

# Multiple electrolyte disturbances as the presenting feature of multiple endocrine neoplasia type 1 (MEN-1)

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## Summary

A 49-year-old teacher presented to his general physician with lethargy and lower limb weakness. He had noticed polydipsia, polyuria, and had experienced weight loss, albeit with an increase in central adiposity. He had no concomitant illnesses and took no regular medications. He had hypercalcaemia (adjusted calcium: 3.34 mmol/L) with hyperparathyroidism (parathyroid hormone: 356 ng/L) and hypokalaemia (K: 2.7 mmol/L) and was admitted for i.v. potassium replacement. A contrast-enhanced CT chest/abdomen/pelvis scan revealed a well-encapsulated anterior mediastinal mass measuring 17 × 11 cm with central necrosis, compressing rather than invading adjacent structures. A neck ultrasound revealed a 2 cm right inferior parathyroid lesion. On review of CT imaging, the adrenals appeared normal, but a pancreatic lesion was noted adjacent to the uncinate process. His serum cortisol was 2612 nmol/L, and adrenocorticotrophic hormone was elevated at 67 ng/L, followed by inadequate cortisol suppression to 575 nmol/L from an overnight dexamethasone suppression test. His pituitary MRI was normal, with unremarkable remaining anterior pituitary biochemistry. His admission was further complicated by increased urine output to 10 L/24 h and despite three precipitating factors for the development of diabetes insipidus including hypercalcaemia, hypokalaemia, and hypercortisolaemia, due to academic interest, a water deprivation test was conducted. An <sup>18</sup>fluorodeoxyglucose-PET (FDG-PET) scan demonstrated high avidity of the mediastinal mass with additionally active bilateral superior mediastinal nodes. The pancreatic lesion was not FDG avid. On <sup>68</sup>Ga DOTATE-PET scan, the mediastinal mass was moderately avid, and the 32 mm pancreatic uncinate process mass showed significant uptake. Genetic testing confirmed multiple endocrine neoplasia type 1.

## Learning points:

- In young patients presenting with primary hyperparathyroidism, clinicians should be alerted to the possibility of other underlying endocrinopathies.
- In patients with multiple endocrine neoplasia type 1 (MEN-1) and ectopic adrenocorticotrophic hormone syndrome (EAS), clinicians should be alerted to the possibility of this originating from a neoplasm above or below the diaphragm.

- Although relatively rare compared with sporadic cases, thymic carcinoids secondary to MEN-1 may also be associated with EAS.
- Electrolyte derangement, in particular hypokalaemia and hypercalcaemia, can precipitate mild nephrogenic diabetes insipidus.

## Background

The most typical causes of hypercalcaemia are primary hyperparathyroidism (PHPT) or malignancy (1). Although the majority of cases of PHPT are due to a parathyroid adenoma, up to 10% of PHPT in patients under the age of 45 has an underlying genetic mutation resulting in multi-gland endocrinopathy (2).

Multiple endocrine neoplasia type 1 (*MEN1*) is one such mutation. It is a rare genetic disorder classically characterised by a triad of the pituitary, parathyroid, and pancreatic islet cell tumours. Other endocrine and non-endocrine neoplasms including adrenocortical and thyroid tumours, visceral and cutaneous lipomas, meningiomas, facial angiofibromas and collagenomas, and thymic, gastric, and bronchial carcinoids also occur. The phenotype of *MEN1* is broad, and over 20 different combinations of endocrine and non-endocrine manifestations have been described (3). The culprit mutation in the *MEN1* gene, which codes for menin, a tumour-suppressing protein, and is inherited autosomal dominant, although 10% may be *de novo* mutations.

The most typical presentation is with PHPT, occurring in 90% of cases (3), and we present a case of MEN-1 indeed presenting initially with primary hypercalcaemia.

