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Case Report

CASE REPORT

Refractory hyperparathyroidism with a T3 bony lesion—differential diagnoses

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Abstract

We report a case of severe hyperparathyroidism complicated by osteitis fibrosa cystica in an 83-year-old man post-myocardial infarction. The lesions were evident on magnetic resonance imaging only. A diagnosis of parathyroid carcinoma was considered due to clinical appearance of the parathyroid intraoperatively and the presence of an invasive T3 lesion mimicking metastatic disease. Differentiating parathyroid carcinoma from the benign causes at presentation can be difficult due to overlapping clinical, biochemical, radiological and histological features. The presence of bony lesions increases the diagnostic complexity of the case and demonstrates the challenges involved in the management of this disorder.

INTRODUCTION

Primary hyperparathyroidism (pHPT) is a common endocrine disorder, with a prevalence of 0.1–0.3%. Sporadic solitary adenoma accounts for up to 85% of cases with 10–15% due to multiglandular disease. Parathyroid carcinoma accounts for less than 1% [1]. Differentiating carcinoma from benign causes can be difficult due to overlapping clinical, biochemical, radiological and histological features. The presence of bony lesions increases the diagnostic complexity and demonstrates the challenges involved in management of this disorder.

CASE REPORT

An 83-year-old man presented with incidental severe hypercalcaemia (Ca^{2+} 3 mmol/l, reference 2.10–2.55) and hyperparathyroidism (PTH 124.2 pmol/l, reference 1.5–7.6) after a myocardial infarction complicated by cardiac failure. Thirst was his only symptom of hypercalcaemia and may have been related to loop diuretics therapy. There was no history of thiazide diuretic or lithium exposure. He did not have any clinically evident neurological deficits. He had mild vitamin D insufficiency (48 nmol/l) and acute renal impairment (eGFR 27 ml/min). Past history included hypertension, stage 3 CKD, schizophrenia, ischaemic cardiomyopathy with a poor ejection fraction (25%) and diastolic dysfunction.

Treatment of hypercalcaemia with intravenous fluids was hampered by poor cardiac function. Cinacalcet slowly titrated up to 60 mg bi-daily adequately controlled his serum calcium at <3 mmol/l without intravenous fluids.

After failed localization with sestamibi scan and ultrasound, an magnetic resonance imaging (MRI) (Fig. 1) showed enlarged

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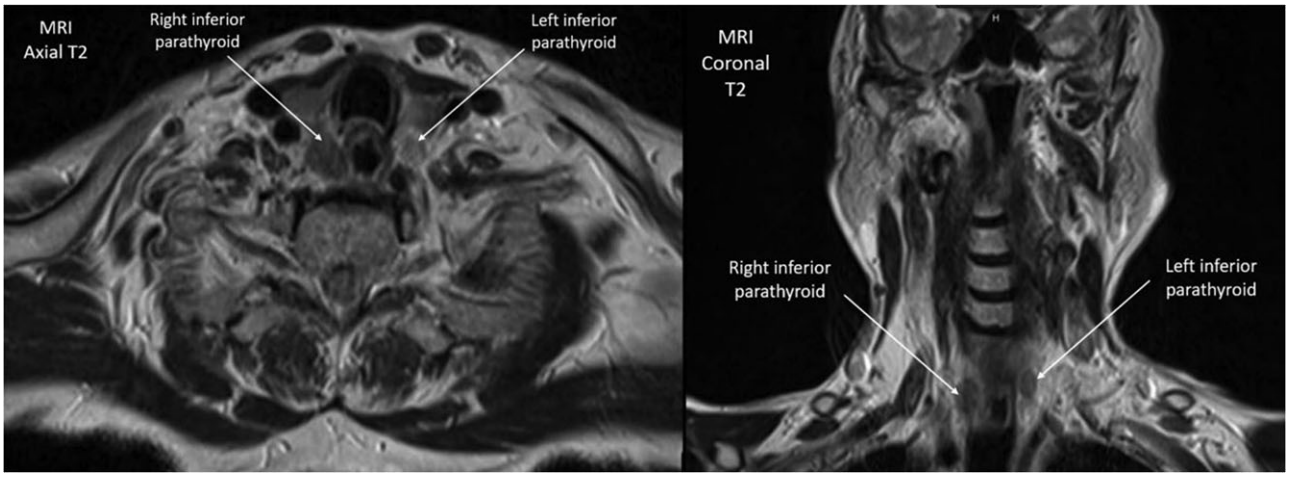

Figure 1: MRI showed two non-specific soft tissue structures deep to the thyroid on both sides of the oesophagus, suspicious for enlarged parathyroid glands.

