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Recurrent Primary Hyperparathyroidism due to Multiglandular Parathyroid Hyperplasia: A Case Report.

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Abstract

Background: Primary hyperparathyroidism (PHPT) is commonly caused by a single parathyroid adenoma; however, multiglandular disease (MGD) remains an important differential, especially in recurrent or persistent cases. This case illustrates recurrent PHPT due to parathyroid hyperplasia involving all four glands, mimicking a solitary adenoma initially.

Case Presentation: A 60-year-old woman presented in 2022 with a right ureteric calculus and was incidentally found to have asymptomatic hypercalcemia (peak corrected calcium 2.98 mmol/L). Further workup revealed elevated serum intact parathyroid hormone (iPTH) at 17.72 pmol/L, normal phosphate, and renal function. Sestamibi scan showed persistent tracer uptake in the mid-left thyroid region, suggestive of an intrathyroidal parathyroid adenoma. She underwent left parathyroidectomy, with intraoperative findings of bilateral left gland enlargement. Histopathology confirmed parathyroid hyperplasia.

Despite initial improvement, she had biochemical recurrence within 6 months, with serum calcium of 3.02 mmol/L and iPTH of 14 pmol/L. Neck ultrasound revealed a right inferior parathyroid lesion. She underwent right parathyroidectomy in February 2025. Intraoperative findings revealed an enlarged right superior gland (1.5 cm) and a small right inferior gland (5 mm), the latter of which was partially autotransplanted into the right sternocleidomastoid muscle. Intraoperative PTH monitoring showed a >50% drop post-excision, satisfying the Miami criterion. Histopathology again confirmed parathyroid hyperplasia.

Postoperative recovery was uneventful. She was discharged on calcium carbonate and calcitriol supplementation. At 6-week follow-up, serum calcium normalized (2.5 mmol/L) with suppressed iPTH (0.58 pmol/L).

Conclusion: This case emphasises the diagnostic challenges of MGD in PHPT. Although Sestamibi may localise a dominant lesion, underlying multiglandular hyperplasia must be considered, especially in recurrent disease. Surgical management with subtotal parathyroidectomy and auto transplantation is effective in such cases.

Keywords: Recurrent parathyroid adenoma, Multiglandular disease.

1. Case Report

A 60-year-old female presented in 2022 with a right ureteric calculus. During laboratory workup, the patient was noted to have hypercalcemia, with the highest reading being 2.98mmol/L. Otherwise, she is well and shows no signs or symptoms of hypercalcemia. Apart from that, she also didn't have any family history of hypercalcemia or endocrine diseases or tumours. She was then referred to the endocrine team for further workup for hypercalcemia. Noted the iPTH was also high, 17.72 pmol/L.Renal profile and phosphate level were normal. In view of the blood result, she probably has primary hyperparathyroidism, and a Sestamibi scan was ordered to localise the disease. In the sestamibi report, noted persistent focus of tracer uptake was noted at the middle of the left thyroid gland measuring 1x0.8x1.1cm. This concluded as an intrathyroidal hyperfunctioning parathyroid adenoma. She was then referred to an Endocrine surgeon for surgery, and a bedside ultrasound noted, left thyroid nodule with an enlarged left parathyroid at the superior pole of the thyroid gland. Intraoperatively, the surgeon found that both superior and inferior parathyroid gland was enlarged, measuring 1x1cm each. Both parathyroid gland was removed. Histopathology confirmed parathyroid hyperplasia. However, 6 months after the operation, her calcium level was elevated at 3.02 mmol/L, and her iPTH level was also high at 14 pmol/L. Ultrasound neck was arranged, and the result showed a right inferior parathyroid lesion measuring 1.1x1.3x0.4cm. The second operation was scheduled in February 2025, and the patient underwent right parathyroidectomy with intraoperative parathyroid hormone level and autotransplant. Intraoperative findings noted the right superior parathyroid gland enlarged, measuring 1.5cm with a small right inferior parathyroid gland 5mm. A small portion of the right inferior parathyroid was autotransplantated into the right sternocleidomastoid muscle. Intraoperative parathyroid hormone level was dropped 50% as expected when the abnormal parathyroid gland was removed, concordance with Miami criteria

