Rare disease

Primary hyperparathyroidism due to an intrathyroidal parathyroid adenoma associated with chronic lymphocytic thyroiditis

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Summary

This is a case of a 44-year-old woman with an anterior neck mass and hypothyroidism who presented with an incidental finding of an elevated serum calcium level and was found to have primary hyperparathyroidism and osteoporosis. During surgical exploration no parathyroid adenoma was found, although a nodule was palpated within the right thyroid lobe. Examination of the excised right thyroid lobe revealed an intrathyroidal parathyroid adenoma and chronic lymphocytic thyroiditis. After surgery, she did not develop severe hypocalcaemia and this was attributed to preoperative treatment with pamidronate. In the months following surgery, parathyroid hormone remained undetectable.

BACKGROUND

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia and is usually due to a parathyroid adenoma. The location of parathyroid adenomas may vary and in rare instances they may be found within the thyroid gland, such as in this case. This case is also of interest as the patient had concomitant Hashimoto's thyroiditis and parathyroid hormone (PTH) remained persistently undetectable after parathyroidectomy, despite unilateral surgical exploration only and no manipulation of the other parathyroid glands. We discuss, in addition, how bisphosphonate use may have attenuated the development of hungry bone syndrome.

CASE PRESENTATION

This case is of a 44-year-old woman who presented with a right-sided anterior neck mass that gradually grew in size over the course of 2 years. She had no history of irradiation to the neck during childhood and had no family history of thyroid disease. She was not taking any medications. For the preceding 3 months, she complained of generalised weakness, unintentional weight loss, constipation and bilateral knee pain. Examination of the neck revealed a visible anterior neck mass, measuring 4 × 5 cm, and was firm but non-tender (figure 1). No cervical lymphadenopathy was noted and the remainder of the physical examination was unrevealing.

INVESTIGATIONS

Thyroid assessment

On initial consultation, thyroid function tests showed primary hypothyroidism with an elevated thyroid-stimulating hormone (TSH) of 4.0 µIU/ml (NV: 0.4–3.8) and a low free thyroxine (T4) level of 0.07 pmol/l (NV:

11–24). As the TSH was only minimally elevated for such a low free T4 level, a repeat test was done and the level was found to be 8.5 µIU/ml. Thyroid peroxidase antibody was elevated at 136 U/ml (NV: <100). Neck ultrasound revealed a hypoechoic thyroid gland consistent with chronic lymphocytic thyroiditis with an enlarged cystic right thyroid lobe and no lymphadenopathy. Fine-needle aspiration biopsy of the cystic mass yielded colloid fluid, with no atypical cells. Given the size of the mass, the patient opted for right thyroid lobectomy and she was prepared for surgery.

Biochemical tests

Baseline laboratory tests showed mild normocytic normochromic anaemia with a haemoglobin level of 11.8 g/l (NV: 120–180) and a mean corpuscular volume of 88 fl (NV: 80–100). There was an incidental finding of an

Figure 1 A 44-year-old woman with a 2-year history of a right-sided anterior neck mass.

elevated serum calcium (corrected for albumin) level at 3.19 mmol/l (NV: 2.12–2.52). Repeat measurements showed the calcium level to be as high as 3.58 mmol/l. Intact PTH was found to be elevated at 1487.00 pg/ml (NV: 12.00–65.00), indicating PHPT. Phosphorus was low normal at 0.8 mmol/l (NV: 0.8–1.6).

Additional tests

Multiple endocrine neoplasia (MEN) 2A was a consideration given the thyroid mass and hyperparathyroidism, although less likely owing to the absence of family history and the absence of any signs or symptoms related to pheochromocytoma. Serum calcitonin was within normal at 2.15 pg/ml (NV: 2–11). A 24 h urine collection for metanephrines was also within normal at 0.91 mg/24 h (NV: up to 1).

With the patient's weight loss, knee pain, hypercalcaemia and anaemia, a skeletal survey was done to identify the presence of lytic lesions that might indicate malignancy. Plain films of the skull showed a moth-eaten appearance (figure 2), although no other films showed any lytic lesions or fractures. Bone marrow aspiration and core biopsy were negative for malignancy, ruling out multiple myeloma. Protein electrophoresis likewise did not show any serum monoclonal proteins.

Serum creatinine was normal at 68.64 µmol/l (NV: 39–91). Urinary calcium and creatinine levels were within normal from a 24 h collection at 2.97 mmol/24 h (NV: 1.0–8.8) and 0.384 g/24 h (NV: 0.3–1.4), respectively.

