Mediastinal parathyroid adenoma: diagnostic and management challenges

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ABSTRACT

Primary hyperparathyroidism due to ectopic parathyroid adenomas can pose diagnostic and management challenges, especially when imaging studies have localised the lesions to different sites. We report a case of symptomatic hypercalcaemia due to a mediastinal parathyroid adenoma. Ultrasonography identified a nodule posterior to the right thyroid gland. However, computed tomography and technetium-99m sestamibi scintigraphy revealed an ectopic parathyroid adenoma located in the anterior mediastinum. The adenoma was successfully removed through a median sternotomy. However, postoperatively, the patient developed prolonged symptomatic hypocalcaemia, possibly due to suppression of the normal parathyroid gland function, although the presence of concomitant hungry bone syndrome was possible. The histopathology of the mediastinal mass was consistent with a parathyroid adenoma.

Keywords: ectopic parathyroid adenomas, hungry bone syndrome, hypercalcaemia, primary hyperparathyroidism, sestamibi scintigraphy

Singapore Med J 2011;52(4):e70-e74

INTRODUCTION

Primary hyperparathyroidism can be diagnosed in the absence of significant renal failure, when an inappropriately high level of parathyroid hormone is present in a high concentration of serum calcium.[1] Primary hyperparathyroidism occurs in approximately 1% of the adult population and is commonly due to solitary parathyroid adenomas (85%). Other causes of primary hyperparathyroidism are related to multiple gland hyperplasia affecting all parathyroid glands (10%), double adenomas (4%) and rarely, parathyroid carcinoma (1%).[1]

Ectopically located parathyroid adenoma is uncommon, and thus, its diagnosis and management can sometimes be challenging. Difficulties in locating the ectopic parathyroid adenoma may delay the diagnosis and subsequent surgery. The incidence of ectopic parathyroid adenoma is reported to be 6%–25%.[2] Technetium-99m (Tc-99m) sestamibi scintigraphy is often used as the gold standard preoperative technique for localisation of hyperfunctioning parathyroid tissue.[3] Other imaging modalities may include a combination of high resolution ultrasonography (USG), computed tomography (CT) and/or magnetic resonance (MR) imaging.[3]

We report a patient who presented with symptoms of hypercalcaemia, with the biochemical results supportive of primary hyperparathyroidism. Imaging studies revealed an ectopic parathyroid gland in the anterior mediastinum.

CASE REPORT

A 48-year-old Malay woman presented to the outpatient clinic with a one-month history of constipation associated with frequent urination, bodyache and lethargy. There was no significant past medical illness. On examination, the patient was conscious and alert. Her pulse was 76/min and blood pressure was 114/76 mmHg. There was no lymphadenopathy or palpable mass in the neck or breasts. Examination of the cardiovascular, respiratory and nervous systems was unremarkable. Liver and spleen were not palpable, and funduscopic examination was normal. The investigation results showed serum calcium 3.48 mmol/L, phosphate 0.66 mmol/L, creatinine 82 μmol/L and alkaline phophatase 258 IU/L. Electrocardiogram showed sinus rhythm with normal QTc interval. Her intact serum parathyroid hormone (iPTH) was markedly elevated at 1,296 (normal range 7–53) pg/ml.

The patient was initially treated with saline hydration, but no significant reduction in her serum calcium levels was observed. However, four days after an intravenous dose of pamidronate 60 mg, her symptoms improved and her serum calcium level decreased to 2.72 mmol/L. USG of the neck showed an ill-defined nodule isoechoic to the thyroid at the posterior midsection of the right thyroid gland. However, Tc-99m sestamibi scintigraphy showed a focal intense uptake and retention of tracer in the right side of the mediastinum, which was suggestive of an ectopic parathyroid adenoma (Fig. 1). No retention of tracer in the thyroid was seen in the delayed image.