Table 1 -Intraoperative Parathyroid Hormone Level

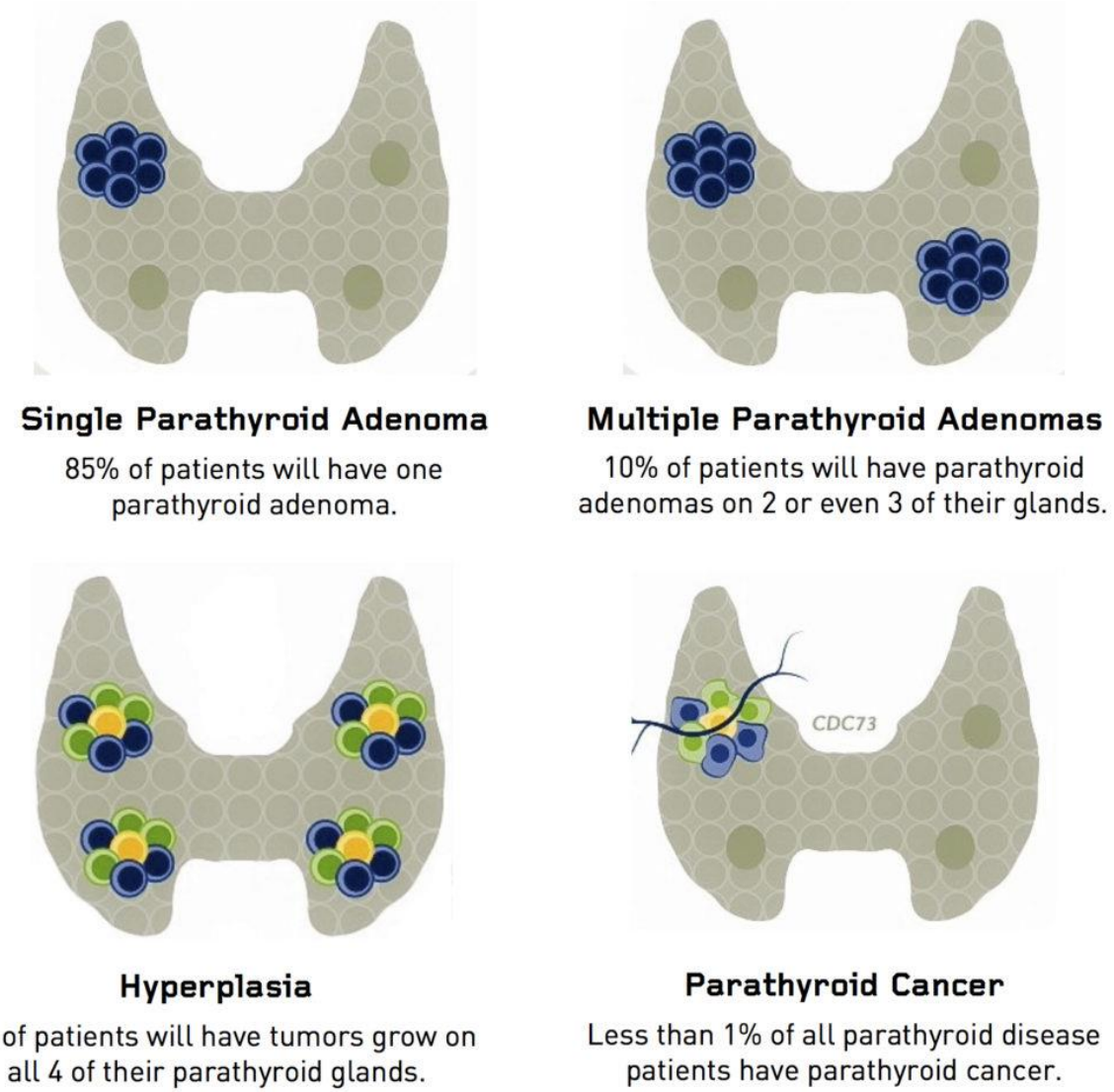
Pre Incision	21,70
Pre Excision	11.7
Post Excision	2.42

Final histopathology revealed that both right parathyroid glands removed was parathyroid hyperplasia. The patient had an uneventful postoperative recovery and discharge with oral calcium supplementation. The lowest calcium level was 2.20 mmo/L. Upon review 6 weeks in the clinic, wound healed with her blood results showing calcium was 2.5mmol/L with calcium carbonate 1gm DB and rocaltriol 0.5mcg BD. Her iPTH level was 0.58 pmol/L.

Discussion

Primary parathyroid hyperplasia is defined as a multiglandular disease which contains 2 or more hyperplastic glands. It is non-neoplastic and commonly has asymmetric enlargements. The aetiology is usually sporadic and can also be familial, related to MEN1, MEN2AFIHP, HPT-JT. This is due to germline mutation of MEN1, RET, and CDC73 oncogenes, which resulted in polyclonal diffuse expansion of chief cells of parathyroid glands.). These inherited forms also result in diffuse, often symmetrical enlargement of all glands—sometimes even including supernumerary glands [1,2].

Figure 2- Parathyroid disease.



Patients can present as symptomatic as well as asymptomatic hypercalcemia. Usually happens in the younger age group. They can have coexisting endocrine abnormalities (MEN syndromes) or a family history of HPTH or MEN. Their symptoms and biochemical results will show persistent or recurrent hyperparathyroidism after initial treatment. When comparing sporadic and familial features of primary parathyroid hyperplasia, it's common in the sporadic group, in which the incidence is between 70-80% of cases. Sporadic tends to happen in the older age group compared to the younger age group. The glandular enlargement is often symmetrical in familial groups, compared to asymmetrical or probably 1 gland may dominate the enlargement in sporadic groups. The recurrence risk is high in a familial group.