Vitamin D (25-hydroxyvitamin D) levels were within normal at 77.52 nmol/l (NV: 25–125).

A dual emission x-ray absorptiometry (DXA) scan showed osteoporosis, with T scores of –2.9 at the lumbar spine, –3.2 at the right femoral neck and –3.5 at the left femoral neck.

Imaging studies

Parathyroid scintigraphy with technetium (Tc-99m) sestamibi showed increased uptake in the right thyroid lobe with prolonged tracer accumulation in the right inferior pole, even on delayed images (figure 3). Owing to this

Figure 2 Radiograph of the skull showing a 'moth-eaten' appearance.

Figure 3 Technetium (Tc-99m) sestamibi scan showing increased uptake in the right thyroid lobe with prolonged tracer accumulation in the right inferior pole.

delayed washout and the patient's hypothyroidism, levothyroxine was temporarily held and thyroid scintigraphy with radioiodine (I-131) 1 mCi was done to further differentiate thyroid from parathyroid tissue. This showed a generalised depressed thyroid gland uptake function and a hypofunctioning mass in the right thyroid lobe, indicating a cold nodule consistent with the images seen on the sestamibi scan. At this time, an intrathyroidal location of the parathyroid adenoma was considered, given that the lesion could not be clearly distinguished from the thyroid gland.

DIFFERENTIAL DIAGNOSIS

This is a patient with hypercalcaemia and secondary osteoporosis likely due to PHPT secondary to an ectopic parathyroid adenoma, although malignancy and familial hypocalciuric hypercalcaemia should be ruled out. As she presented with an anterior neck mass, MEN 2A should also be considered.

TREATMENT

While awaiting surgery, hypercalcaemia was treated with normal saline and furosemide. When calcium levels remained above 3.0 mmol/l, pamidronate 60 mg infusion was given with a modest decrease in calcium levels from 3.47 to 3.14 mmol/l (NV: 2.12–2.52).

Exploration of the right side of the neck revealed an enlarged right thyroid lobe (figure 4) with a large nodule

Figure 4 Intraoperative finding of an asymmetrically enlarged right thyroid lobe measuring 5 × 4 × 3 cm weighing 10 g.

palpated in the inferior pole. Right thyroid lobectomy was done but further dissection did not reveal any discrete mass that correlated with the area of intense uptake on a sestamibi parathyroid scan. Several structures resembling parathyroid tissue were excised and sent for frozen section, but none of these were identified to be parathyroid tissue. PTH drawn immediately after excision of the right thyroid lobe was markedly lower at 36 pg/ml (NV: 12–65).

Final histological examination of the right thyroid lobe showed the presence of chronic lymphocytic thyroiditis and a 5 cm parathyroid adenoma within the thyroid gland, surrounded by a pseudocapsule of thyroid tissue (figures 5 and 6).

After operation, the patient began to complain of mild paraesthesia over the face and the extremities although calcium levels were within normal. She did not exhibit Chvostek's sign or carpopedal spasm at this time. Corrected calcium level was 2.96 mmol/l immediately after surgery and was within normal after 24 h at 2.39 mmol/l. By the third hospital day, her calcium level was below normal at 2.08 mmol/l, and as low as 1.86 mmol/l by the fifth hospital day, although she did not develop any new signs or symptoms of hypocalcaemia. Intravenous correction with 4 g of calcium gluconate was given, which promptly resolved her generalised paresthesia, and the patient was started on oral calcium carbonate 500 mg, two tablets twice daily, and calcitriol 0.25 mcg.

OUTCOME AND FOLLOW-UP

By the 10th hospital day, corrected calcium levels remained stable at 2.18 mmol/l. The patient was sent home on levothyroxine 75 mcg once a day, calcium carbonate 1000 mg three times a day, calcitriol 0.25 mcg once a day, and alendronate 70 mg once a week. A repeat PTH at 2 weeks after surgery was undetectable at <3 pg/ml (NV: 12–65).