Post-intravenous contrast-enhanced CT of the

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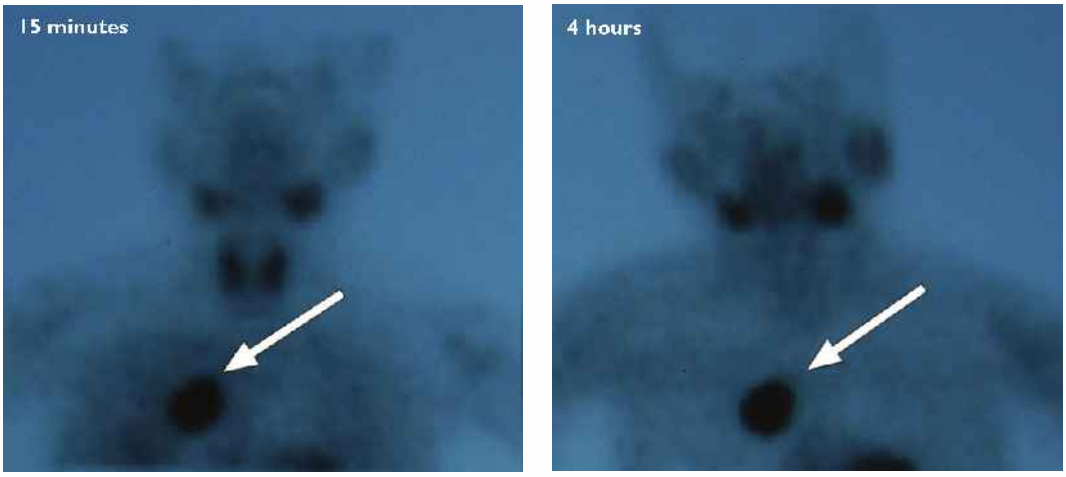

Fig. 1 Technetium-99m sestamibi scintigraphy shows an intense uptake and retention of tracer in the right side of the mediastinum (white arrows). The uptake of tracer in the thyroid glands was not retained in the delayed image.

thorax showed a well-defined soft tissue mass, measuring 1.8 cm × 3.1 cm × 4.0 cm, in the anterior mediastinum to the right of midline (Fig. 2). A diagnosis of primary hyperparathyroidism due to an ectopic parathyroid adenoma was made, and surgical removal was planned. The patient underwent neck exploration and median sternotomy. Neck exploration was performed, as the USG showed an ill-defined nodule in the right thyroid gland; however, no abnormality was found during the procedure. Following sternotomy, a mass (Fig. 3) was successfully removed from the anterior mediastinum. The resected mass was an oval nodule measuring 3.5 cm × 3.0 cm × 1.5 cm and covered by a thin capsule. On section, the mass showed a greyish cut surface with foci of haemorrhage and cystic changes. Histopathological examination revealed an encapsulated cellular lesion with a well-delineated outer margin. The lesion was composed predominantly of chief cells and transitional cells arranged in a diffuse and vague nesting pattern. Follicular structures containing pink colloid-like materials were noted. Scattered foci of cystic changes, water-clear cells and oncocytic cells were also seen. The features were consistent with a parathyroid adenoma (Fig. 4).

The patient's serum calcium level decreased to 2.76 mmol/L on the first postoperative day. However, her postoperative period was complicated by prolonged symptomatic hypocalcaemia (serum calcium was about 1.8 mmol/L) requiring continuous intravenous infusion of 10% calcium gluconate (2.2 mmol/L of calcium in 10 ml) at 5 ml/hr initially but was later changed to bolus intravenous calcium gluconate 10 ml tds. Her serum phosphate was low, at 0.74 mmol/L (normal range 0.87–1.45 mmol/L), with a marked increase in the serum alkaline phosphatase level (791 U/L) (normal range 39–117 U/L). Her 24-hour urine calcium was 7.31 mmol/L (normal range 2.5–7.5 mmol/L/24-hrs). One month after the operation, her serum calcium stabilised at approximately 2.17–2.18 mmol/L on high-dose oral calcium (calcium lactate 1.2 g tds and calcium carbonate 2 g tds) and rocaltriol 1 µg bd supplementation. Bolus intravenous calcium gluconate was stopped and the patient was discharged. The dose of oral calcium and rocaltriol was gradually reduced during follow-up, as her serum calcium normalised at about 2.23 mmol/L. Her iPTH level was < 3 pg/ml on postoperative Day 1 but gradually increased to 10.4 pg/ml on postoperative Day 25 and 122 pg/ml on Day 37.

DISCUSSION

Primary hyperparathyroidism is a common metabolic bone disease characterised by hypercalcaemia due to autonomous overproduction of parathyroid hormone.[1] Most cases are usually asymptomatic and detected only incidentally due to hypercalcaemia. A diagnosis of primary hyperparathyroidism in a symptomatic patient is reached in the presence of hypercalcaemia, hypophosphataemia, raised levels of alkaline phosphatase and iPTH, as demonstrated in our case.[1]

Though uncommon, ectopic location of active parathyroid glands is an important reason for failure to locate the glands during parathyroidectomy. A single imaging study is usually utilised to locate the active parathyroid glands in unexplored patients.[4] A combination of imaging studies is often performed in patients with recurrent or persistent hyperparathyroidism. This involves the use of a functional study such as parathyroid scintigraphy and an anatomic imaging study