Although symptoms of neoplasms usually occur via their mass effect, some can secrete bioactive substances, which may not be related to their tissue of origin, giving rise to endocrine paraneoplastic syndromes (4). Our case was complicated by such paraneoplastic phenomena. Despite a large anterior mediastinal tumour, the patient did not experience any significant mass effect. Instead, ectopic adrenocorticotrophic hormone (ACTH) secretion led to an ectopic ACTH syndrome (EAS), which was uncovered through additional electrolyte abnormalities.

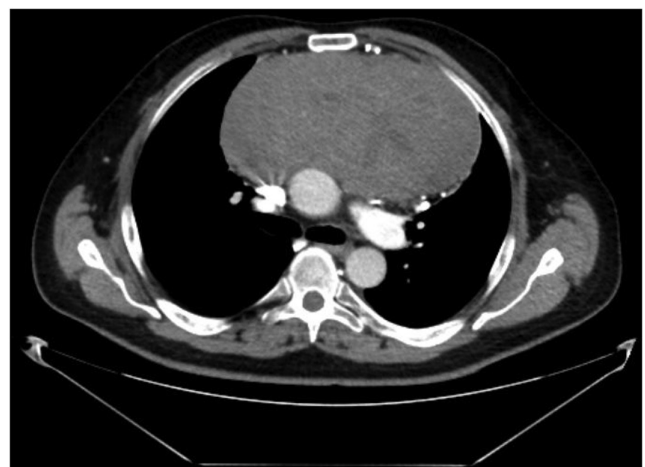
## Case presentation

A 49-year-old male Caucasian White teacher presented to his general physician with lethargy and lower limb weakness. He had noticed significant polydipsia and polyuria, with overall weight loss albeit with an increase in central abdominal fat. He had previously undergone cholecystectomy and colonic polypectomy but took no

regular medications. He did not notice any rashes and had no skin lesions on examination.

## Investigation

He had moderate hypercalcaemia 3.34 mmol/L (2.15–2.6 mmol/L) with high parathyroid hormone (PTH) of 356 ng/L (15–65 ng/L) and hypokalaemia measuring 2.7 mmol/L (3.5–5 mmol/L). He was admitted for i.v. fluid therapy and potassium replacement. Renal function was normal and phosphate concentration measured low at 0.42 mmol/L (0.8–1.4 mmol/L). A contrast-enhanced CT of the chest, abdomen, and pelvis revealed a well-encapsulated anterior mediastinal mass measuring 17 × 11 cm with central necrosis, compressing rather than invading adjacent structures (Fig. 1). A neck ultrasound (US) revealed a 2 cm right inferior parathyroid lesion. The patient underwent a US-guided core biopsy of the mediastinal lesion that revealed a well-differentiated neuroendocrine neoplasm, positive for synaptophysin, and CD56 with weak patchy staining for PAX8; the Ki67 index was 3%. Histology was consistent with a well-differentiated neuroendocrine neoplasm, grade 2 of thymic origin.



**Figure 1**  
Large, well-encapsulated anterior mediastinal mass measuring 17 × 11 cm with central necrosis, compressing rather than invading adjacent structures on CT imaging.



His serum cortisol level was measured in the context of remaining electrolyte abnormalities and finding of PHPT. His serum cortisol was 2612 nmol/L (133–537 nmol/L), and ACTH was inappropriately elevated at 67 ng/L (0–46 ng/L). However, in the absence of clinical features, it was decided that artefactual hypercortisolaemia should be excluded, and therefore, an overnight dexamethasone suppression test (ODST) was performed with inadequate cortisol suppression to 575 nmol/L, confirming ACTH-dependent hypercortisolaemia. Contrast-enhanced MRI of the pituitary fossa was normal, and the remaining anterior pituitary biochemistry was unremarkable. On review of the previous CT imaging, the adrenals appeared normal, but a 32 mm lesion was noted adjacent to the uncinate process of the pancreas with internal calcification.

The admission was further complicated by an increase in his urine output to 10 L/24 h with significant thirst, for which a water deprivation test was conducted. Desmopressin was administered at 17:00 h with no effective response (Table 1). A complete gut peptide panel was obtained and was unremarkable except for significantly elevated chromogranin A (CgA) and B (CgB) at 126 nmol/L (0–6 nmol/L) and 217 pmol/L (<150 pmol/L), respectively.

