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Fever as the First Clue: an Atypical Case of Occult Brown Tumor

La fiebre como primer hallazgo: un caso atípico de tumor marrón oculto

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Abstract

A 46-year-old asian male presented with throat pain, hoarseness, dry cough and persistent high-grade fever unresponsive to antibiotics. Imaging showed left upper lobe consolidation and bronchoscopy revealed no infectious cause. Although the patient initially improved with intravenous antibiotics, fever recurred post-discharge, prompting further evaluation. Imaging identified multiple lytic bone lesions, initially suggestive of malignancy. However, bone biopsy revealed osteitis fibrosa cystica (Brown tumor), indicating metabolic bone disease. Laboratory tests showed markedly elevated parathyroid hormone (PTH) levels with high-normal serum calcium, confirming primary hyperparathyroidism. PET-CT and parathyroid scintigraphy localized a left inferior parathyroid adenoma. Surgical resection of the adenoma led to normalization of PTH levels and resolution of systemic symptoms, including fever. This case highlights fever as an atypical presentation of primary hyperparathyroidism and underscores the importance of considering endocrine disorders in cases of pyrexia of unknown origin, especially when conventional infectious and malignant causes are excluded.

Keywords: brown tumor, fever, hyperparathyroidism, parathyroid hormone (PTH), osteitis fibrosa cystica, pneumonia.

Introduction

Brown tumors (BT) are rare bone lesions, occurring in about 0.1% of individuals, most often in women over 50 with poorly controlled hyperparathyroidism.[1] Excess parathyroid hormone (PTH) increases osteoclastic activity, leading to bone resorption, demineralization, microfractures, haemorrhage, and accumulation of fibrous tissue and giant cells. These changes form tumor-like lesions. Although they can develop in any bone, BT is most commonly found in the ribs, clavicles, long bones of the extremities and pelvic bones.[2]

Diagnostic evaluation of BT involves serum calcium, phosphorus and PTH levels, followed by imaging such as X-rays and CT scans to detect lytic bone lesions. Parathyroid scintigraphy (99mTc-sestamibi) helps localize hyperactive or enlarged parathyroid glands, while bone scintigraphy, when done, shows increased uptake in affected areas. Histopathology is essential for confirmation, but its findings—mononuclear cells mixed with multinucleated giant cells—are also seen in giant cell tumors (GCTs), leading to possible misdiagnosis. Imaging features may mimic other osteolytic lesions like multiple myeloma or lytic metastases.[3-6] Thus, identifying under-

lying hyperparathyroidism is key. Although elevated PTH is a hallmark of the condition, it is not routinely tested, making the diagnosis of BT especially challenging for clinicians.[3,7]

BT typically causes bone pain, swelling or pathological fractures. Atypical symptoms include nerve compression, spinal cord involvement or incidental imaging findings in uncommon sites[8]. This case report describes a middle-aged man with fever of unknown origin initially thought to have infective pneumonitis, later diagnosed with BT.

Case report

A 46-year-old Asian male (BMI: 24.34) presented with throat pain, hoarseness of voice, dry cough and intermittent high-grade fever for eight days, unresponsive to one week of oral empirical antibiotics. Vital signs were normal. Respiratory examination revealed left-sided crepitations; other systemic examination was unremarkable. Serological tests showed elevated erythrocyte sedimentation rate (ESR) of 44 mm/hr and C-reactive protein (CRP) at 15.67 mg/L. Liver function tests revealed elevated alkaline phosphatase (ALP) at 498.19 U/L. Refer to Table 1 for detailed laboratory investigations.

Table 1.
Routine laboratory investigations.