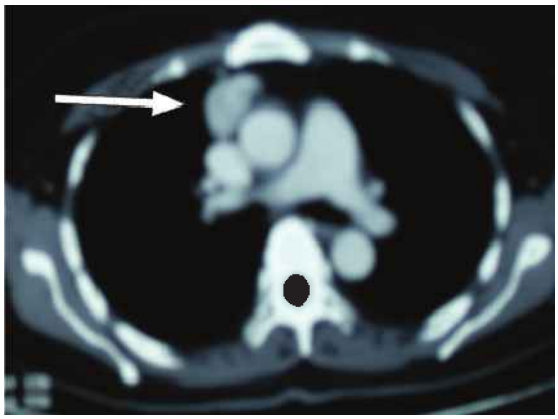

Fig. 2 CT image of the thorax shows the ectopic parathyroid adenoma in the anterior mediastinum to the right of the midline (white arrow).

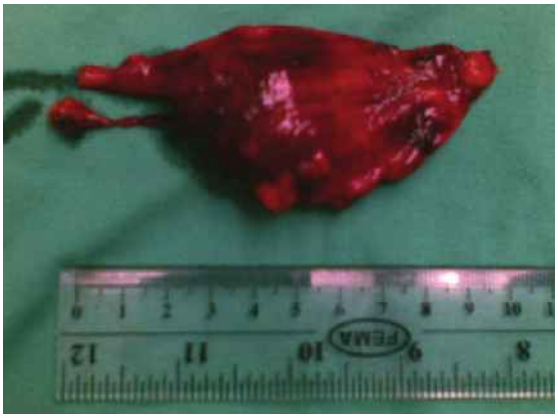

Fig. 3 Photograph shows the resected mediastinal parathyroid adenoma measuring 3.5 cm × 3.0 cm × 1.5 cm.

such as USG, CT or MR imaging.[4] Tc-99m sestamibi scintigraphy is often used for preoperative localisation. Its sensitivity is 71%–93%, depending on the imaging protocols utilised.[4] USG is commonly used to locate enlarged parathyroid glands due to its convenience and low cost. However, its ability to detect abnormalities depends on the experience and skill of the operator, and therefore, its sensitivity in localisation of enlarged parathyroid glands varies greatly (44%–87%).[5] USG has poor sensitivity (≤ 30%) for locating ectopic glands or multigland disease.[5] In our case, USG had given a false positive result, leading to unnecessary neck exploration. A differential diagnosis of the nodule identified by the USG in our case would include thyroid adenoma, hyperplastic nodule, thyroid cyst, malignant thyroid nodule and perithyroid veins, which can be mistaken for enlarged parathyroid glands.

The use of CT imaging for localising enlarged parathyroid glands in unexplored patients can give a sensitivity of 76%–83%.[4] However, the sensitivity is even higher (up to 100%) when a combination of Tc-99m sestamibi scintigraphy and helical CT imaging is used.[4] Several studies have explored the usefulness of a combination of two or more imaging techniques, but it is still unclear which combination of procedures should be used routinely in unexplored patients.[6,7] In our case, the USG result was misleading, but a combination of sestamibi scintigraphy and CT imaging accurately localised the tumour to the anterior mediastinum, thus highlighting the usefulness of combining multiple imaging techniques to locate ectopic active parathyroid gland. At our institution, we routinely perform these two investigations to localise the parathyroid gland, as experience has proven that USG is unreliable, and that preoperative localisation can direct the operation and decrease operation time.

In cases of disease recurrence or failed surgery, localisation of parathyroid adenoma by sestamibi scintigraphy is considered mandatory.[8] In cases with a co-existing thyroid nodule, the tracer may localise to the thyroid gland initially, but tends to get washed away more quickly. Retention of tracer within the thyroid gland is suggestive of intrathyroidal parathyroid tumour. In our patient, no retention of tracer in the thyroid was observed in the delayed image, suggesting that the active parathyroid was not located in the thyroid gland. USG and USG-guided fine needle aspiration cytology studies may help in confirming the diagnosis in such cases. Intraoperative iPTH assays can also be performed, and a reduction of iPTH by at least 50% within ten minutes of excision confirms successful surgery.[9] We did not perform an intraoperative iPTH assay, but a sample taken on postoperative Day 1 showed an almost undetectable iPTH level, implying a complete removal of the hyperactive adenoma. The gradual increase in iPTH levels is consistent with gradual recovery of the suppressed normal parathyroid glands.

