Case Report

A rare case of symptomatic hyperparathyroidism in an elderly patient with dual pathology

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Abstract: Primary hyperparathyroidism secondary to true sporadic synchronous parathyroid cancer (PTCa) and adenoma (PTa) is rare. This is a case of an 80-year-old female admitted with symptomatic hypercalcaemia, raised serum calcium (Ca) of 3.39 mmol/L and raised parathyroid hormone (PTH) of 44.3 pmol/L. Ultrasonic evaluation of the neck revealed a mass posterior to the right thyroid lobe. Imaging of the left neck was unremarkable. Subsequent sesta-MIBI and single-photon emission computed tomography-computed tomography (SPECT-CT) scanning highlighted conspicuous activity over the right lower neck consistent with the neck ultrasound scan findings. Pre-operatively, PTa was suspected. Intra-operatively, malignancy was suspected due to infiltration of the parathyroid tumour into the thyroid. The right inferior parathyroid and right thyroid gland were resected. Histology confirmed PTCa. Despite surgical treatment, she was found to have persistently high Ca and PTH levels. Further investigation with a repeat sesta-MIBI and SPECT-CT suggested a left inferior parathyroid tumour. Excision of this mass revealed a PTa. Recovery was unremarkable and serum biochemistry returned to normal ranges.

Keywords: Parathyroid adenoma (PTa); parathyroid cancer (PTCa); hyperparathyroid

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Introduction

Parathyroid cancer (PTCa) is extremely rare. It is responsible for only 0.005% of all cancers (1) and has an incidence rate of 0.15 per 1,000,000 individuals per year (2). The median age of occurrence is 56 years and it occurs equally between males and females (3,4). It is responsible for <1% of cases of primary hyperparathyroidism (3,5). The most common cause of primary hyperparathyroidism is parathyroid adenoma (PTa) (93.0%). Unlike PTCa, it is more common in women and the elderly (6). Few cases of co-existent PTCa and PTa have been reported, and usually in the context of an underlying familial disease process (7,8). Here, we present a case of a true sporadic synchronous PTCa and PTa in an elderly patient.

Case presentation

An 80-year-old woman presented to hospital with a 6-month history of constipation and abdominal pain. She was recently diagnosed with hypercalcaemia and referred to an endocrinologist after routine blood work from her general practitioner revealed a corrected serum calcium (Ca) of 3.39 mmol/L (normal range, 2.10–2.55 mmol/L), parathyroid hormone (PTH) of 52 pmol/L (normal range, 1.2–9.3 pmol/L), serum phosphate (PO_4) of 0.64 mmol/L (normal range, 0.74–1.50 mmol/L) and alkaline phosphatase (ALP) of 94 IU/L (normal range, 40–150 IU/L). Her only co-morbidity of note was hypertension for which she received angiotensin-converting enzyme (ACE) inhibitor therapy. There was no known family history of endocrine

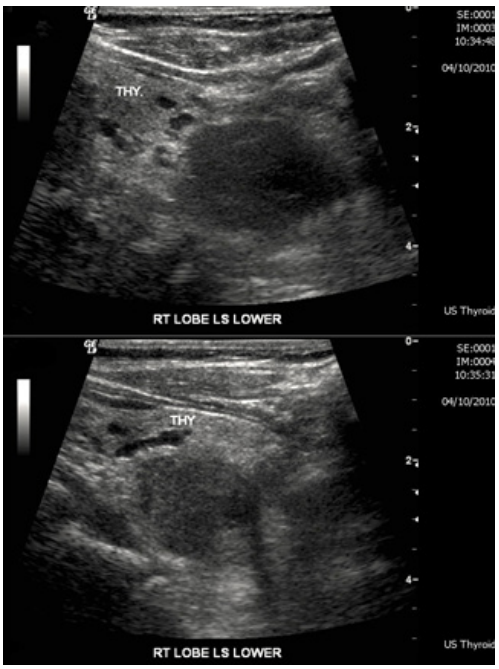

Figure 1 Ultrasound of right neck mass showing a well demarcated 26-mm lesion posterior to the inferior third of the right lobe of the thyroid gland.

disease. During her hospital stay physical examination did not reveal any systemic abnormality, no neck masses and no lymphadenopathy.