After 6 months she reported no further recurrence of hypocalcaemic symptoms, with calcium levels within

Figure 6 Low power magnification (100×) reveals the hypercellular nature of the parathyroid adenoma. Compact solid nests and lobules (and trabeculae) of neoplastic round to polygonal cells with single centrally located round to ovoid nuclei and moderate amount of cleared cytoplasm are held together in compartments by a delicate network of capillaries. No significant nuclear pleomorphism is evident. No mitotic figures are seen.

normal while on calcium replacement. When calcium replacement was held, however, she experienced some perioral numbness with calcium levels noted below the reference range (1.98–2.04 mmol/l) and PTH still undetectable (<3 pg/ml). Calcium replacement was resumed with calcium carbonate 500 mg with vitamin D 200 IU twice a day. She was also maintained on levothyroxine 75 mcg daily and alendronate 70 mg once a week. A repeat PTH level and DXA scan will be done at 1 year.

DISCUSSION

Parathyroid adenoma

PHPT is the most common cause of hypercalcaemia and the third most common endocrine diagnosis.^{1 2} The diagnosis is confirmed in the presence of hypercalcaemia and an elevated or inappropriately normal PTH. It is important to exclude familial hypocalciuric hypercalcaemia, as in this patient, and to ensure the absence of medications, such as lithium and thiazide diuretics, which can contribute to hypercalcaemia and elevations in PTH.³ In the past, this has been associated with findings of bone disease and nephrolithiasis. In the present day setting, however, most cases are asymptomatic and are discovered on routine laboratory screening.⁴ The incidence of PHPT peaks in the seventh decade, with most cases occurring in women (74%), but the incidence is similar in men and women before 45 years of age.²

Most cases are due to a benign parathyroid adenoma in 80–89%, with multiglandular involvement in 5–20%.^{4 5} Majority present as a solitary parathyroid adenoma usually found in traditional anatomic locations behind the superior and inferior poles of the thyroid gland.⁶ Parathyroid location may vary, however, and this is attributed to abnormal migration during embryogenesis. During embryonic development at day 26, five pairs of pharyngeal pouches form. The superior parathyroids develop from the fourth pharyngeal pouch and the inferior parathyroids from the third pouch. The inferior

Figure 5 Scanning microscopic examination (40×) demonstrating the intrathyroidal location of the parathyroid adenoma. The surrounding thyroid tissue has been pushed outward and flattened to form a compact semi-fibrous pseudocapsule (top). Blood vessels are prominent above and below the capsule but there is no peritumoral lymphovascular space invasion.

parathyroids migrate a greater distance, and do so in conjunction with thymic tissue. Therefore, these are more likely to be found in ectopic sites.^{7 8}

PHPT from ectopically located parathyroid glands occurs in 5–20% of all cases of parathyroid adenomas.⁹ Ectopic parathyroid adenomas are associated with larger glands, higher calcium levels and a higher frequency of bone disease.^{8 9} It is speculated that this may be due to delayed diagnosis and the adenomas have a longer time of evolution.⁸

Ectopic locations include intrathyroidic, mediastinal and retroesophageal locations.⁸ Less frequently, the parathyroid adenoma may be found in an intrathyroidal location,^{6 8–14} with a reported incidence of <1–6.7% in larger series.^{15 16} The incidence of true intraparenchymal intrathyroidal parathyroid adenomas may in fact only be <1% of cases. Some parathyroid adenomas are found beneath the thyroid capsule and only partially within the thyroid substance but are still visualised with careful dissection along the thyroid capsule as part of the parathyroid gland is extrathyroid.^{10 15 16}

Need for preoperative localisation

Indeed, the presence of ectopic parathyroid tissue is a possible cause of failed neck explorations in the treatment of PHPT.^{6 8 10 13 17} Some patients may undergo surgery and parathyroidectomy only to have persistent hypercalcaemia, reinforcing the need for proper localisation before surgery to ensure success rates.¹²

A hyperfunctioning parathyroid gland often appears ‘cold’ by thyroid scintigraphy with I-131 and, on the basis of scanning alone, is indistinguishable from a solitary non-functioning thyroid nodule.¹⁸ Tc-99m sestamibi scanning is a better modality and is reported to have a sensitivity of 88% in the preoperative localisation of a parathyroid adenoma.⁵ In the case of intrathyroidal adenomas, however, preoperative or intraoperative ultrasonography may be the most informative imaging method. It is recommended that it be performed routinely when a repeated procedure for persistent hyperparathyroidism is being considered.^{5 17} Although ultrasonography by itself has an overall sensitivity of 60–65% for detecting parathyroid adenomas, when combined with the Tc-99m sestamibi scan in the evaluation of patients with a single adenoma, the sensitivity improves to 100%.¹²