Abnormal migration of parathyroid glands during embryological development may result in their ectopic locations. The superior parathyroid glands and the lateral analges of the thyroid gland arise from the fourth pharyngeal pouches. The third pair of pharyngeal pouches forms the inferior parathyroid glands and thymus. The inferior parathyroid glands are prone to be ectopically located, as they have to descend a great distance to arrive at the inferior pole of the thyroid glands.[10] The locations of ectopic parathyroid glands include the posterior mediastinum behind the cervical oesophagus, the thymus, tracheo-oesophageal groove and anterior mediastinum,[10] as in our patient.

Ectopic parathyroid tissue can be normal or hyperplastic, but it can also give rise to adenoma or

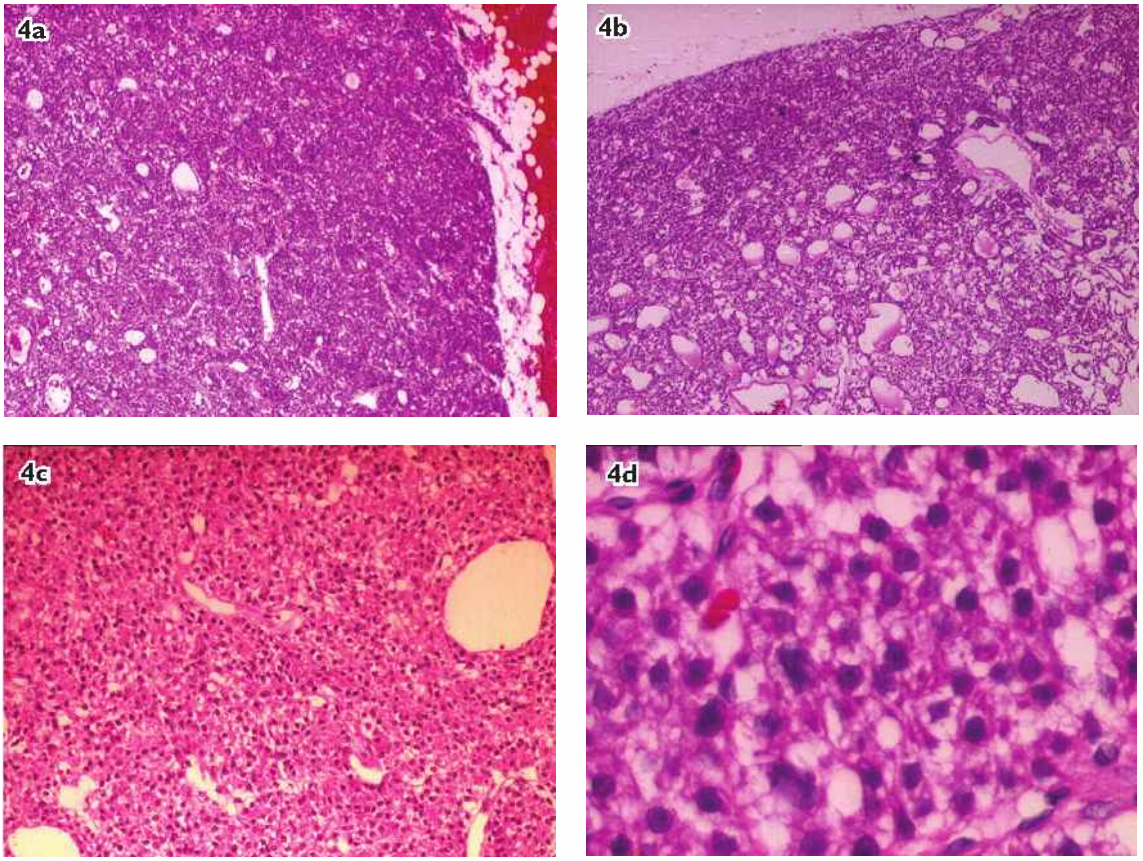

Fig. 4 Photomicrographs of the adenoma show (a) diffuse and vague nesting pattern of cells (Haematoxylin & eosin, x 40); (b) follicular structures containing colloid-like material with the sharp outer margin seen on the upper left side (Haematoxylin & eosin, x 40); (c) a predominance of chief cells (Haematoxylin & eosin, x 100); and (d) a focus of transitional water-clear cells in the adenoma (Haematoxylin & eosin, x 400).

carcinoma.[11] Histologically, both hyperplasia and adenoma resemble parathyroid tissue, which is composed of any of the various cell types that make up the normal parathyroid gland, such as chief cells, oxyphil cells and transitional cells. In cases of hyperplasia, the major difference is in the increased cellularity. The adenoma, however, is a well-circumscribed, encapsulated oval lesion that causes variable enlargement of the gland with foci of haemorrhage, calcification and cystic changes. Microscopically, the tumour is highly cellular and may contain chief cells, oxyphil cells, water-clear cells and transitional elements in various combinations, but usually, the chief cells predominate. The cells are arranged in a diffuse, nesting, follicular or pseudopapillary pattern. The follicles may contain colloid-like material. A parathyroid carcinoma differs microscopically from an adenoma in its trabecular arrangement of cells, dense fibrous bands, spindly tumour cells, mitotic figures and presence of capsular and vascular invasion.[12] In our case, the macroscopic and microscopic features of the resected mediastinal mass were consistent with a parathyroid adenoma.