On admission, she was treated with fluid rehydration, diuretics and bisphosphonates. Investigations revealed a decrease in Ca to 2.86 mmol/L, serum PTH of 44 pmol/L, a negative myeloma screen and normal levels of tumour markers cancer antigen 125 (CA125) and carcinoembryonic antigen (CEA). Remaining bloods showed no abnormality. She was referred for localisation imaging for suspected parathyroid adenoma and underwent an ultrasound of the neck, sesta-MIBI scan and single-photon emission computed tomography-computed tomography (SPECT-CT). Neck ultrasound revealed a well-demarcated, solid, hypoechoic, 26-mm mass posterior to the lower third of the right lateral lobe (*Figure 1*). A sesta-MIBI highlighted conspicuous activity over the lower right neck on the 2-hour images (*Figure 2*). SPECT scan (*Figures 3,4*) showed an enlarged right inferior parathyroid gland with increased radioisotope uptake. All three findings were in keeping with a right inferior PTa. Hence, the working diagnosis was primary hyperparathyroidism secondary to a right-sided

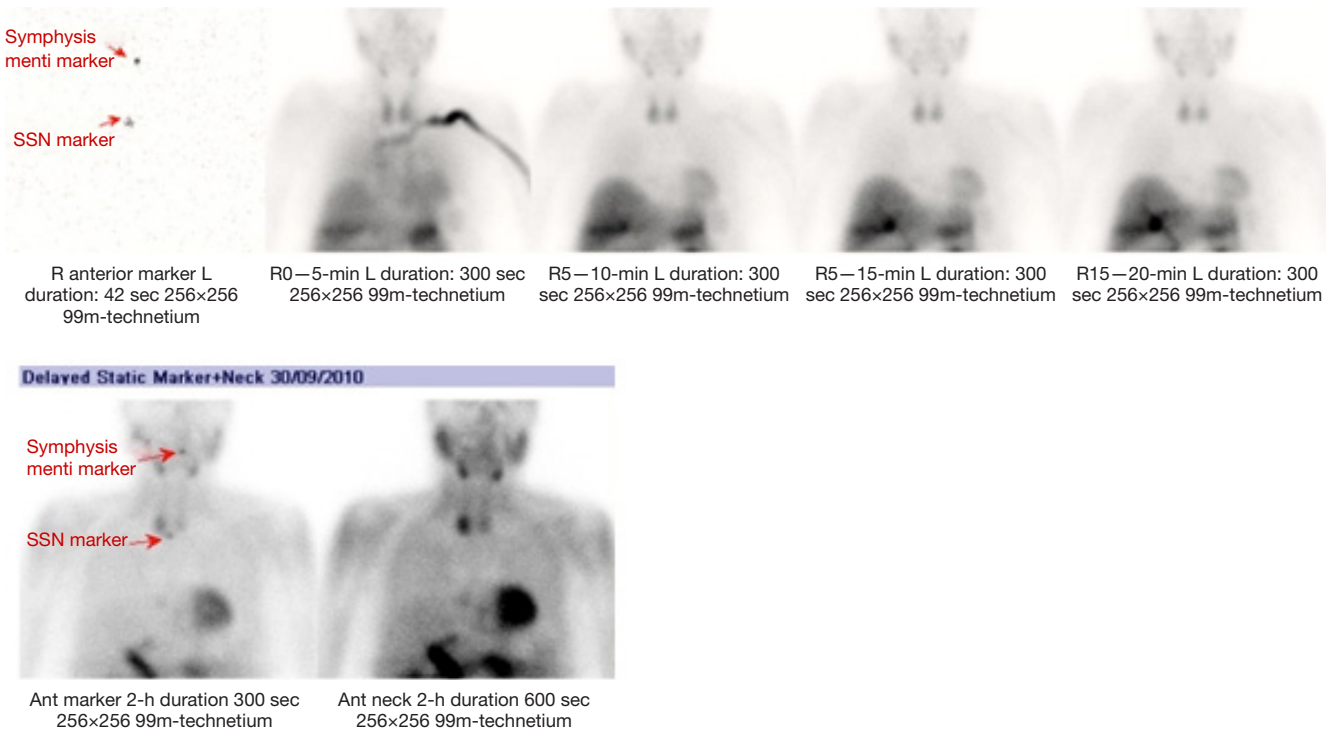

Figure 2 Sesta-MIBI scan showing retained radioactivity in the right inferior portion of the neck on delayed imaging.

