectomy [6]. Similarly, in our case, Ca and PTH level went down to normal level and bone pain was drastically alleviated after parathyroidectomy. According to a previous report, Ca level may decline remarkably as a result of osteogenesis after surgery, which may induce hypocalcemic symptoms such as tetany. Therefore, prophylactic administration of calcium and activated vitamin D may be necessary to maintain normal Ca levels [7].

Hyperparathyroidism is categorized into three main types, primary, secondary and tertiary. Primary hyperparathyroidism (PHPT) is characterized by persistent hypercalcemia in the setting of elevated or inappropriately normal PTH levels. Secondary hyperparathyroidism is the elevation of PTH in response to hypocalcemia. Tertiary hyperparathyroidism can develop after any long-standing period of hypocalcemia which also causes parathyroid chief cell hyperplasia and excess PTH. PHPT occurs in approximately 1% of adults, particularly in middle-aged women. Parathyroid adenomas are the leading cause of PHPT, accounting for approximately 80% of cases [8]. Other causes are multiple adenomas, hyperplasia, and parathyroid

cancer, with the latter estimated to occur in only 1% of patients [9]. Many patients diagnosed with PHPT do experience bone pain prior to having the symptoms such as gastrointestinal dysfunction, or neurological disturbance or having osteopenia or osteoporosis [10]. From this point of view, physicians including orthopedists should pay attention to the presence of PTPH-induced brown tumors in patients with osteolytic lesions with thyroid/parathyroid mass.

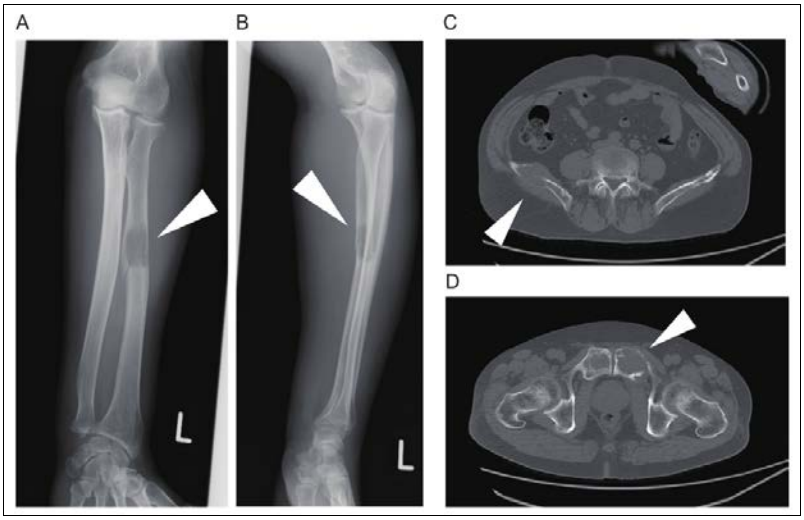


**Fig 1:** The left radial pathological fracture and multiple osteolytic lesions in the right ilium and the left pubis
Plain X-ray AP view (A) and lateral view (B) showing osteolytic lesion and the fracture line without marginal sclerosis in the left radius. CT depicted osteolytic lesions in the right ilium (C) and left pubis (D). Arrowheads indicate osteolytic lesions.

