CASE REPORT

A garden of parathyroid adenomas

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SUMMARY

Despite improvements in parathyroidectomy success rates, patients with persistent primary hyperparathyroidism (PHPT) after initial surgery continue to challenge clinicians. Some of the challenges are due to ectopic parathyroid adenomas, including thymic, intrathyroidal, carotid sheath and mediastinal glands, and others are because of supernumerary glands. While uncommon in PHPT, multigland disease is also an important consideration in patients requiring reoperative surgery for persistent disease. For this reason, localisation studies including sestamibi, ultrasound, CT scan and venous sampling for abnormal glands may be an essential component of the preoperative workup. In this report, we describe an unusual case of a patient who required a total of four operations to cure PHPT arising from seven parathyroid adenomas.

BACKGROUND

As a result of modern developments in imaging and hormone assays, parathyroidectomy can often be performed as a minimally invasive, outpatient procedure with success rates as high as 95%.¹ However, patients with persistent primary hyperparathyroidism (PHPT) after initial surgery, or those with recurrent PHPT, continue to represent a challenge for clinicians.² Scar tissue in the operative field, combined with the possibility of ectopic or supernumerary parathyroid glands, results in decreased success rates and increased complication rates. Higher rates of both temporary and permanent hypocalcaemia and recurrent laryngeal nerve injury have been reported in the reoperative neck.^{3,4} For this reason, success rates for reoperative parathyroid surgery range from 73% to 100%.^{5,6}

Multiple case reports in the literature describe ectopic locations of adenomas, including thymic, intrathyroidal, tracheo-oesophageal groove, carotid sheath and mediastinal sites. In this report, we describe an unusual case of a patient who required four operations and removal of a total of seven parathyroid adenomas in order to finally cure her persistent PHPT.

CASE PRESENTATION

A 42-year-old woman initially presented in 2004 to an outside hospital with hypercalcaemia. The patient's medical history was significant for leukaemia, diagnosed at the age of 4 years and treated with chemotherapy only. At presentation, the patient complained of significant fatigue and diffuse muscle aches. Workup confirmed PHPT and she subsequently underwent a focused

parathyroidectomy with excision of a 3-gram left superior parathyroid adenoma. The detailed operative report from the outside hospital of the initial surgery was not available. Postoperatively, the patient was followed up annually with reported resolution of hypercalcaemia and symptoms.

In 2011, routine lab work revealed an elevated serum calcium of 11.8 mg/dL (normal range: 8.4–10.5 mg/dL), ionised calcium 1.74 mmol/L (normal range: 1.13–1.32 mmol/L) and parathyroid hormone (PTH) of 319 pg/mL (normal range: 10–65 pg/mL). The patient was referred to our clinic with symptoms of hypercalcaemia, including fatigue, loss of appetite and weight loss, insomnia, anxiety, dizziness, leg cramps, back pain, memory loss, and confusion over the course of 1 year. She had no family history of hyperparathyroidism or personal exposure to ionising radiation. Physical examination revealed a well-healed Kocher incision and a normal thyroid gland with no associated palpable nodules or lymphadenopathy.

Neck ultrasound performed at an outside institution revealed two hypoechoic areas in the central neck inferior to the left thyroid lobe, but no enlarged parathyroid glands. Sestamibi scan showed an ectopic parathyroid adenoma in the superior anterior mediastinum, likely a left inferior adenoma (figure 1A). The patient then underwent reoperative parathyroidectomy (November 2011). During a focused left neck exploration, a 1653 mg left parathyroid adenoma located inferior to the thyroid gland was removed. No additional adenomas were identified in this location. Intraoperative PTH level dropped from a baseline of 343 to 127 pg/mL within 10 min, meeting Miami criteria. As a result, no further exploration was undertaken.

