# Parathyroid adenoma, Pituitary Macroadenoma and Hypergastrinaemia in a patient with negative genetic testing for Multiple Endocrine Neoplasia Type 1: a mere coincidence?

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## Aims

1. To highlight the main tumour types associated with MEN1 and the lesser associated tumour types.
2. To highlight the different criteria for the diagnosis of MEN1.
3. To address the concept of MEN1 phenocopies.

## Introduction

- Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare, autosomal dominant condition with an estimated prevalence of 1-10/100,000.
- MEN1 is inherited through mutation of the MEN1 gene located on chromosome 11q13.
- MEN1 involves tumour development in two or more endocrine glands associated with the syndrome, in a single patient (see Table 1)[1-3].

**Table 1[9]: MEN1 associated tumours**

| Primary Manifestations | Associated tumours |
|---|---|
| • **Parathyroid adenoma (90%)**<br>• **Enteropancreatic tumours (30-70%)**<br>- Gastrinoma (40%)<br>- Insulinoma (10%)<br>- Non-functioning and PPoma (20-55%)<br>- Glucagonoma (<1%)<br>- VIPoma (<1%)<br>• **Pituitary adenoma (30-40%)**<br>- Prolactinoma (20%)<br>- Somatotropinoma (10%)<br>- Corticotropinoma (<5%)<br>- Non-functioning (<5%) | • Adrenal cortical tumour (40%)<br>• Pheochromocytoma (<1%)<br>• Bronchopulmonary NET (2%)<br>• Thymic NET (2%)<br>• Gastric NET (10%)<br>• Lipomas (10%)<br>• Angiofibromas (85%)<br>• Collagenomas (70%)<br>• Meningiomas (8%) |

PPoma = Pancreatic polypeptide secreting tumour; VIPoma = Vasoactive intestinal peptide secreting tumour; NET = Neuroendocrine tumour

**Fig. 1[10]: MEN1 diagnostic criteria**

| Clinical Diagnosis | Familial Diagnosis | Genetic Diagnosis |
|---|---|---|
| Two or more primary MEN1 associated tumours in a single patient | One MEN1 tumour in a first degree relative of a patient with a clinical diagnosis of MEN1 | Confirmed germline MEN1 mutation – with or without features of tumour development |

## Case Report

- A 56 year old lady presented to the endocrinology clinic following an incidental finding of hypercalcaemia (see Figure 2). She was normally fit and well, on no regular medication and had no significant family history.
- Primary hyperparathyroidism was diagnosed. A solitary parathyroid adenoma was identified through parathyroid MIBI Scan. Renal calculi were present on US imaging.
- Her hypercalcaemia progressed and sequelae of uncontrolled hypercalcaemia developed, requiring surgical intervention.
- Unrelated investigation for suspected TIA identified a pituitary mass. MRI imaging revealed an intrasellar pituitary mass. Pituitary function tests confirmed a non-functioning pituitary macroadenoma (see Figure 2).
- Presence of two primary MEN1 tumours required further investigation for the syndrome.
- Fasting gut peptide profile showed raised gastrin levels. She denied use of proton pump inhibitors and had no symptoms of hypergastrinaemia. An MRI pancreas and subsequent octreotide scan failed to locate gastrinomas. Genetic analysis did not identify a germline mutation of the MEN1 gene.

**Fig. 2: Investigation results**

**Initial presentation**

Asymptomatic hypercalcaemia: $Ca^{2+}$ = 2.77 mmol/L; PTH = 11.9 pmol/L
24h urinary $Ca^{2+}$ = 7.5 mmol/24h (1-7.5)
USS neck and parathyroid MIBI = 27 x 12 x 10mm parathyroid adenoma
US renal tract = 9.4 x 8mm calculus in right kidney
Renal Profile = normal
DEXA scan = normal

**Diagnosis = Primary hyperparathyroidism**

**Incidental finding on A+E presentation for ?TIA**

CT head = expansile mass originating from pituitary gland
MRI Brain = 16 x 12 x 10mm intrasellar mas

| Short synacthen test | 24h urinary cortisol | TSH = 1.99 mU/L | Prolactin = 88 mU/L (0 - 700) | IGF-1 = 23.7 nmol/L (7 - 26.6) |
|---|---|---|---|---|
| 0 m = 202 nmol/L<br>30 m = 597 nmol/L | 26 nmol/24h (0-165) | Free T4 = 8.6 pmol/L | | |

**Diagnosis = Non-functioning pituitary macroadenoma**

**Screening for other MEN1 tumour types**

| Gastrin | Pancreatic polypeptide | Glucagon | Somatostatin | VIP | Chromogranin A |
|---|---|---|---|---|---|
| 375 pmol/L (0-40) | <10 pmol/L (0-300) | 12 pmol/L (0-50) | <10 pmol/ (0-50) | <4 pmol/L (0-30) | 25 pmol/L (0-60) |

MRI Pancreas + Octreotide scan = no focal lesion

**Diagnosis =  Hypergastrinaemia of unknown cause**

## Discussion

- This case highlights an uncommon presentation, where two primary MEN1 tumours exist in addition to hypergastrinaemia of unknown cause. Genetic testing did not identify the MEN1 mutation, suggesting she may be a MEN1 phenocopy.
- MEN1 can occur through familial inheritance or occur sporadically, where there is no family history of MEN1. Diagnosis is achieved by meeting one of three criteria: clinical, familial or genetic[1] (see Figure 1).
- Between 5-30% of patients with clinical MEN1 do not harbour the MEN1 mutation (phenocopies)[4-8]. The MEN1 mutation negative patients were found to have a higher age of MEN1 diagnosis, age related penetrance of the first tumour and better overall survival compared to MEN1 mutation positive cases[2].
- There are suggestions that MEN1 phenocopies have a MEN1 mimicking syndrome, where mutations exist outside of the MEN1 coding region[4,7,8].
- Screening MEN1 phenocopies can be challenging. Clinically diagnosed MEN1 patients receive annual biochemical and radiological investigation, which are extended to first degree relatives. This monitoring has a cost burden and can cause considerable anxiety. Consensus guidelines support annual screening for relatives of MEN1 phenocopies, however its clinical value remains up for debate[1,2].

## Conclusion

This case highlights an unusual history of suspected MEN1. The patient qualifies for diagnosis of MEN1 on clinical grounds, although the negative finding for MEN1 gene testing could suggest that this patient is a MEN1 phenocopy. Existence of phenocopies posed challenges in reaching a diagnosis and providing screening for family members. MEN1 phenocopies may have a milder clinical course than MEN1 mutation positive patients, but this area requires further study.

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