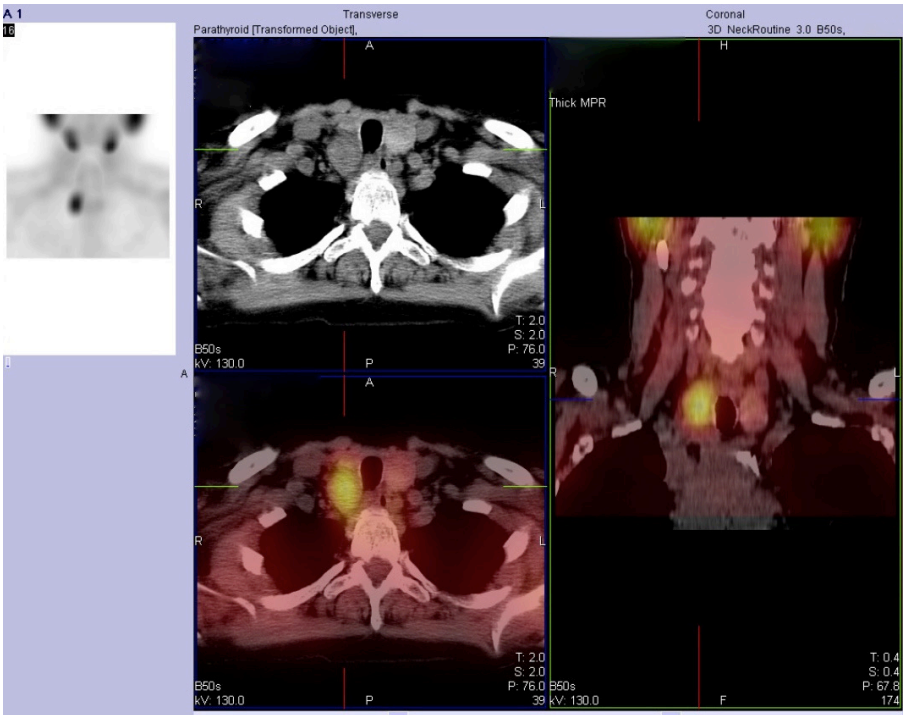

Figure 3 SPECT with corresponding sesta-MIBI, showing an enlarged right inferior parathyroid gland with increased radioisotope uptake in the transverse and coronal slices. SPECT, single-photon emission computed tomography.