Three months after her second operation, the patient had persistent hypercalcaemia with a total serum calcium of 10.4 mg/dL, ionised calcium of 5.9 mmol/L and PTH of 161 pg/mL. Repeat ultrasound revealed a 1.1 cm × 0.8 cm × 0.6 cm hypoechoic nodule suggestive of a parathyroid adenoma, again, inferior to the left thyroid lobe. A sestamibi scan also demonstrated increased radiotracer uptake in this location (figure 1B). The patient underwent a third parathyroidectomy (June 2012), and a 477 mg left inferior parathyroid, this time, located posterior to the left thyroid lobe was removed. PTH at baseline was 192 pg/mL and dropped to 65 pg/mL at 10 min, again meeting Miami criteria. To rule out the presence of four-gland disease, further exploration was performed on the right side, and revealed both superior and inferior normal appearing parathyroid glands. The patient's postoperative day 1 total serum calcium

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Figure 1 Preoperative parathyroid sestamibi scan. (A) Imaging demonstrates an ectopic parathyroid adenoma in the superior anterior mediastinum, slightly left to the midline. (B) Imaging demonstrates a parathyroid adenoma inferior to the left thyroid lobe. (C) Imaging is suspicious for an ectopic parathyroid adenoma superior to the junction of superior vena cava and left innominate vein.

levels normalised at 10.1 mg/dL. However, 10 days after surgery, the patient still had a slightly elevated total serum calcium of 10.6 mg/dL and a PTH of 97 pg/mL.

In 2015, 3 years after her third operation, the patient was again referred for complaints of fatigue, sleep disturbance and lower extremity aches. Biochemical workup revealed an elevated calcium of 12.0 mg/dL and a PTH of 225 pg/mL. Ultrasound showed a 9 mm probable parathyroid adenoma with two additional 7 and 8 mm nodes representing additional parathyroid adenomas or lymph nodes in the midline level VI region. However, sestamibi suggested an ectopic parathyroid adenoma at the junction of the superior vena cava and left innominate vein (figure 1C).

During her fourth operation, the patient underwent excision of a mediastinal parathyroid adenoma, complete cervical

lymphadenectomy and a total thyroidectomy through a cervical approach. At the time of surgery a 350 mg parathyroid was located between the innominate vein and innominate artery on the left and removed. However, the PTH only dropped from 200 pg/mL at baseline to 138 pg/mL at 10 min, not meeting Miami criteria. A redo neck exploration was therefore performed. A right superior parathyroid gland was noted and carefully preserved in the normal position. The right thyroid lobe was then excised due to concern for an intrathyroidal parathyroid. After removal, PTH levels were 131 pg/mL at 0 min and 111 pg/mL at 10 min. After this, a lymphadenectomy was done and the PTH dropped from 104 pg/mL at 0 min to 68 pg/mL at 10 min. Similarly, due to concern for a left intrathyroidal parathyroid, the left thyroid lobe was also removed. After removal of the left thyroid lobe, PTH levels dropped to 30 pg/mL at 10 min. Table 1 summarises

Table 1 Parathyroid hormone (PTH) and calcium levels for remedial parathyroidectomy

	Calcium (mg/dL)		PTH (pg/mL)				
	Pre-op	Follow-up	Pre-op	Baseline	0 min postgland excision	10 min postgland excision	Follow-up
Re-op 1	11.8	11.5	319	343	258	127	148
Re-op 2	10.4	10.1	161	192	113	65	72
Re-op 3	12.0	8.4	225	200	Right parathyroid excision		65
					142	138	
					Right thyroid lobectomy		
					131	111	
					Mediastinal lymphadenectomy		
					104	68	
					Left thyroid lobectomy		
					44	30	

the course of each reoperation the patient underwent, including baseline, 0 and 10 min postexcision PTH levels corresponding to each removed gland.

Surgical pathology revealed an enlarged 350 mg mediastinal parathyroid adenoma, a 0.9 cm parathyroid adenoma located in the right central neck, a 0.4 cm intrathyroidal parathyroid gland in the right lobe and another intrathyroidal 1.0 cm parathyroid gland in the left lobe. Four parathyroid adenomas were removed during this fourth and final operation and in total seven parathyroid adenomas had been removed. On postoperative day 1, the patient had a PTH of 65 pg/mL and total serum calcium of 8.4 mg/dL with no need for calcium supplementation. At 10 days follow-up, total serum calcium was 8.9 mg/dL (normal range: 8.6–10.2 mg/dL) and PTH was 125 pg/mL (normal range: 14–64 pg/mL).