Hypocalcaemia is a common complication of parathyroid surgery. Up to 40% of the individuals who undergo parathyroidectomy for primary hyperparathyroidism develop hypocalcaemia postoperatively.[13] The serum calcium usually falls and reaches its lowest level within 24–36 hours after parathyroidectomy. The serum iPTH level usually returns to normal within 30 hours, but the secretory response of the normal parathyroid tissues to hypocalcaemia may not be normal for several weeks postoperatively.[14] Consequently, transient hypocalcaemia is frequently encountered postoperatively; in fact, the presence of mild hypocalcaemia reassures the surgeon that the hyperactive adenomatous gland has been successfully removed.

Our patient developed prolonged hypocalcaemia that required high doses of calcium and vitamin D. This is explained by hypoparathyroidism due to suppression of the remaining normal parathyroid glands by the preoperative hypercalcaemia, as evidenced by the low iPTH level on postoperative Day 1. Additionally, our patient may have hungry bone syndrome, as hypocalcaemia persisted despite large amounts of intravenous and oral calcium supplementation. Furthermore, her 24-hour urine calcium excretion was

only 7.31 mmol, implying that there was no significant renal calcium loss. Her serum phosphate level was also relatively low (0.74 mmol/L), while her serum alkaline phosphatase was markedly elevated (791 U/L), features that are consistent with hungry bone syndrome.[15] In addition, her preoperative alkaline phosphatase was markedly increased (258 IU/L), which alerted us to the possibility of postoperative hungry bone syndrome. The hypocalcaemia could also be related to the neck exploration, causing vascular compromise of the normal parathyroid tissues.

The presence of vitamin D deficiency in patients undergoing parathyroidectomy raises the concern of post parathyroidectomy hypocalcaemia due to hungry bone syndrome. Preoperative treatment with vitamin D may reduce the risk of postoperative hypocalcaemia, especially in patients with end stage renal disease, as it may prevent the development of hungry bone syndrome.[15] However, this may not be safe in patients with hypercalcaemia. Although we did not measure the vitamin D level in our patient, we postulate that the level would likely be low due to her dark skin complexion and reduced exposure to sunlight through the covering of her body with clothing in accordance with the local culture and religious belief. Preoperative use of vitamin D in our patient would be inappropriate as she had severe hypercalcaemia, which was difficult to control.

To date, there are no standard preoperative guidelines to avoid prolonged postoperative hypocalcaemia in patients undergoing surgery for primary hyperparathyroidism. At our institution, a calcium level is typically drawn after surgery. If the calcium level is low, intravenous calcium gluconate is given, and oral calcium and vitamin D supplements are commenced once the patient is able to tolerate oral administration.

A combination of imaging modalities is required as a guide in preoperative localisation of the abnormal parathyroid, especially if previous USG shows variable results. Neck exploration is unnecessary if the combination of imaging studies confidently localises the abnormality. This would reduce the risk of vascular compromise of normal parathyroid glands and thereby decrease the risk of postoperative hypocalcaemia. Vitamin D levels should ideally be checked before parathyroidectomy in patients who have risk factors for vitamin D deficiency. These patients should be considered for treatment if their serum calcium levels are not dangerously high. We should anticipate postoperative hypocalcaemia in patients who have undergone neck exploration or have very high preoperative serum calcium, as well as those at risk of hungry bone syndrome. An extended duration of intravenous calcium treatment may be required to correct post parathyroidectomy hypocalcaemia in patients with hungry bone syndrome.

In summary, we described a patient who presented with symptomatic hypercalcaemia due to primary hyperparathyroidism. Tc-99m sestamibi scintigraphy and CT imaging revealed an ectopic parathyroid adenoma in the anterior mediastinum, while USG gave a false localisation to the neck. Postoperatively, the patient developed prolonged symptomatic hypocalcaemia, which was possibly due to suppression of the normal parathyroid glands or concomitant hungry bone syndrome. Our patient required one month of intravenous calcium supplements to correct the hypocalcaemia.

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