Indications for surgery

In this case, the patient was generally asymptomatic for hyperparathyroidism and did not present with nephrolithiasis, nephrocalcinosis or skeletal fractures. Her other symptoms may have also been attributed to hypothyroidism. According to the guidelines set forth at the Third Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, surgical management was a valid option based on elevated calcium levels, osteoporosis and age. The threshold value for serum calcium, above which surgery would seem to be appropriate, has been maintained at more than 0.25 mmol/l (1 mg/dl) above the upper limits of normal. Surgery is also recommended for perimenopausal or postmenopausal women and men aged 50 years and older who have a T-score of –2.5 or less at the lumbar spine, femoral neck, total hip or 33% (one third) of radius. The guidelines also recommend surgery for patients below 50 years.¹⁹

Surgical management

In experienced hands, parathyroidectomy is associated with a cure rate of 95–98% and a low rate (1–3%) of complications (laryngeal nerve palsy and, less frequently, postoperative hypocalcaemia).²⁰ As mentioned, however, ectopic parathyroid adenomas are one cause for failed neck exploration. Historically, it is commonly taught that when performing a parathyroid exploration if a missing parathyroid gland cannot be found, it may lie in an intrathyroidal location and performing a thyroid lobectomy is appropriate. This however is often performed indiscriminately and is typically unsuccessful. At our centre, thyroid lobectomy is performed only when there is a high probability of the parathyroid adenoma being imbedded within the thyroid on the basis of preoperative imaging and palpation of the thyroid lobes. It has been recommended that at the time of exploration any nodule within the thyroid must be considered to be an intrathyroidal parathyroid until proven otherwise.⁶ In the search of an intrathyroidal parathyroid adenoma it should be noted that these occur in predictable locations, with the vast majority (90%) occurring in the lower lateral quadrant of the thyroid, 7% near the recurrent nerve and only 3% in the superior pole.¹⁶

Hungry bone syndrome and bisphosphonates

Hypocalcaemia is a common complication of parathyroidectomy in more than 50% of subjects, with the lowest serum calcium level usually found around the third hospital day, as seen in our patient.²¹ Hungry bone syndrome may occur in approximately 12% and is manifested by severe and prolonged, sometimes life-threatening, hypocalcaemia. This syndrome is related to a sudden decrease in PTH release and attenuation of its effect on the contribution of bone to serum calcium concentration. Features predictive of development of the hungry bone syndrome are a preoperative high serum calcium level and mean PTH concentrations of >80 pg/ml or higher, as well as size of adenoma and patient’s mean age of 60 years or older.⁵

It is possible that the use of pamidronate before surgery may have reduced the severity of hypocalcaemia in this case. The use of bisphosphonates, especially at high doses, can reduce serum and urinary calcium levels by reducing intense bone remodelling existing prior to parathyroidectomy, without affecting PTH secretion directly.^{4 22} The effects are felt after surgery, decreasing the velocity of calcium influx to the bone, preventing its sudden drop and the symptoms of severe hypocalcaemia. The use of bisphosphonates also does not prevent the marked increase in bone mass observed during patient followup.²² Although there are no recommendations at present, different bisphosphonates have been used preoperatively, with varying degrees of success, including pamidronate and alendronate.^{22 23}

PTH recovery

During unilateral parathyroidectomy, PTH levels decline rapidly by about 50% from preoperative values at 10 min and are undetectable at 2 h from clamping of the vascular supply of the adenoma. In our case, PTH levels drawn after excision of the thyroid lobe fell by about 98% from baseline. Recovery of parathyroid secretory activity from the remaining non-surgically manipulated parathyroid

glands is usually seen at 30 h and occurs during the nadir of postoperative hypocalcaemia. This rapid response may be due to the direct response of the parathyroid gland to hypocalcaemia.²⁴ Patients with PTH levels below reference range at 30 h have been observed to be younger than average, with higher preoperative calcium and PTH levels, as in our patient.