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis included multiple endocrine neoplasia (MEN) syndrome and parathyromatosis. Given that the patient had no family history of parathyroid disease or other endocrinopathies, the suspicion for MEN1 disease was low. However, sporadic MEN syndrome can still be a possibility, where *de novo* mutations in *MEN1* are found in 10% of MEN1 patients.⁷ For this reason, it must be considered in her future management.

In review of the second, third and fourth surgeries, there was no point at which the capsule was ruptured during dissection and removal of parathyroid adenomas. While we do not have access to the operative report of the initial surgery, the gland removed at that time appears to be a left upper gland, unlikely to cause seeding of parathyroid tissue in the left lower, right lower and mediastinal area. We would more likely expect seeding to be found in the left upper region. Also, in reviewing the appearance of the adenomas removed at the second, third and fourth surgeries, the appearances of these glands were discrete adenomas as opposed to 'multiple small nodules of hypercellular parathyroid tissue present in soft tissue (fat, skeletal muscle, fibrous tissue) of the neck'.⁸ Moreover, the two intrathyroidal parathyroid glands further argue against parathyromatosis as the cause of persistent hyperparathyroidism.

OUTCOME AND FOLLOW-UP

At 1 year follow-up, total serum calcium was 9.8 mg/dL. The patient is asymptomatic and requires no calcium supplementation.

DISCUSSION

While multigland disease in PHPT is relatively uncommon, it is an important consideration in patients requiring reoperative surgery for persistent or recurrent disease. Among patients with PHPT, 37% have ectopic parathyroid adenomas and 13% have supernumerary glands.^{9–11} Interestingly, ectopic parathyroid adenomas have significantly higher serum calcium levels (12.6 vs 11.4 mg/dL) and larger tumours (2.5 vs 1.9 cm) compared with orthotopic parathyroid adenomas.¹² Ectopic parathyroid glands can be congenital, as a result of arrested or abnormal fetal descent, or acquired, thought to be due to displacement by gravity, loose tissue planes, deglutition and negative intrathoracic pressure. In the case presented, the patient had a total of seven parathyroid adenomas resected, among the highest described in the literature.^{13 14}

To ensure appropriate reoperative surgery, every effort should be made to localise abnormal glands preoperatively, with the use of ultrasound, sestamibi scan or CT scan. If no gland can be

Figure 2 Illustration of parathyroid adenomas removed at each operation (structures not drawn to scale).

localised with imaging, venous sampling may be useful. Venous sampling has been reported with variable success rates (44%–100%), but requires significant radiological expertise.^{15–17} In our case, venous sampling was not indicated as each imaging study showed an adenoma. Furthermore, all localisation studies should be performed at high-volume centres, as highly skilled radiological interpretation is crucial for the success of preoperative localisation.

Despite best efforts, preoperative localisation of all parathyroid adenomas, as in the reported case above, may not be possible. In such cases, familiarity with common locations of ectopic glands is of utmost importance. Thymectomy, thyroidectomy, exploration of the tracheo-oesophageal groove, carotid sheath, paratracheal and retro-oesophageal regions may all be necessary. Our patient had four ectopic glands, including two intrathyroidal glands and two mediastinal glands (figure 2). Because she met Miami criteria at each operation, extensive cervical lymphadenectomy and total thyroidectomy were not performed until her final and definitive operation. These manoeuvres proved to be curative despite the fact that imaging did not suggest an intrathyroidal gland. It is crucial that parathyroid surgeons be comfortable with performing these procedures in patients whose intraoperative PTH does not drop convincingly after removal of a localised adenoma. It is also important to note that in the case presented the mediastinal parathyroid adenoma juxtaposed to the superior vena cava and innominate vein was not seen until the final sestamibi scan.