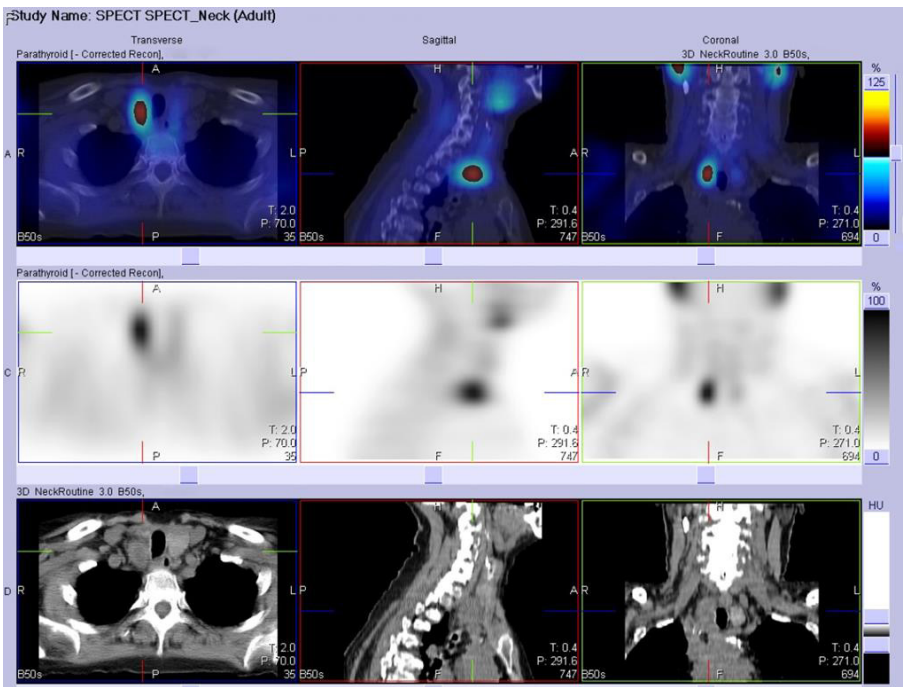

Figure 4 SPECT-CT, with corresponding sesta-MIBI and CT images, showing an enlarged right inferior parathyroid gland with increased radioisotope uptake in the transverse, sagittal and coronal planes. SPECT-CT, single-photon emission computed tomography-computed tomography.

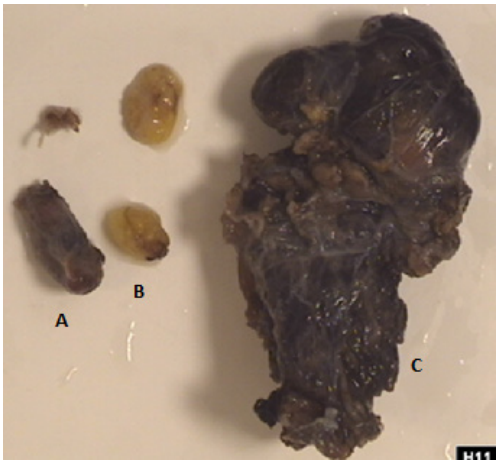

Figure 5 Surgical specimens from right parathyroidectomy and thyroidectomy. A: parathyroid tumour measuring 21 mm weighing 122 mg; B: lymph nodes; C: right lobe of the thyroid measuring 55 mm × 30 mm × 17 mm, weighing 10 g.

inferior PTa. The patient was referred to the surgeons and arrangements were made for a minimally invasive right sided parathyroidectomy.

During surgery the gland was located but was very difficult to dissect and showed signs of infiltration into the thyroid gland. Visualisation of the anatomy became difficult and given the suspicion of malignancy it was decided to convert to a conventional open approach via a midline scar. The patient underwent an en-bloc resection of the right inferior parathyroid and right thyroid lobe (*Figure 5*). Intra-operative examination of the surrounding tissue, including the laryngeal nerve and strap muscles, showed no signs of infiltration. Post-operative recovery was unremarkable and the patient was discharged home on day 2 with a Ca of 2.7 mmol/L and a PTH of 10 pmol/L. Histopathological findings were in keeping with intra-operative findings and a diagnosis of PTCa of the right inferior gland was made (*Figures 6*,7). Diagnosis of PTCa is always difficult histologically (9,10). In our specimen, the mitotic count was considered to be low for a carcinoma, however the dense fibrous bands and infiltrative architecture favoured the diagnosis. Immunostaining for CD34 and factor VIII confirmed endothelial lined space invasion. The Ki67 proliferation index staining is approximately 5%.

The patient was reviewed in clinic 2 weeks later. Blood tests revealed some resolution of the hypercalcaemia (2.57 mmol/L) and normal thyroid function. She was reassured that the margins of the resection were clear and

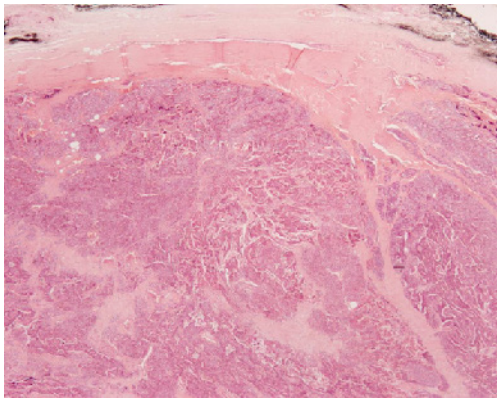

Figure 6 Low power image: dense fibrous bands passing through nests of parathyroid tumour (HE staining, 40×).