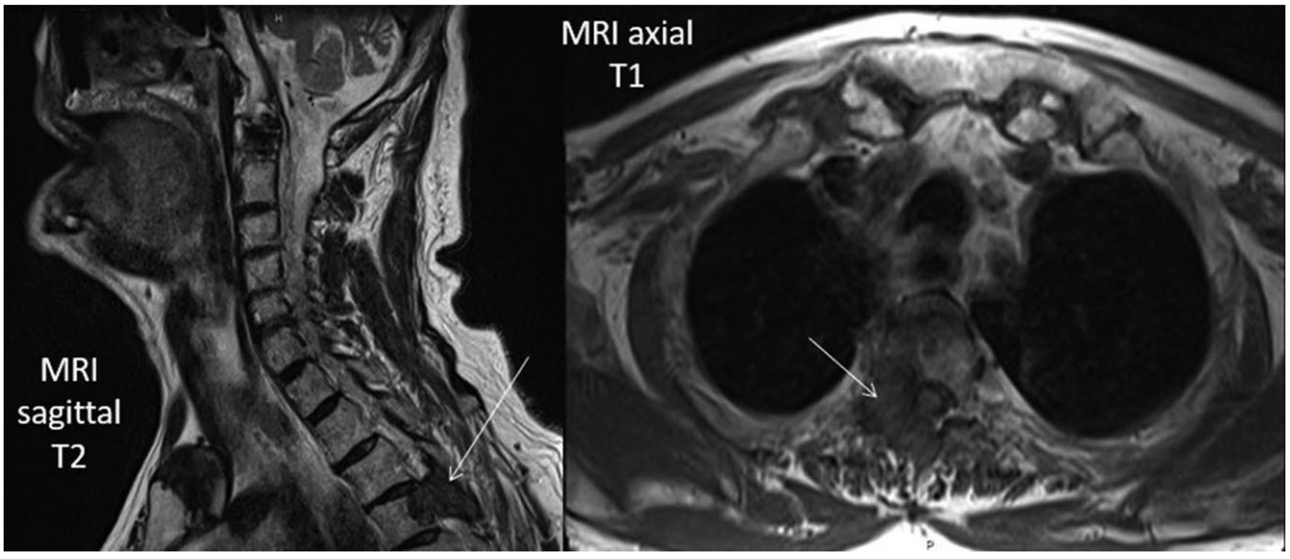

Figure 2: MRI showed a low T1 low T2 lesion in the right posterior vertebral body, pedicle, lamina and spinous process of T3.

inferior parathyroid glands bilaterally (left 7.6 × 12 × 17 mm, right 16 × 14 × 15 mm) and a T3 bony lesion (Fig. 2) not evident on a full body bone scan. Screening for prostate cancer and myeloma was negative.

He was originally consented for bilateral parathyroid exploration. However, at neck exploration, the left parathyroid was adherent to the oesophageal adventitia. As the surgical team believed they were dealing with a parathyroid malignancy, a left inferior parathyroidectomy, left hemithyroidectomy and partial resection of the left recurrent laryngeal nerve were performed with the enlarged right parathyroid gland left *in situ*.

The left parathyroid lesion weighed 2.06 g. Histopathology showed features suspicious but not diagnostic of parathyroid carcinoma (Fig. 3). There were some atypical features, including partial nodularity with fibrovascular septa surrounding tumour nodules. Definite malignant features, namely vascular invasion, perineural invasion or infiltration of adjacent tissues were not identified. Parafibromin and PGP9.5 immunohistochemistry were inconclusive for HRPT2/CDC73 mutations.

Staging computed tomography (CT) showed a lytic lesion with local invasion into the spinal canal (Fig. 4). Fludeoxyglucose positron emission tomography (FDG-PET) demonstrated a destructive hypermetabolic soft tissue bony lesion within the T3 vertebral body, with probable nerve root compression (Fig. 4). A right T3 hemilaminectomy was undertaken for excisional biopsy of a presumed metastasis. Histopathology showed a giant cell rich lesion, with bone extensively replaced by mononuclear spindle cells with scattered multinucleate giant cells, a vascular stroma, and haemosiderin deposition - consistent with a brown tumour (Fig. 5).