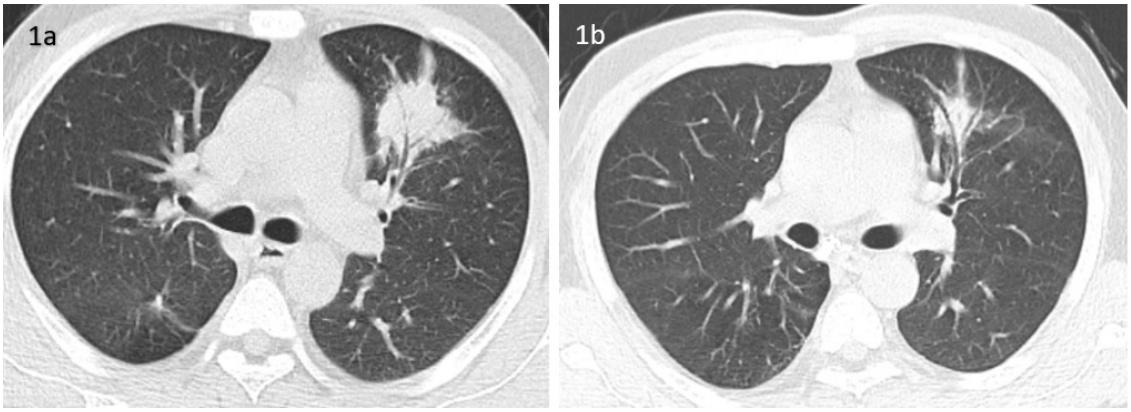
Laboratory investigations	Results	Normal range
1st time admission		
HIV I&II Antibodies	Non -Reactive	
Anti HCV-Total	Non -Reactive	
Australia Antigen (HBsAg)	Negative	
CBC	WNL	
CRP	15.67mg/L	≤ 5
ESR (Wintrobe)	44 mm/1hr. 45(26/3/25)	0-9
Alkaline Phosphatase	498.19 U/L	54-369
Scrub typhus IgG & IgM	Negative	
Urine test	WNL	
BAL for		
Gram staining (Bronchial aspirate)	No organism	
AFB smear examination	Acid Fast Bacilli not seen	
Fungal staining (Bronchial aspirate)	Fungal Elements not seen	
GeneXpert MTB/RIF assay	MTb Not Detected	
Bacterial culture	No growth	
Cytopathology	Negative for malignancy	
2nd time admission		
CBC	WNL	
CRP	31.35 mg/L	≤ 5
Procalcitonin	0.13 ng/ml	< 0.5
Urine routine	WNL	
Malarial Antigen (Vivax & Falciparum) Detection test	Negative	
Widal slide test	No agglutination	
Scrub typhus IgG & IgM	Negative	
Anti-CCP	< 3.5 U/ml	0-5
Pre-operative tests		
TSH (Ultrasensitive)	3.24 µlU/ml	0.35-5.0 µlU/ml
Free T3	2.39	1.71 - 3.71 pg/ml
Free thyroxine (FT4) Free T4	0.79 ng/ml	0.7 – 1.48 ng/ml
PTH	916.6 pg/ml	14-72 pg/ml
Serum calcium	10.16 mg/dL	8.5-10.5 mg/dL
Serum Phosphorous	2.56 mmol/L	2.5-6.4

Laboratory investigations	Results	Normal range
25-Hydroxy Vitamin D (25(OH)D) test	12.10 ng/ml	Deficiency: < 10 Insufficiency: 10-30 Sufficiency: 30-100 Hypervitaminosis: > 100
Post-operative tests		
PTH	7.00	< 1 month: 7.0 - 59 pg/ml
Serum Calcium	8.02 mg/dL	8.5-10.5 mg/dL

Abbreviations: HIV-human immunodeficiency virus; HCV- hepatitis C virus; CBC-complete blood count; CRP- C reactive Protein; ESR- erythrocyte sedimentation rate; IgG- Immunoglobulin G; IgM- Immunoglobulin M; BAL-bronchoalveolar lavage; AFB- acid fast bacillus; MTB/RIF-Mycobacterium tuberculosis/rifampicin; Anti-CCP-Anti-Cyclic Citrullinated Peptide; TSH- thyroid stimulating hormone; T3- triiodothyronine; PTH-Parathyroid Hormone.

The patient was admitted for evaluation of persistent fever. Computed tomography (CT) of the thorax revealed left upper lobe consolidation (superior lingular segment), suggestive of acute bacterial pneumonitis (Figure 1a). This led to a working diagnosis of bacterial pneumonia and bronchoscopy done showed thick secretions in the left bronchial tree. Bronchoalveolar lavage (BAL) was sent for Acid-Fast Bacillus (AFB), Gram and fungal stains, along with bacterial, fungal, AFB cultures and GeneXpert testing—all of which returned negative (Table 1). Empirical intravenous antibiotics were administered for five days. The patient improved symptomatically, became afebrile and was subsequently discharged.

Figure 1.
1.a. Computed tomography (CT) of the thorax reveals a dense airspace consolidation with air bronchogram involving the superior lingular segment of left upper lobe, suggestive of acute bacterial pneumonitis.
1.b. Computed tomography (CT) of the thorax repeated during readmission showing mild resolution in the size of the consolidation.