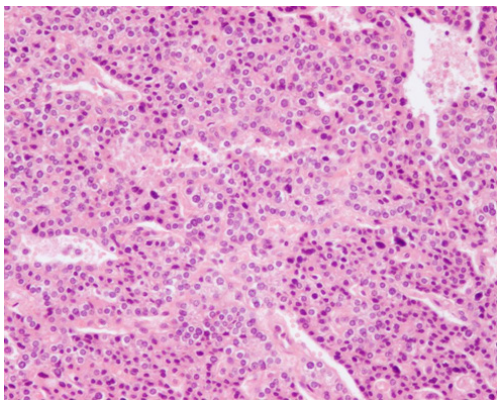

Figure 7 High power image showing tumour cells resembling parathyroid (HE staining, 100×).

underwent a plain chest radiograph and MRI of the neck, which were both reported as normal. Radiotherapy was discussed at the multidisciplinary team meeting (MDT) and concluded not to be of clinical benefit in this situation.

She was placed on close observation with serial Ca and PTH level monitoring over the next few months (*Figures 8*,*9*). The case was reviewed again in MDT 6 weeks post-operatively. At this point the PTH had risen to 11.2 pmol/L from 10.2 pmol/L with a Ca of 2.55 mmol/L since the previous month. Concern was raised as to the source of the raised parathyroid activity given the previous carcinoma and a repeat sesta-MIBI scan was performed. This revealed no uptake in the bed of the right thyroid; however, activity was noted in the left lateral lobe of the thyroid and the left half of the isthmus. SPECT-CT revealed a small 11-mm left paraoesophageal mass behind the lower left lateral thyroid

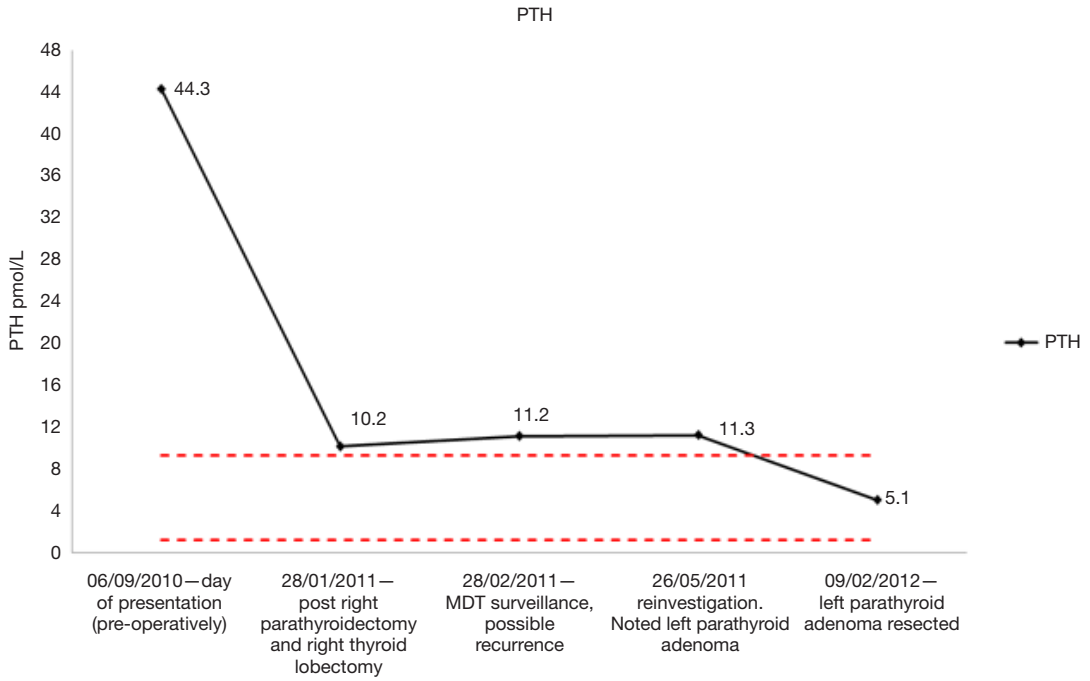

Figure 8 Parathyroid hormone (PTH) levels (solid black line) from initial admission through to left parathyroid adenoma resection. Normal PTH range is represented by the area between the red broken lines. PTH, parathyroid hormone.