With surgical cure of PHPT, serum calcium levels normalise and remain stable at 6 and 12 months, indicating PTH recovery.²⁵ Our patient, however, continued to require calcium replacement and had a persistently low PTH level 6 months after surgery. Persistent hypocalcaemia is usually seen in patients who undergo bilateral neck exploration with manipulation of the other parathyroid glands. Our patient only had a unilateral neck exploration with purposeful avoidance of manipulation of the other side of the neck to avoid this complication; however, PTH levels have remained undetectable. This suggests a possible anatomic variation such as a solitary parathyroid gland in this patient, although in the reported literature a minimum of two glands has been identified.²⁶

Postparathyroidectomy management

Studies have shown that bone mineral density usually increases after parathyroidectomy in patients with PHPT, about 12% after 1 year. The timing of initiation of osteoporosis treatment after parathyroidectomy, however, is not clear.²⁷ Some physicians start treatment immediately for patients who are at high risk for fractures and who have established osteoporosis. Serial bone mineral density measurements are done annually or every 2 years after parathyroidectomy.²⁸

Concomitant thyroid disease

Our patient presented with hypothyroidism, with a very low free T4 level and TSH levels slightly above normal (above 3.8 but below 10 µIU/ml). In the absence of hypothalamic–pituitary dysfunction we would expect a much higher TSH level for such a low level of free T4. As this patient was asymptomatic in childhood and for most of her adult life, it would lead us to the possibility of central hypothyroidism due to a hypothalamic or pituitary disorder with acquired TSH deficiency.²⁹ In central hypothyroidism, basal serum TSH values can be low, normal or even slightly elevated (up to 10 µIU/ml).^{29–30} Possible aetiologies for acquired TSH deficiency are infiltrative, infectious or neoplastic processes.²⁹ Multiple pituitary deficiencies are associated with such processes, with symptoms of hypothyroidism, as well as symptoms of gonadotropin, growth hormone and usually adrenocorticotrophic hormone deficiencies. Acquired isolated TSH deficiency is rarely seen.^{29–31–32} TSH deficiency also usually manifests after the development of growth hormone and gonadotropin deficiencies,³³ which were not evident in this patient. Our patient had regular menses and an unremarkable obstetric and gynaecological history. She was also normotensive and did not have any signs or symptoms of other hormonal deficiencies. She likewise did not present with any neurological symptoms indicative of an expanding sellar or suprasellar mass. As there were no other significant findings to suggest that her hypothalamic–pituitary function was anything but normal, central

hypothyroidism was considered to be a less likely diagnosis in this case.

Thyroid disease has been found to be coexistent with hyperparathyroidism in 20–60% of patients undergoing neck exploration. In one series, it was identified to be 18% in all patients undergoing surgery for hyperparathyroidism, with 12% of these being well-differentiated papillary carcinomas, 8% chronic lymphocytic thyroiditis and the remaining majority as follicular adenomas and nodular hyperplasia.³⁴ Hypothyroidism may also be a coincidental finding during the evaluation of hyperparathyroidism³⁵ or vice versa as seen in our patient.

This coexistence has raised the issue of a possible aetiological relationship between these two entities. Two studies in rats using propylthiouracil to stimulate TSH showed that chronic TSH stimulation led to parathyroid hyperplasia and an increase in circulating PTH. It is postulated that prolonged TSH stimulation and may lead to hyperparathyroidism in animal models.^{36–37}

It has been observed that subjects with hypothyroidism may develop hyperparathyroidism even after levothyroxine therapy has been initiated. In one report, 17 cases of Hashimoto's thyroiditis developed symptoms of hyperparathyroidism anywhere from 2 months to 30 years after replacement therapy.³⁸ Our patient had a 2-year history of an anterior neck mass before the diagnosis of hyperparathyroidism and may have had undiagnosed Hashimoto's thyroiditis in the preceding years. It has been suggested that patients with Hashimoto's thyroiditis should be evaluated for parathyroid disease.

Some authors propose that the parathyroid glands have a spectrum of autoimmunity analogous to that of the thyroid gland and that autoimmune antibodies stimulate PTH secretion. It is possible that parathyroid hyperplasia in conjunction with lymphocytic parathyroiditis could be due to a stimulating antibody or to cytokines produced by the lymphocytic infiltrate.³⁹ A second possibility is that the mononuclear inflammatory infiltrate in the thyroid gland associated with Hashimoto's disease can irritate the neighbouring parathyroid gland parenchyma and cause release of PTH.⁴⁰

Learning points

- In the setting of hyperparathyroidism, an intrathyroidal parathyroid adenoma should be considered in the presence of a thyroid nodule and negative surgical neck exploration.
- Neck ultrasound combined with Tc-99m sestamibi scanning improves preoperative localisation of single parathyroid adenomas.
- Preoperative bisphosphonate use may attenuate hungry bone syndrome after parathyroidectomy.
- Parathyroid hormone recovery is usually rapid after unilateral parathyroidectomy.
- Hyperparathyroidism may develop in patients with chronic hypothyroidism and Hashimoto's thyroiditis.

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