A day after discharge, the patient developed high-grade fever and was re-admitted. A comprehensive workup for pyrexia of unknown origin (PUO) was initiated. Investigations including CBC, urine analysis and culture, WIDAL, peripheral smear for malarial parasite, dengue NS1 antigen, procalcitonin, anti-CCP and scrub typhus IgG/IgM were all negative. However, CRP was elevated to 31.35 mg/L (Table 1). Repeat HRCT chest showed mild resolution of the consolidation (Figure 1b). Further evaluation with abdominal ultrasonography revealed a large, heterogeneous lesion in the left lobe of liver, with hyperechoic areas suggestive of a benign space-occupying lesion with intralesional haemorrhage or early abscess.

Contrast-enhanced CT of the abdomen and pelvis confirmed the hepatic lesions as haemangiomas. Nevertheless, the presence of multiple well-defined lytic lesions in the pelvic bones and lumbar vertebrae warranted further investigation via biopsy to exclude the possibility of bony

metastasis. Additional findings of cholelithiasis and bilateral non-obstructing renal calculi with simple renal cysts were also noted.

A CT-guided bone biopsy of the left iliac bone was performed using a Jamshidi needle. The specimen was sent for histopathological and cytological evaluation. Cytology showed oval to spindle-shaped cells within fibrous strands, with mild atypia and no malignancy. Histopathology revealed numerous osteoclast-like giant cells in a fibroblastic spindle cell stroma—features consistent with osteitis fibrosa cystica (BT) of the iliac bone (Figure 2).

An 18F-FDG PET/CT scan was performed. Head and neck imaging revealed an enlarged left parathyroid gland posterior and inferior to the left thyroid, measuring 15×16 mm (SUV Max <1). In the chest, a consolidation in the left upper lobe measuring 19×10 mm (SUV Max 1.5), with calcified mediastinal lymph nodes, was noted. Musculoskeletal findings included a lytic lesion in the left postero-superior iliac spine (SUV Max 7.8) and multiple permeative lumbar vertebral lesions (SUV Max <1). No other metabolically active disease was detected (Figure 3).

Neck ultrasonography showed a well-defined iso- to hypoechoic nodular lesion abutting the inferior pole of the left thyroid lobe, likely a benign parathyroid adenoma. Parathyroid scintigraphy and Single Photon Emission Computed Tomography scan (SPECT scan) showed abnormal tracer uptake in a hypodense nodule below the left thyroid lobe, measuring 1.8 × 1.4 × 2.5 cm, consistent with parathyroid adenoma (Figure 4).

Figure 2.
Histopathological analysis of the biopsy specimen showed numerous scattered osteoclast-like giant cells within a fibroblastic spindle cell stroma. Tiny vessels with red blood cells are seen within. These features were consistent with brown tumor of the iliac bone