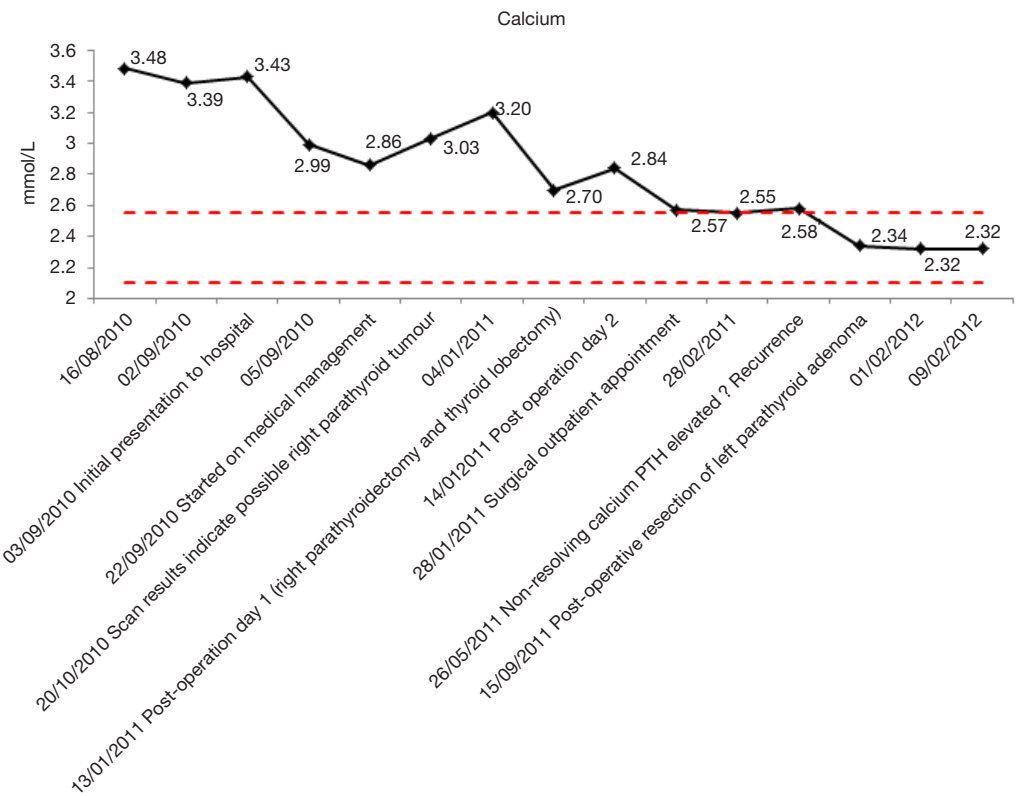

Figure 9 Corrected serum calcium levels from initial presentation until the end of treatment

Table 1 Summary of patient characteristics in the four case reports documenting functional synchronous PTCa and PTa

Ref	Age (years)	Sex	Ca level (mmol/L)	PTH level	PTCa location	PTa location
Khan *et al.*, 2018. (our case)	80	F	3.39	44.3 pmol/L	Right lower parathyroid gland	Left lower parathyroid gland
Chatterjee *et al.*, 2013	45	M	3.73	195.3 pmol/L	Right lower parathyroid gland	Left lower parathyroid gland
Goldfarb *et al.*, 2009	59	M	3.60	214.4 pmol/L	Left lower parathyroid gland	Right lower parathyroid gland
Shapiro *et al.*, 1989	78	F	2.86–3.08	30–70× above normal	Left upper parathyroid gland	Right upper parathyroid gland

PTH, parathyroid hormone; PTCa, parathyroid cancer; PTa, parathyroid adenoma; Ca, serum calcium.

lobe suggestive of a left inferior parathyroid adenoma. She was counseled as to the result and advised to undergo a repeat operation to remove the parathyroid tumour.

