

A management dilemma - Emergency treatment of primary hyperparathyroidism in suspected but unconfirmed Multiple Endocrine Neoplasia type 1

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Introduction

- Multiple Endocrine Neoplasia type 1 (MEN1) is caused by mutations in the tumour suppressor gene *MEN1* which encodes the protein Menin and is an autosomal dominant disorder characterized by pleuri-glandular dysfunction primarily involving the parathyroids, anterior pituitary and pancreatic islets.
- The incidence of MEN1 has been estimated to be 1–18% among patients with primary hyperparathyroidism¹. Parathyroid tumors are the first manifestation of MEN1 in over 85% of patients², and primary hyperparathyroidism (PHPT) is the most common feature of MEN1, with penetrance of over 95% by the fifth decade³.
- PHPT in MEN1 presents relatively earlier in the second to fourth decade of life, nearly two decades before sporadic hyperparathyroidism.

Presentation

A 27-year-old male presented acutely with cardiogenic shock. He had severe dilated cardiomyopathy secondary to Epirubicin chemotherapy in infancy for a rhabdomyosarcoma. His cardiac function was severely compromised and his condition progressively declined despite escalating inotropic support. Emergency insertion of Biventricular Assist Device was undertaken and he was listed for an urgent cardiac transplantation.

He was noted to be hypercalcaemic at admission and further investigations suggested primary hyperparathyroidism. His brother had confirmed acromegaly and had undergone transsphenoidal surgery, and his now deceased paternal grandfather also had a pituitary tumour.

Investigations

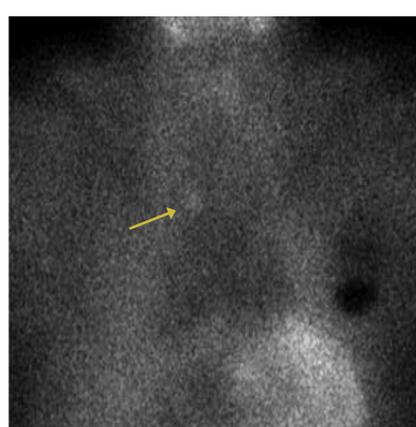
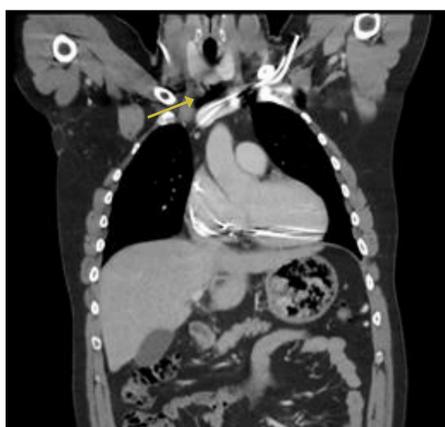
Initial investigations:

	Result	Reference range/ Units
Corrected Calcium	3.05	2.2 - 2.60 mmol/L
Parathyroid Hormone	22.0	1.5 - 9.3 pmol/L
25-hydroxy Vitamin D3	21.7	> 75 nmol/L
Urine Calcium/ Creatinine ratio	0.43	>0.02

Biochemical profile after Cholecalciferol supplementation:

	Result	Reference range/ Units
Corrected Calcium	3.08	2.2 - 2.60 mmol/L
Parathyroid Hormone	21.2	1.5 - 9.3 pmol/L
25-hydroxy Vitamin D3	77.0	>75 nmol/L

CT scan suggested the presence of a right inferior parathyroid adenoma and NM SPECT Sestamibi Parathyroid scan corroborated this finding with increased focal uptake below the lower pole of the right thyroid gland.



Discussion

With a young age of onset of primary hyperparathyroidism along with family history of pituitary tumours, Multiple Endocrine Neoplasia 1 was considered to be highly likely. He was investigated for pituitary and pancreatic involvement, but pituitary profile and MRI Pituitary were normal as was the fasting hormonal gut profile.

He required cardiac transplantation urgently given the severity of cardiac compromise, however resolution of hypercalcaemia was a requirement before transplantation. Genetic testing for MEN-1 was arranged, but with a reporting time of several weeks, a decision on management was required prior to availability of these results.

The two management options were

- Treat as sporadic PHPT and perform single right inferior pole parathyroidectomy. However, if he did have MEN1, then hypercalcaemia could well persist and he would require a second surgery with its associated complications.
- Presuming that PTPH was a part of MEN1 syndrome, perform three and a half gland parathyroidectomy. This carried a risk of over-treatment and hypoparathyroidism if he did not have MEN1.

After discussion at a multidisciplinary meeting involving endocrinologist, endocrine surgeon, cardiologist and anesthetist, a decision was made in favour of the latter option as this had a higher probability of achieving eucalcaemia. A second surgery was deemed to be very high-risk and if required could potentially delay cardiac transplantation.

Management

He underwent cervical exploration and three and a half parathyroid glands were excised. Intra-operative findings were consistent with a right inferior pole parathyroid adenoma.

Post-operative serial biochemistry showed resolution of hyperparathyroidism and histology confirmed the presence of a single parathyroid adenoma.

	1 day	1 week	2 weeks	3 weeks
Corrected Calcium	2.27	2.33	2.20	2.23
Parathyroid Hormone	1.6	3.4	2.5	3.2

Cardiac transplantation was successfully carried out a few weeks following parathyroidectomy when a donor heart became available.

Further discussion

Genetic testing

- MEN1 mutation analysis is recommended in individuals younger than 30 years with parathyroid adenoma and multi-gland parathyroid disease if PHPT is the sole endocrinological manifestation¹.
- Although sequence analysis of the MEN1 gene in our patient did not detect a mutation (NM_130799.2), other inactivating mutations outside the sequenced gene may be responsible and further results are outstanding.

Management

- Patients with MEN1 are at high risk of recurrent PHPT after apparently successful parathyroidectomy. Persistent or recurrent hyperparathyroidism and hypercalcaemia with less than subtotal parathyroidectomy is seen in over 50% patients with MEN1 within 10 years as compared to ~4% in non-MEN1 patients^{4,5}.
- Most patients with MEN1 have multiple parathyroid tumors and full neck exploration of previously un-operated patients is recommended regardless of pre-operative localization studies, and the consensus is for three and a half gland subtotal parathyroidectomy rather than less extensive surgery.

Our patient required urgent treatment of PHPT due to the impending cardiac transplantation, and the unavailability of results of genetic analysis meant a decision had to be taken about the extent of surgery based on the clinical presentation.

References

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