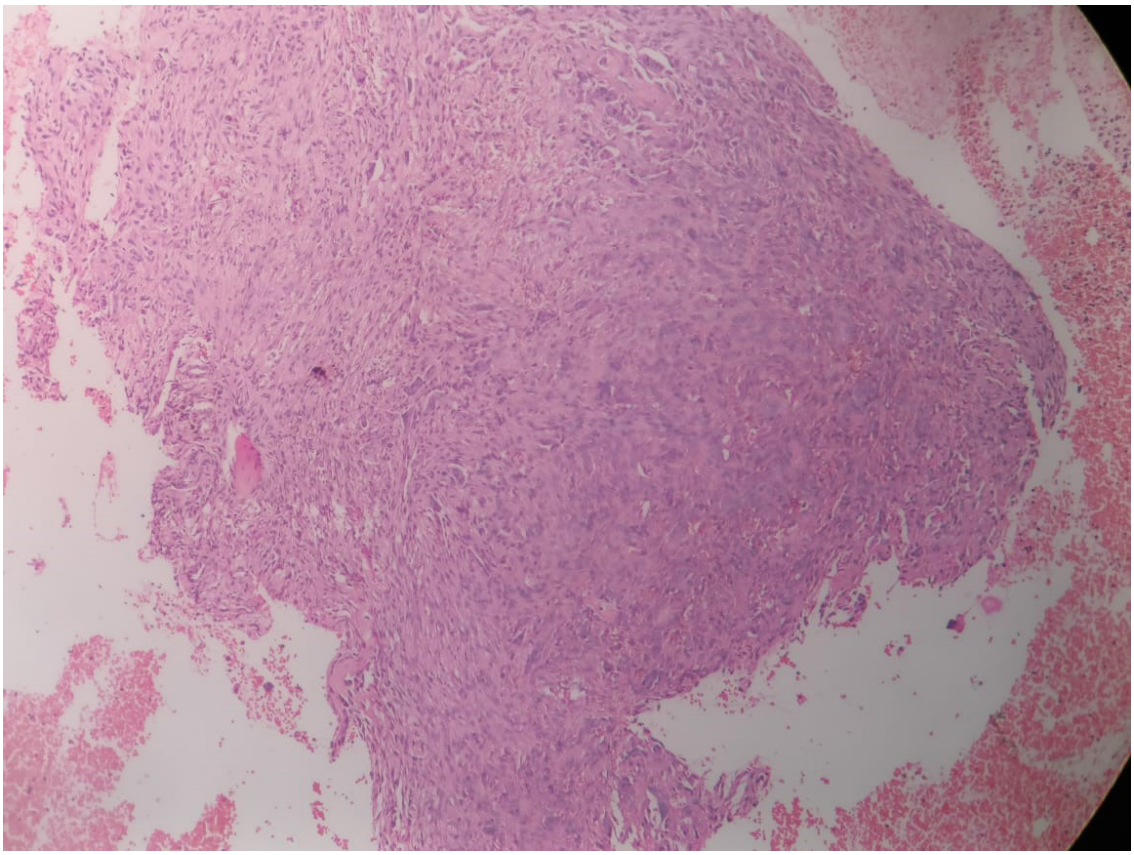


Figure 3.
An 18F-FDG PET/CT scan showing a lytic lesion in the left postero-superior iliac spine with an SUV max of 7.8.