Hypercalcaemia (Ca^{2+} 2.6–2.96 mmol/l) and hyperparathyroidism (109.4 pmol/l) persisted post-operatively. At a second neck exploration a month later, a right parathyroidectomy was performed. The lesion weighing 2.19 g showed no atypical histological features consistent with parathyroid adenoma or glandular hyperplasia.

Calcium and PTH levels normalized immediately and he subsequently developed permanent mild hypocalcaemia requiring calcium and calcitriol supplements.

DISCUSSION

pHPT is mostly asymptomatic in developed countries, due to early detection from biochemical testing [2]. In severe and

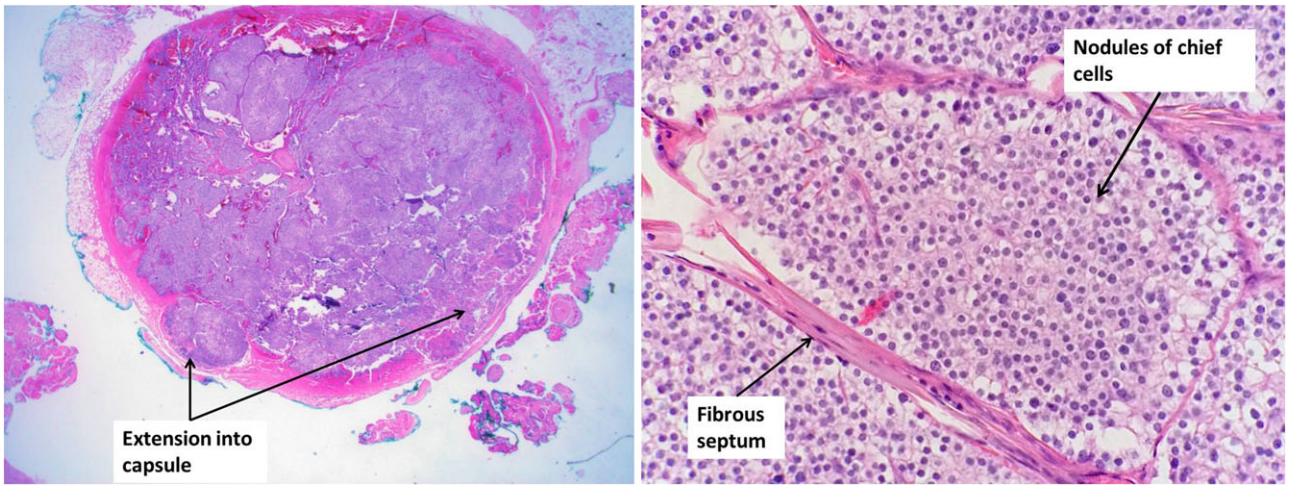

Figure 3: First parathyroid lesion (left inferior parathyroid gland) showing atypical features—focal extension into the capsule (left), nodules of tumour cells surrounded by thickened fibrous septa (right). Definite malignant features such as vascular/perineural invasion or infiltration of adjacent tissues were not identified. Left, H&E (×1.25); Right, H&E (×20).