An <sup>18</sup>F-fluorodeoxyglucose-PET (FDG-PET) scan demonstrated high avidity of the mediastinal mass (SUV max 7.0) with additionally active bilateral superior mediastinal nodes (Fig. 2), but the pancreatic lesion was not FDG-PET avid. However, on <sup>68</sup>Ga DOTATE-PET, the mediastinal mass was moderately avid, whereas the 32 mm pancreatic mass of the uncinate process demonstrated significant uptake (Fig. 3).

## Treatment

Intravenous fluids with 3000 cm<sup>3</sup> of 0.9% NaCl successfully treated hypercalcaemia. Metyrapone was initiated at 250 mg QDS (four times daily) and up titrated to 500 mg QDS using metyrapone day curves to assess the adequacy of dosing. Although the target therapeutic average cortisol concentration was between 100 and 200 nmol/L, this metyrapone dose achieved an adequate pre-surgery average cortisol of 222 nmol/L. On metyrapone, there is cross-

reaction with cortisol precursors around 20% (with most assays other than gas chromatography mass spectrometry).

Genetic testing for the MEN-1 phenotype was requested, and he was referred urgently for thoracic multidisciplinary meeting (MDM) review and surgery. The patient underwent a midline sternotomy for thymus excision and simultaneous bilateral subtotal parathyroidectomy with lymph node dissection at level Vb on the right. The thymic tumour reached the inked resection margins, equating to an R1 resection. The outcome of the thoracic MDM was to start adjuvant cytotoxic treatment for R1 thymic carcinoid resection. Upon discussion at the neuroendocrine MDM, it was decided that the patient was a good candidate for pancreatic surgery. However, it was decided to commence s.c. somatostatin analogue (SSA) until chemotherapy had been completed followed by surgery. Subsequently, Lanreotide Autogel 120 mg every 28 days was initiated to manage the pancreatic neuroendocrine tumour (pNET).

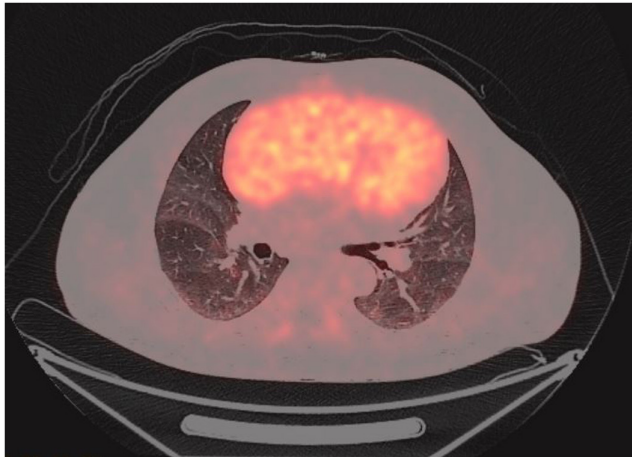
## Outcome and follow-up

Histology of the mediastinal mass confirmed a locally invasive well-differentiated neuroendocrine neoplasm (Fig. 4) (expressing synaptophysin, CgA, and CD56) with areas of necrosis, a proliferation index of 10%, up to six mitoses per ten high-powered fields, and no atypical mitotic figures. This was consistent with a grade 2 (intermediate) classification of neuroendocrine neoplasm, so-called atypical carcinoid (5). Parathyroid histology demonstrated one adenoma (Fig. 5) and two glands with mild atrophic changes, but adjacent lymph nodes yielded histopathological characteristics suggestive of infiltration from the mediastinal neoplasm.