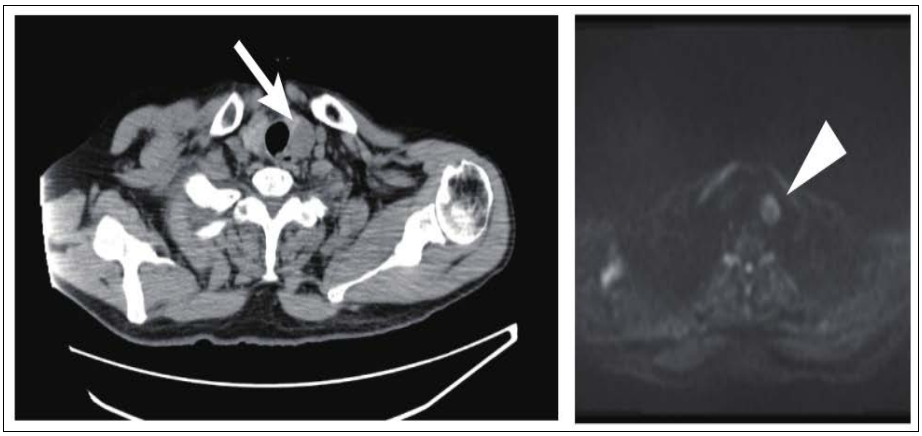

**Fig 2:** A mass observed in the left thyroid.
A low-density mass in the left thyroid was identified on CT (A) and is highlighted in diffusion-weighted MRI (B). Arrow and arrowhead indicate the tumor mass.

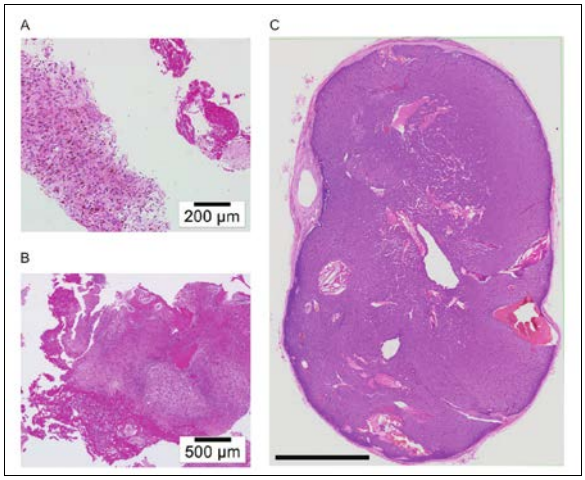


**Fig 3:** Histologic findings of brown tumor association with parathyroid adenoma
Left iliac biopsy demonstrating a fibroblastic proliferation admixed with hemosiderin laden macrophages (A; hematoxylin and eosin [HE] stain, x 100). Open biopsy revealing fibrous tissue with supporting vasculature, accompanied by reparative woven bones (B; HE, x 40). Section showing a well circumscribed nodule, 4 cm in largest diameter, composed of compact parathyroid-chief cells without capsular invasion (C; HE, loupe view; black bar, 5 mm).

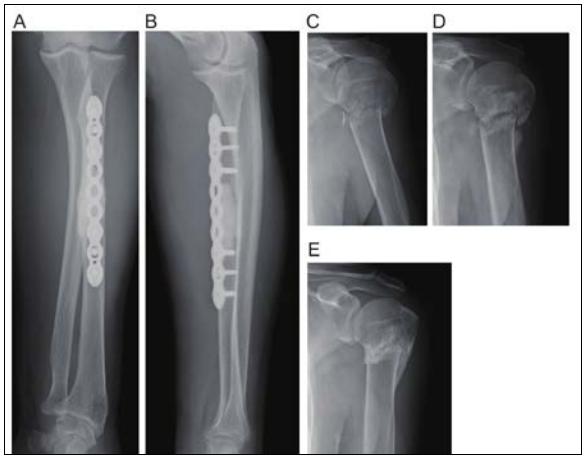


**Fig 4:** Postoperative images of the left radial fracture and bone healing of the left proximal humeral fracture
Plain X-ray AP view (A) and lateral view (B) one year after open reduction and internal plate fixation and open biopsy of the left radial fracture. Radiographic images of the left proximal humeral fracture 1 month before (C), 3 months (D) and 11 months after (E) parathyroidectomy are shown.

**Table 1:** Levels of serum calcium, alkaline phosphatase, and intact-PTH before and after parathyroidectomy

| | Preoperative state | Postoperative state |
|---|---|---|
| Ca (8.8-10.1 mg/dl) | 14.7 | 9.1 |
| ALP (106-322 U/I) | 862 | 448 |
| Intact-PTH (10-65 pg/ml) | 1070 | 67 |

## Conclusion
We experienced brown tumors that mimicked bone metastases. It is important to examine serum PTH level in case of hypercalcemia with thyroid mass for appropriate diagnosis.

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## Declaration of conflicting interests
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Author contributions
All authors reviewed and approved the final manuscript.

## Informed consent
The patient provided consent to participate and publish this case report.

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