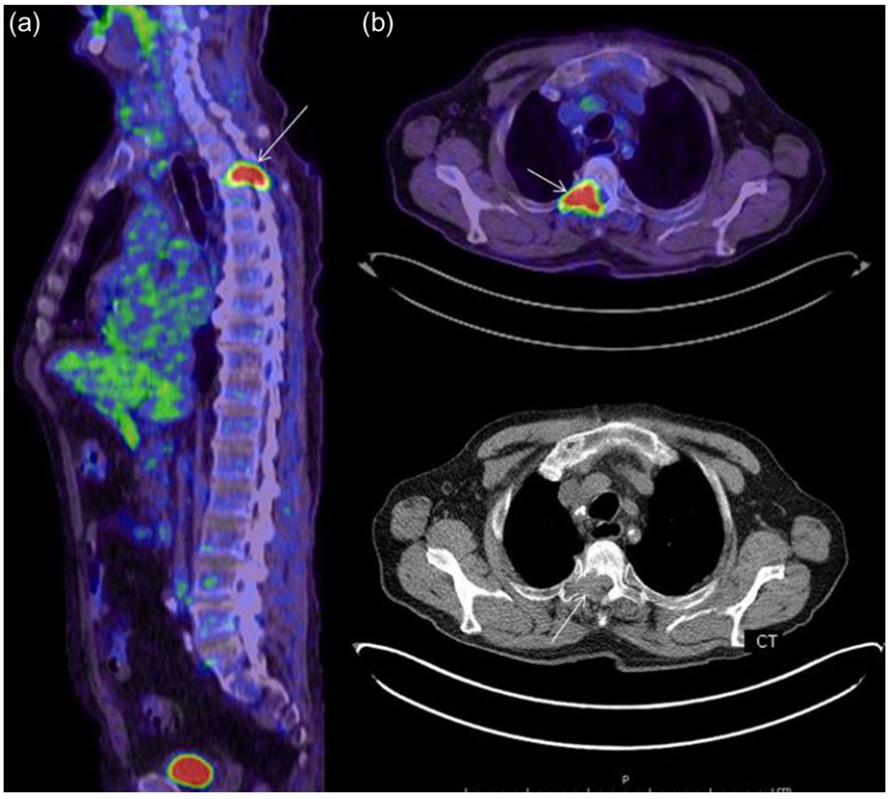

Figure 4: Staging CT showed a lytic lesion (**b** bottom image) with some local invasion into the spinal canal. FDG PET scan (**a** and b top image) demonstrated a destructive hypermetabolic soft tissue bony lesion within the T3 vertebral body, with probable compression of the right exiting nerve root.

symptomatic cases, parathyroidectomy is the mainstay of treatment. In patients who either refuse or have contraindications for parathyroidectomy and those with intractable disease post-surgery, cinacalcet has been shown to effectively lower serum calcium and PTH levels. It may be useful as a bridging therapy in patients who have progressive hypercalcaemia awaiting for parathyroidectomy [3].

The commonest causes of persistent and recurrent hyperparathyroidism post-parathyroidectomy are multiglandular disease and ectopic parathyroid glands. Among benign parathyroid tumours, double adenoma have the highest recurrence rate (up to 7%) compared to solitary adenoma and hyperplasia [4]. Four gland exploration is indicated if localization studies are inconclusive.