Post-operative ODST 6 weeks after the procedure, utilising second-generation cortisol assay, showed complete cortisol suppression to 32 nmol/L (adequate suppression if cortisol suppressed to <50 nmol/L). A short synacthen test was normal, with a peak cortisol response to synacthen of 649 nmol/L (normal response according to Roche Generation II immunoassay is considered when cortisol >420 nmol/L at 30 min). CgA also normalised to 4.9 nmol/L (0–6 nmol/L) following surgery. The patient remained on active vitamin D metabolite alfacalcidol 2

**Table 1** Water deprivation test yielding a lack of response with desmopressin administered at 17:00 h.

Time (h)	11:00	12:47	15:06	17:00	18:40	19:30	20:30	21:30
Serum osmolality (mOsm)	300	301	304	304	298	301	294	291
Urine osmolality (mOsm)	253	275	377	348	391	412	355	304
Serum Na <sup>+</sup> (mmol/L)	150							

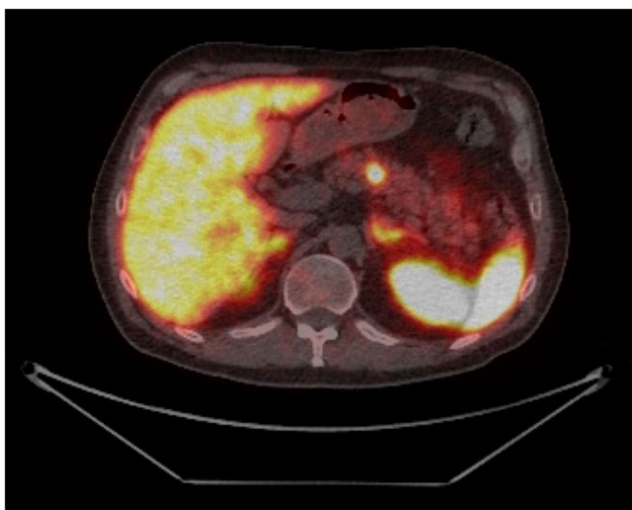


**Figure 2**  
FDG-PET scan demonstrating FDG high avidity of the mediastinal mass (SUV max 7.0) with additionally active bilateral superior mediastinal nodes.

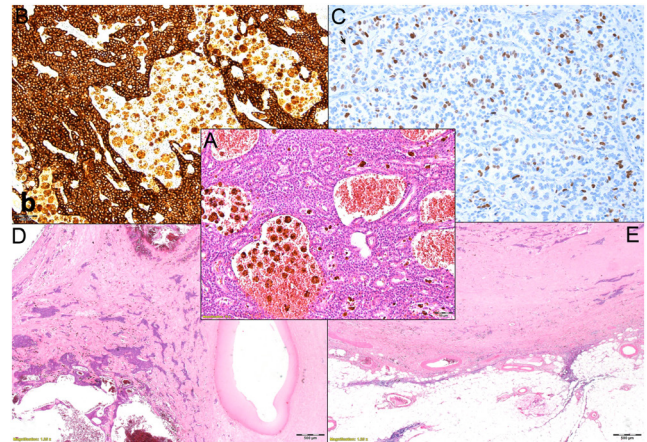
µg daily and achieved normocalcaemia with an adjusted calcium measurement of 2.26 mmol/L (2.15–2.6 mmol/L).

A <sup>68</sup>Ga DOTATE-PET scan revealed no focal uptake in the anterior mediastinum post-operatively with DOTATE avidity (SUV max 56, previously 41) of the known 32 mm pancreatic lesion of the uncinete process. Metastatic lesions, however, were detected in the right lung and right iliac blade.

Both metyrapone and hydrocortisone were stopped, and the patient underwent adjuvant chemotherapy with temozolomide and capecitabine for six cycles for R1 thymic carcinoid, alongside ongoing treatment with lanreotide followed by pancreatic surgery upon chemotherapy