Table 3 : Sporadic versus Familial Hyperparathyroidism

	Sporadic	**Familial**
Incidence	70 - 80%	20 - 30%
Age group	Older	Younger MEN1 90% <50yrs MEN2A 30%
Glandular enlargement	Asymmetric 2-4 glands One gland may dominate	Often symmetrical 4+ glands (supernumer All 4 abnormal
Size	Moderate	Larger
Associated endocrine pathology	None	Present (pituitary,pancr
Recurrence risk	~10%	20 - 30%

Genetic Testing and Clinical Implications

Genetic testing is recommended in the following situations: when the patient is less than 40 years old at diagnosis, multiglandular involvement, especially in recurrent disease, family history of hypercalcemia or endocrine tumours and atypical parathyroid histology such as carcinoma or atypical adenoma.

In our patient, although no family history or syndromic features were identified, the early recurrence and involvement of all four glands raise the possibility of a subtle hereditary component. Genetic testing may be considered not only for diagnostic clarity but also to inform screening of at-risk relatives. In MEN1, for instance, biochemical screening for hypercalcemia and imaging for pancreatic or pituitary lesions may begin in adolescence [3].

Furthermore, identifying a germline mutation has implications for surgical planning. In MEN1-related PHPT, a more aggressive approach such as subtotal or total parathyroidectomy with auto transplantation, is often preferred to reduce recurrence. In contrast, sporadic hyperplasia might be managed with a more conservative strategy if only two glands appear involved.

The Imaging Paradox: Why Sestamibi Scan May Mislead

The case also brings attention to one of the central paradoxes in parathyroid surgery: imaging studies that appear definitive but are misleading in multiglandular disease. The patient's initial Sestamibi scan localized tracer uptake to the mid-left thyroid region, consistent with a dominant intrathyroidal parathyroid adenoma. This aligned with ultrasound findings and led to targeted excision of the left superior and inferior parathyroid glands. Histopathology confirmed hyperplasia, yet the presence of right-sided hyperplastic glands was not recognized until biochemical recurrence occurred six months later.

This limitation is well documented, in which Sestamibi scans can fail to detect up to 30% of hyperplastic glands due to their smaller size, lower mitochondrial activity, or diffuse uptake patterns [4,5]. While useful in localising dominant lesions, Sestamibi's performance drops significantly in MGD, especially when compared to single gland disease, where sensitivity may approach 90–95%.

To overcome this, newer imaging modalities such as 4D-CT, dynamic contrast-enhanced MRI, and fluorocholine PET/CT are increasingly employed. These techniques offer better anatomical resolution and functional detail, improving the likelihood of detecting smaller or metabolically less active glands [6,7]. Nevertheless, imaging should guide but not dictate the surgical strategy, especially in cases with elevated suspicion for multiglandular disease.

Surgical Judgment and Intraoperative Monitoring: A Powerful Pairing

Given the limitations of imaging, the surgeon's intraoperative assessment becomes paramount. In this case, although only the left-sided glands appeared abnormal on imaging, bilateral exploration during the second surgery revealed significant right superior gland enlargement and subtle hypertrophy of the right inferior gland. This reinforces a critical surgical principle: in MGD, intraoperative findings may be discordant with preoperative imaging, and definitive management may require excision of more than one or two glands.

Intraoperative PTH (ioPTH) monitoring has become a cornerstone in modern parathyroid surgery. The Miami criteria—a ≥50% drop in PTH from baseline within 10 minutes after gland excision—is widely validated as a predictor of cure [8]. In our patient, ioPTH levels fell from 21.70 to 2.42 pmol/L post-

excision, confirming the adequacy of resection. This not only minimized the risk of persistent disease but also avoided unnecessary further exploration.

Moreover, a portion of the small right inferior gland was autotransplanted into the sternocleidomastoid muscle to preserve long-term parathyroid function. Auto-transplantation is recommended in subtotal or total parathyroidectomy to reduce the risk of permanent hypoparathyroidism.

Lessons from Recurrence

Recurrent PHPT following initial surgery should always prompt reevaluation for missed MGD. Our patient's recurrence within six months highlighted an important pitfall: even a well-localized and successfully resected gland may not represent the entire disease burden. In such scenarios, the absence of familial history does not preclude multiglandular hyperplasia.

In patients with recurrent disease, repeat imaging should be paired with comprehensive clinical review. The presence of previously resected hyperplastic glands, elevated calcium and iPTH levels, and new imaging findings should all be interpreted in light of the initial pathology. Reoperation should be performed by experienced surgeons with access to intraoperative adjuncts such as IoPTH monitoring and frozen section analysis to confirm gland type and completeness of resection.

Conclusion

Primary parathyroid hyperplasia remains a diagnostic and surgical challenge, particularly when it masquerades as a solitary lesion. This case reinforces the need for a high index of suspicion for MGD, the limitations of sestamibi in multiglandular disease, and the value of intraoperative PTH monitoring in ensuring operative success. A tailored surgical approach, based not just on imaging but on intraoperative judgment and pathology, is essential for achieving lasting cure and preventing recurrence.

1. Conflict of Interest

No conflict of interest

2. Acknowledgement

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3. Authors' Biography

Dr Nur Aziah is currently a Breast and Endocrine Surgeon at Hospital Kuala Lumpur. She manages all simple and complicated breast and endocrine cases.Her main interest is oncoplastic breast surgeries and had presented cases in local and international conferences.

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