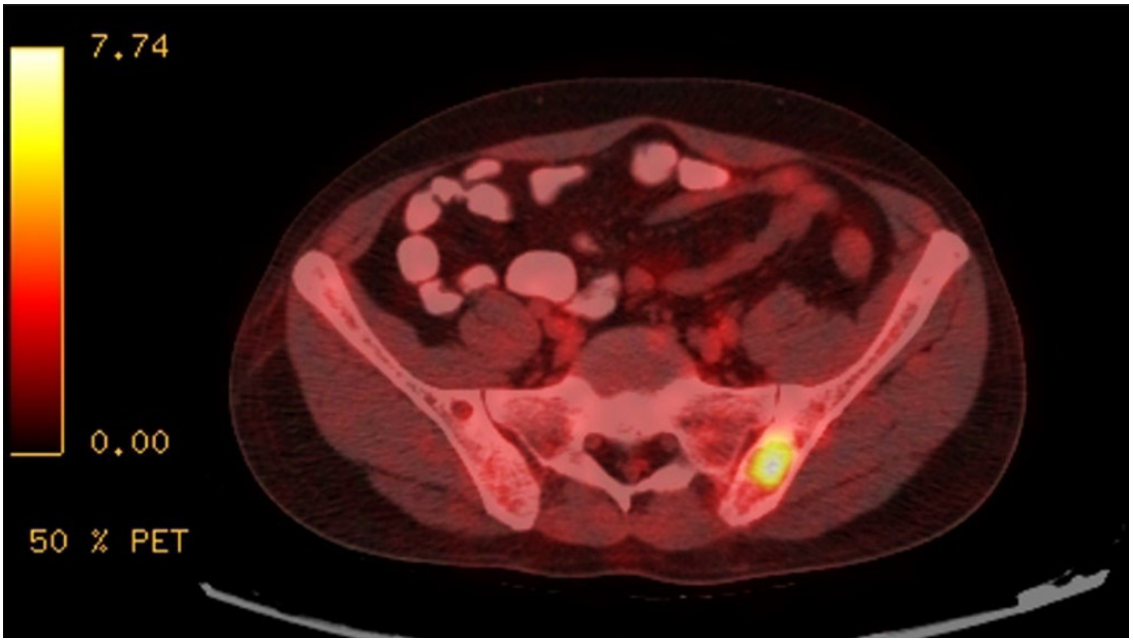
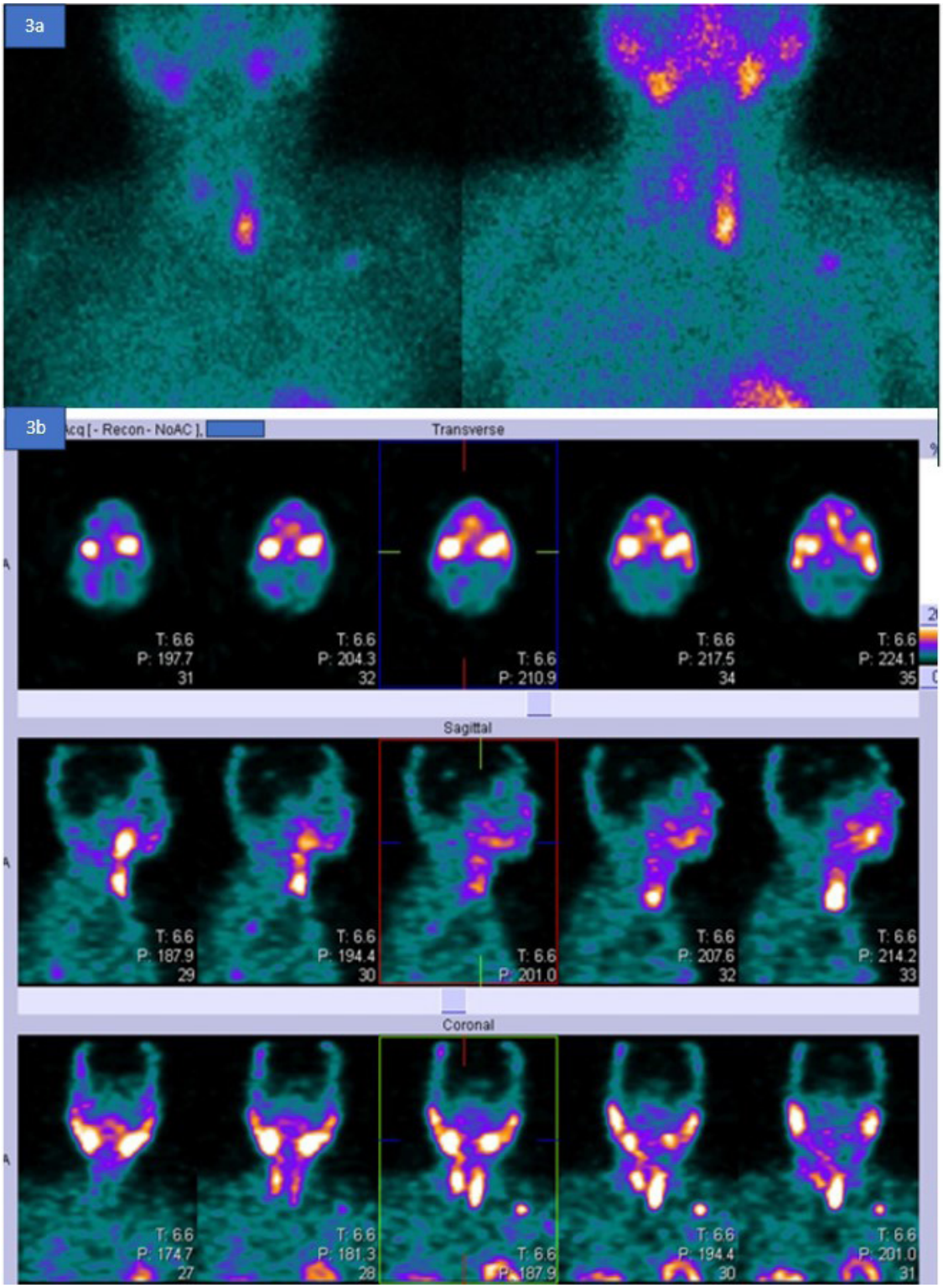


Figure 4.

4a. Parathyroid scintigraphy using 12 mCi Tc-99m Tetrofosmin including early and delayed images reveal focal increased tracer uptake inferior to in left thyroid lobe. Diffuse relatively low-grade tracer uptake is seen in the rest of the thyroid gland region, with very sluggish washout of tracer from thyroid gland, with focal tracer retention seen inferior to left thyroid lobe.

4b. SPECT-CT showing abnormal tracer uptake in a hypodense nodule below the left thyroid lobe, measuring 1.8 × 1.4 × 2.5 cm, consistent with parathyroid adenoma.



Surgical removal of the tumor was advised and an endocrinology consult was obtained. Preoperative labs showed normal phosphorus, TSH, FT4, and FT3, but markedly elevated PTH (916.6 pg/mL), low vitamin D (12.10 ng/mL) and serum calcium at the upper limit of normal (10.16 mg/dL). Following surgical clearance and informed consent, the left lower parathyroid adenoma was resected under general anaesthesia. Postoperatively, the patient developed hypocalcaemia, which was corrected. His PTH levels normalized postoperatively and the patient was discharged in stable condition with follow-up scheduled. Pre- and post-parathyroidectomy blood investigations are shown in Table 1.