**Figure 3**  
DOTATE-PET scan demonstrating avidity of the 32 mm pancreatic lesion of the urcinate process.

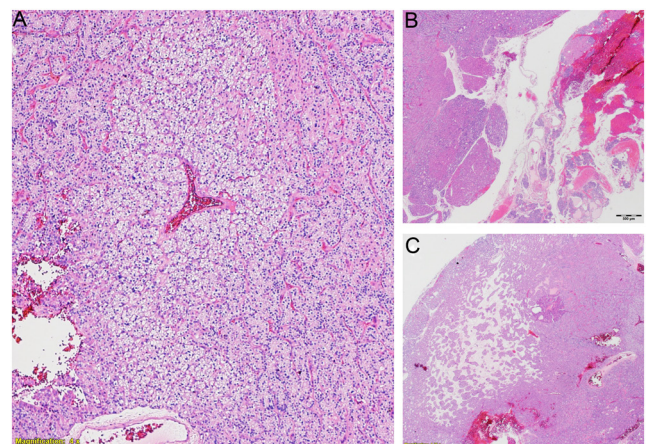


**Figure 4**  
Well-differentiated neuroendocrine neoplasm of the thymus revealed a nested pattern (A), diffuse and intense expression of chromogranin (B), and a Ki-67 index of 10% (C). The neoplasm was locally invasive (D) and showed a rim of atrophic thymus at the periphery (E).

completion. The nephrogenic diabetes insipidus (DI) was resolved. Genetic analysis confirmed the underlying diagnosis of MEN-1 with a heterozygous pathogenic deletion of four base pairs at the cytogenetic location 11q13.1, and his family was offered genetic counselling.

## Discussion

The initial presentation was consistent with symptomatic hypercalcaemia secondary to PHPT, evidenced by the elevated calcium concentration with high PTH. However, average PTH concentrations in PHPT range between 112 and 128 ng/L (6), and thus suspicion for an alternative underlying diagnosis was raised in this case.



**Figure 5**  
Parathyroid adenoma showed trabecular pattern without diffuse areas and transitional chief cells (A) with a rim of atrophic parenchyma at the periphery (B), and focal interstitial oedema (C).



As imaging demonstrated, a large anterior mediastinal mass, persistent hypokalaemia, and mild hypernatremia (serum Na: 147mmol/L) triggered a cortisol measurement, elevated at 2612 nmol/L. The ODST and serum ACTH concentration confirmed non-artefactual, ACTH-driven hypercortisolaemia. Pituitary imaging did not localise a pituitary fossa neoplasm. Thus, EAS was the likely aetiology, also considering the high baseline cortisol value. According to European Society for Endocrinology) 2020 'Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion', EAS diagnosis is based on a 24-h urinary free cortisol assay and/or measurement of cortisol and ACTH concentrations in several samples drawn during the day and at midnight. Aside from exceptional cases of cyclic EAS, urinary free cortisol, serum cortisol, and ACTH concentrations are usually dramatically increased and are associated with loss of circadian rhythm (7).

However, as in our case, we felt this is a life-threatening situation with two potential sources of EAS (thymic carcinoid and/or pNET) and further endocrinopathies (PHPT and DI), justifying an urgent initiation of specific treatment of hypercortisolism, based on reduced to minimal biochemical evaluation including only one or two blood samples for cortisol and ACTH measurements as stipulated in the above expert opinion article (7).

The likeliest source of EAS was the mediastinal tumour which was reported as an atypical carcinoid on histology. The uptake on FDG-PET scan supported the diagnosis of a thymic carcinoid. However, on a detailed review of CT imaging, a 32 mm pancreatic lesion of the uncinate process was identified. In total, there is one pancreatic lesion, which demonstrated avidity to DOTATE-PET scan, representing intense somatostatin receptor expression in keeping with a well-differentiated neuroendocrine neoplasm. This finding provided a potential alternative source of EAS.

The critical components of the case therefore are:

- PHPT secondary to parathyroid gland adenoma,
- an anterior mediastinum FDG-PET scan avid locally invasive well-differentiated neuroendocrine neoplasm, grade 2 with features of atypical carcinoid neoplasm,
- EAS,
- DOTATE-PET scan avid pancreatic lesion, and
- nephrogenic DI.