Defining cure by intraoperative PTH levels is also important for standardising surgery across institutions. The use of intraoperative PTH has made less invasive approaches to parathyroidectomy possible. Using the Miami criteria, at 10 min postadenoma excision, an intraoperative PTH decrease of $\geq 50\%$ from baseline or time 0 min PTH has a reported sensitivity of 98%.¹⁸ However, it is important to recognise the limitations of Miami criteria. Success rates using the Miami criteria are higher when preoperative localisation using sestamibi and ultrasound is concordant. However, discordant preoperative imaging is quite common, occurring in up to 48% of cases and making the Miami criteria less dependable.¹⁸

Miami criteria is also less dependable in patients with multigland disease.¹⁸

Understanding its limitations is particularly useful for patients with multigland disease. Wachtel *et al* examined 2185 subjects and found that patients with persistent hyperparathyroidism had a significantly smaller decrease in intraoperative PTH, suggesting that failure of intraoperative PTH to drop into the normal range may portend persistent disease in patients with unsuspected multigland disease.¹⁹ However, the use of more stringent variations of the Miami criteria, such as a 50% baseline PTH decline at 5 min, has been shown to increase the risk for unnecessary bilateral exploration.²⁰ The extent to which PTH levels should fall has also been a subject of debate. Multiple retrospective studies have concluded that a final PTH level meeting Miami criteria and <40 pg/mL is a strong indicator of operative success due to a significantly lower risk of persistence or recurrence.^{21–23} Among these studies, Wharry *et al* reported that when PTH meets Miami criteria but does not fall into normal range (<65 pg/mL), surgical failure was 19 times more likely (3.8% vs 0.2%; $p=0.015$). This protocol has not been evaluated prospectively however, but likely would have been helpful in this difficult case during which a normal PTH value was only achieved after resection of the seventh and final adenoma.

At the time of the second operation, given the preoperative ultrasound showing two hypoechoic nodules, these would have been either parathyroid adenomas or lymph nodes. During focused exploration of the left side, a search was performed to correlate with ultrasound findings however only one adenoma was found after an extensive search. Therefore, it was felt that the other hypoechoic structure may have been a lymph node. This, coupled with meeting Miami criteria, led to termination of this second operation. Moreover, as previously mentioned, the use of more stringent variations of the Miami criteria, such as a 50% baseline PTH decline at 5 min, has been shown to increase the risk for unnecessary bilateral exploration.²⁰ In hindsight, perhaps more stringent criteria including a drop in the PTH to the normal level may have led to a more extensive search. However, since our patient had four ectopic glands (two intrathyroidal glands and two mediastinal glands), performing a bilateral exploration during the patient's second operation and achieving a normal postexcision PTH would not have cured the

patient. We would still have had to reoperate to resect the mediastinal and intrathyroidal glands at a later date.

In summary, particularly in reoperative cases, surgeons should maintain a high index of suspicion when intraoperative PTH levels do not fall within the normal range after removal of an abnormal gland, because this may signify the presence of multigland disease, including the presence of abnormal ectopic or supernumerary glands. Surgeons who perform this procedure should remember the limitations of preoperative imaging, which may not show all involved parathyroid adenomas. The combination of high-quality preoperative imaging, judicious interpretation of intraoperative PTH and an experienced surgeon lead to the highest chance of cure in these challenging cases.

Contributors ZTS and FK conducted the literature review, and drafted and revised the manuscript. MAZ managed the case, revised the manuscript and, as the contributing author, takes full responsibility.

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Learning points

- Localisation studies should be performed at high-volume centres, as high-quality radiological studies and highly skilled interpretation are crucial to the utility of preoperative localisation studies.
- Surgeons performing this procedure must be familiar with exploring the thymus, performing thyroidectomy, exploring the tracheo-oesophageal groove, carotid sheath, paratracheal and retro-oesophageal regions to identify ectopic glands.
- Surgeons should maintain a high index of suspicion when intraoperative PTH levels do not fall within the normal range after removal of an abnormal gland, because this may signify the presence of multigland disease including the presence of abnormal ectopic or supernumerary glands.
- Multiple endocrine neoplasia syndrome and parathyromatosis should be considered in patients presenting with persistent hyperparathyroidism, especially in those requiring multiple reoperations.

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