Discussion

BT, also known as osteitis fibrosa cystica, are rare benign bone lesions. They are frequently misdiagnosed, leading to delayed treatment and an unnecessary economic burden for patients.[9] They typically present with localized bone pain, tenderness, swelling or palpable masses, especially near the surface.[10,11] Fragile bones can lead to pathological fractures and advanced lesions may cause deformities.[12] Symptoms of hypercalcemia from underlying hyperparathyroidism include fatigue, constipation, nausea, kidney stones, muscle weakness and polyuria.[13] Atypical manifestations include neurological deficits due to nerve compression, facial asymmetry, jaw expansion and dental mobility in maxillofacial lesions, and rare skull base involvement causing visual disturbances.[14-17] Respiratory difficulties are uncommon unless tumors affect airway structures, potentially causing breathing problems as reported by Can Ö et al.[11] BT are infrequent in developed countries because of routine calcium screening and early hypercalcemia treatment. However, they remain more common in developing countries like India, where delayed diagnosis and untreated hyperparathyroidism contribute to BT development.[18,19] Radiographically, BT may resemble primary bone malignancies or metastases because of their aggressive appearance and often mimic giant cell tumors and osteosarcomas. BT lytic lesions with increased metabolic activity on PET-CT are hard to distinguish from malignancies without histopathological confirmation.[20–22] Khomariyah E et al. reported four patients initially misdiagnosed as ossifying fibroma, low-grade proximal femur fibrosarcoma, multiple myeloma, bone cyst and fibrous dysplasia, delaying treatment before being confirmed as BT.[6]

Fever, though atypical in HPT, can mislead clinicians toward infectious or inflammatory causes. A multinational study by Erdem H et al. on classical fever of unknown origin (FUO) across 21 countries identified infections and malignancies as the most frequent causes, followed by collagen vascular diseases; endocrine causes were rare.[23] Among endocrine etiologies, thyroiditis was most common, while parathyroid disorders were not typically reported. Donald C et al. (1979) described fever as an uncommon manifestation of primary hyperparathyroidism (PHPT).[24] Though rare case reports have noted its presence, particularly in the context of severe bone disease or parathyroid carcinoma as described by Nagpure KB et al.[25] It is hypothesized that inflammatory cytokines such as IL-1, IL-6 and TNF-α—implicated in infections and malignancies—may also be released during intense bone resorption seen in HPT, such as in BT. This cytokine-driven fever, though plausible in rapid skeletal turnover, remains speculative without large-scale evidence.[26]

Multiple lytic pelvic bone lesions initially suggested metastatic malignancy (radiologically) which significantly altered the clinical approach in this case. However, CT-guided biopsy showed hallmark features of BT—osteoclast-like giant cells, fibroblastic stroma and haemorrhage thus, excluding neoplastic disease. Biochemical findings supported the diagnosis in this case as the serum PTH level was markedly elevated indicating autonomous parathyroid activity. Serum calcium was at the upper limit of normal, likely masked by concurrent vitamin D deficiency thus complicating the biochemical picture.

Tc-99m tetrofosmin SPECT-CT identified a parathyroid adenoma, the most common cause of HPT. These imaging modalities are crucial for preoperative localization with high sensitivity.[27]

In most cases, parathyroidectomy leads to the normalization of PTH levels and the gradual regression of BT. Larger or symptomatic lesions may require orthopaedic intervention. Postoperative management must also include monitoring for hungry bone syndrome, a condition of profound hypocalcaemia that can occur after the removal of a PTH-secreting adenoma due to rapid skeletal remineralization.[28]

Conclusion

This case highlights the need to include endocrine and metabolic disorders, particularly hyperparathyroidism, in the differential diagnosis of patients presenting with unexplained fever and lytic bone lesions when infectious and malignant causes have been excluded. BT, though uncommon, should be considered in such scenarios, especially in populations without routine calcium screening. The diagnosis can be challenging due to their radiological and clinical resemblance to malignancy or osteomyelitis. A high index of suspicion, supported by targeted biochemical testing and confirmed through imaging and histopathology, is essential for accurate diagnosis. Early identification and definitive surgical management of hyperparathyroidism can reverse systemic symptoms and prevent further skeletal complications.

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