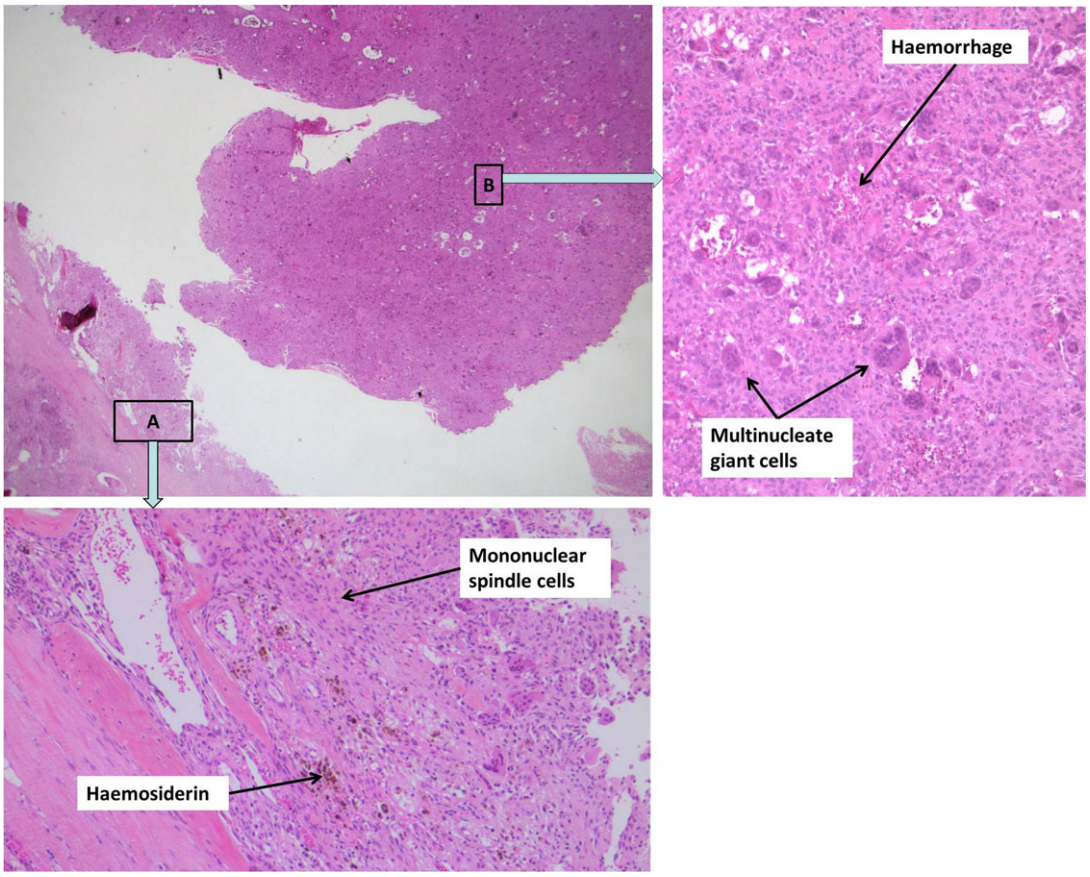

Figure 5: Brown tumour (within T3 vertebral body), showing a giant cell rich lesion, with bone extensively replaced by a proliferation of mononuclear spindle cells with scattered multinucleate giant cells. These are set in a vascular stroma with some haemosiderin deposition. Upper left, H&E (×1.25); Lower left—A, H&E (×10); Upper right—B, H&E (×20).

The presence of the bony lesion raised the possibility of a parathyroid carcinoma metastasis with a differential diagnosis of primary bone tumour, metastasis with co-existing hyperparathyroidism or brown tumour arising from severe hyperparathyroidism. Multiple myeloma and metastases from renal cell carcinoma, melanoma, thyroid, bladder, lung and breast cancers usually appear osteolytic or mixed lytic/blastic on imaging, whereas bony metastases from prostate cancer are predominantly osteoblastic [5].

Parathyroid carcinoma is associated with high morbidity and mortality. Imaging and fine needle aspiration is not helpful in differentiating parathyroid carcinoma from other benign causes preoperatively [2]. There have been no reports of bilateral multiglandular parathyroid carcinoma, however, bilaterality alone cannot be used to exclude malignancy. The histological features of parathyroid carcinoma and atypical adenoma overlap, as do the features of simple adenoma and parathyroid hyperplasia. Serum calcium, PTH levels and weight of resected tumours were significantly greater in parathyroid carcinomas compared to adenomas [6]. Mutations in the HRPT2/CDC73 gene, resulting in loss of immunohistochemical staining for its protein product parafibromin are seen more frequently in parathyroid carcinomas than in typical adenomas. Although non-specific, it may be used to help predict clinical outcomes [1].

As 90% of carcinomas are hormonally functional [2], patients are more likely to present with symptoms including severe hypercalcaemia, pathological fractures or rarely, bony pain from brown tumour [2]. Brown tumour (osteitis fibrosa cystica) occurs in <5% of patients with pHPT in developed countries [7]. It also occurs in secondary and tertiary hyperparathyroidism particularly among dialysis patients, particularly with PTH > 50 pmol/l [8]. It is a benign, non-neoplastic tumour characterized by subperiosteal bone resorption and osteopenia [9]. It may arise in any bone, but appears to have a craniofacial predilection. Lesions can be single or multiple, and may be locally aggressive resembling primary bone tumours or bony metastases [10]. The role of fine needle aspiration in differentiating these and other tumours is controversial [9].

Radiologically, brown tumours appear attenuated on CT because of hemosiderin deposition and fibrous tissue in the lesion. Similar to other benign tumours such as giant cell tumour or aneurysmal bony cyst, brown tumours appear osteolytic on imaging. A wide spectrum of MRI findings has been reported, including solid, cystic or mixed lesions and different intensities on T1- and T2-weighted images [10]. Surgical removal of brown tumour lesions is traditionally unnecessary, as these lesions generally resolve spontaneously once hyperparathyroidism is corrected [7]. Rarely, surgical intervention might be necessary in the case of late bone recovery or in the presence of pathological fractures or compressive symptoms [10].

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CONFLICT OF INTEREST STATEMENT

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

ETHICAL APPROVAL

None required.

CONSENT

We are unable to obtain a consent from the patient or his next of kin as the patient passed away 6 years ago and we feel it is inappropriate to contact his family ethically for this purpose. We have ensured there is no identifiable information in the text or images of the submission to preserve patient's anonymity.

GUARANTOR

Prof Mark Kotowicz as corresponding author agrees to be guarantor for the accuracy of the final submitted manuscript of this case.

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