The operation was via an open approach and the left inferior parathyroid gland was removed without complication as a day case procedure. Histopathologically, a hypercellular parathyroid gland composed of a mixture of chief cells, water clear cells and oxyphilic cells arranged as microfollicles, sheets and nodules were seen. These features are consistent with a PTa. No features of malignancy were observed. Post-operative review showed good function of her two remaining parathyroid glands with a Ca level of 2.30 mmol/L, PTH level of 5.1 pmol/L and thyroid stimulating hormone (TSH) level of 1.49 mU/L (normal range, 0.35–5.00 mU/L). Given the rare nature of her synchronous parathyroid tumours she was further investigated to check whether these were sporadic or part of a syndrome. Two years on from her diagnosis she is well and remains disease free with calcium and PTH within the normal range.

Discussion

Functional PTCa occurrence is well documented, however, its sporadic synchronous occurrence in the presence of PTa in individuals with no identifiable risk factors has rarely been published. To our knowledge, only three (7,11,12) clearly documented cases have been previously reported (*Table 1*), with one case of non-functioning PTCa and PTa (13).

Diagnosing malignancy is difficult pre- and post-operatively. Patients with malignancy are more likely to be symptomatic of hypercalcaemia, present with Ca levels of >3.5 mmol/L and PTH levels of >3–10 times the upper limit of normal or a palpable neck mass, lymphadenopathy or recurrent laryngeal nerve palsy (3). However, individuals with benign disease may also present similarly (3). Our patient did present with symptoms of hypercalcaemia however, due to a Ca of 3.39 mmol/L, absence of a neck lump or lymphadenopathy and rarity of PTCa as the aetiology of primary hyperparathyroidism, it was presumed that the primary hypercalcaemia in our patient was secondary to a PTa.

The first suspicion of malignancy versus adenoma became apparent intraoperatively when infiltration of the tumour into the thyroid gland was visualised. The tumour was dark greyish-brown and firm (*Figure 5*). These are features consistent with carcinoma whereas adenomas are non-invasive, a tan-dark yellow colour and soft (14). Histologically, the collective presence of a fibrous trabecular architecture, vascular and capsular invasion, mitotic activity or aneuploidy suggests carcinoma (9,15-17). In our patient, the presence of a fibrous trabecular architecture with vascular and capsular invasion (*Figures 6,7*) confirmed PTCa diagnosis.

Suspecting and treating PTCa early is essential. This is because complete resection of the carcinoma independently affects disease-free survival (15,17). Unfortunately, difficulties in diagnosing malignancy results in patients presenting years after initial resection with symptoms of hypercalcaemia and metastasis (2,9,10). At this stage mortality is high (15). Hence, although PTCa is an uncommon cause of primary hyperparathyroidism, it is important to suspect and exclude it. Routine bilateral neck exploration with identification of all four parathyroid glands should be performed in individuals with suspected PTCa to minimise this risk (12).

Cancer occurrence in conjunction with adenomatous disease is more commonly reported in the context of underlying familial hyperparathyroidism (18,19), i.e., familial isolated hyperparathyroidism, jaw tumour syndrome, multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia type 2A (MEN2A) syndromes

(20-22). We retrospectively analysed head and neck images of our patient to look for evidence of ossifying jaw or pituitary tumours; serum calcitonin levels were measured (and normal) and the history for uncontrolled hypertension or family history of hyperparathyroidism were clarified. None of these were evident suggesting clinically non-syndromic primary hyperparathyroidism. Given its rarity, genetic testing was not performed. Prior neck radiation and chronic renal failure have also been associated with synchronous PTCa and PTa (3,23,24). Our patient had no history of these conditions, leading us to recognize the case as a true sporadic case of synchronous parathyroid tumours.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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