With this in mind, the likely underlying diagnosis of MEN-1 syndrome emerges. The lack of cutaneous manifestation reduced the likelihood of the standard differential,

including neurofibromatosis type 1 and tuberous sclerosis, while the absence of intracranial or renal neoplasms made a diagnosis of Von Hippel-Lindau syndrome unlikely (8).

Thymic neuroendocrine neoplasms have a significant male preponderance and are reported to occur in heavy smokers in contrast to our case (9). In a review of 21 cases of thymic neuroendocrine neoplasms, 18 were identified as atypical carcinoid, with three associated with ectopic Cushing's syndrome (CS) (10). A systematic review and narrative synthesis published in 2021 included 105 cases of sporadic thymic carcinoids. They concluded that thymic carcinoids associated with paraneoplastic CS affect a younger population under the age of 40 with male preponderance (11).

Atypical thymic carcinoid tumours have a higher mitotic rate (2–10 per high-powered field) than typical thymic carcinoid tumours and usually have some degree of necrosis (12). PNETs may be functional (insulinoma, gastrinoma, or glucagonoma), although the majority are non-functional (13). PNETs may secrete ACTH but are rarer than ACTH-secreting thymic neuroendocrine neoplasms and are associated with a poorer prognosis (14).

The mutation responsible for MEN-1 is located on chromosome 11q13, which codes for the tumour suppressor protein MENIN. MENIN controls cell proliferation by regulating the transcription of genes involved in the control of the cell cycle and is also crucial in maintaining genomic integrity; thus, the breakdown of these pathways leads to tumour formation (15).

Treatment of neuroendocrine neoplasms includes surgery, chemotherapy, and radiotherapy. As a bridge to surgical resection, it was essential to minimise the effects of hypercortisolaemia. Metyrapone is used in the treatment of CS and was utilised in this case. Metyrapone inhibits enzymes of the cytochrome P45011B and P4502B family, which includes 11-beta-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), enzymes required for the synthesis of cortisol from 11-deoxycortisol and of aldosterone from 11-deoxycorticosterone. Neuroendocrine neoplasms frequently express somatostatin receptors, and thus SSA therapy such as lanreotide can be beneficial (16), in not only both control of symptoms of functioning tumours but also in controlling tumour proliferation (17). Our patient fulfils the criteria for pNET surgery due to the size of the lesion (>2 cm) and the absence of advanced or metastatic pancreatic disease (18). However, lanreotide was offered until the completion of chemotherapy for thymic carcinoid.

The presence of nephrogenic DI further complicated this case. The likely aetiology was renal dysfunction and



polyuria due to hypercalcaemia, which was potentiated by hypokalaemia and hypercortisolaemia. Animal studies have demonstrated that decreased aquaporin-2 expression in the renal collecting ducts occurs in hypokalaemia and hypercalcaemia (19, 20, 21).

In summary, here we have a case of MEN-1 syndrome presenting with a range of electrolyte disturbances secondary to a parathyroid adenoma, EAS with paraneoplastic CS to a thymic carcinoid, and subsequent nephrogenic DI.

Some early studies suggested that MEN-1-related thymic carcinoids are not associated with the EAS, in contrast to sporadic cases of thymic carcinoids. However, there are now numerous case reports showing that MEN-1 patients with thymic carcinoids could also produce ectopic ACTH leading to paraneoplastic CS (22, 23, 24).

#### Declaration of interest

The authors of this manuscript report no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Georgios Dimitriadis is on the editorial board of *Endocrinology, Diabetes, and Metabolism Case Reports*. Georgios Dimitriadis was not involved in the review or editorial process for this paper, on which he is listed as an author.

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#### Patient consent

Written informed consent has been obtained for publication of the submitted article.

#### Author contribution statement

A P Z L treated the patient and wrote the manuscript, S S treated the patient and reviewed the final version of the manuscript, S A treated the patient and reviewed the final version of the manuscript. R P V provided biochemical analysis and reviewed the final version of the manuscript. S J B A treated the patient and reviewed the final version of the manuscript. G K D treated the patient, wrote the manuscript and supervised the project.

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