

# An Unusual Presentation of Cushing's Syndrome

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**Topic: Adrenal and steroids**

**Introduction:** Cushing's syndrome results from chronic exposure to excess glucocorticoids. It is rare, with an incidence of 0.2-5.0 per million people per year, and a prevalence of 39-79 per million people.<sup>1</sup> Endogenous causes are divided into adrenocorticotropic hormone (ACTH)-dependent, and ACTH-independent causes. Pituitary corticotroph adenomatous disease (Cushing's disease) is the most common cause of endogenous Cushing's syndrome.

Clinical manifestations include<sup>2</sup>; proximal myopathies, abnormal fat distribution (particularly in the abdomen, torso and face), disruption to fertility and menstruation, osteoporosis, increased tendency to infection, hypertension, diabetes mellitus, dyslipidaemia, cognitive impairment, psychiatric complications and non-specific symptoms such as fatigue and weight gain.

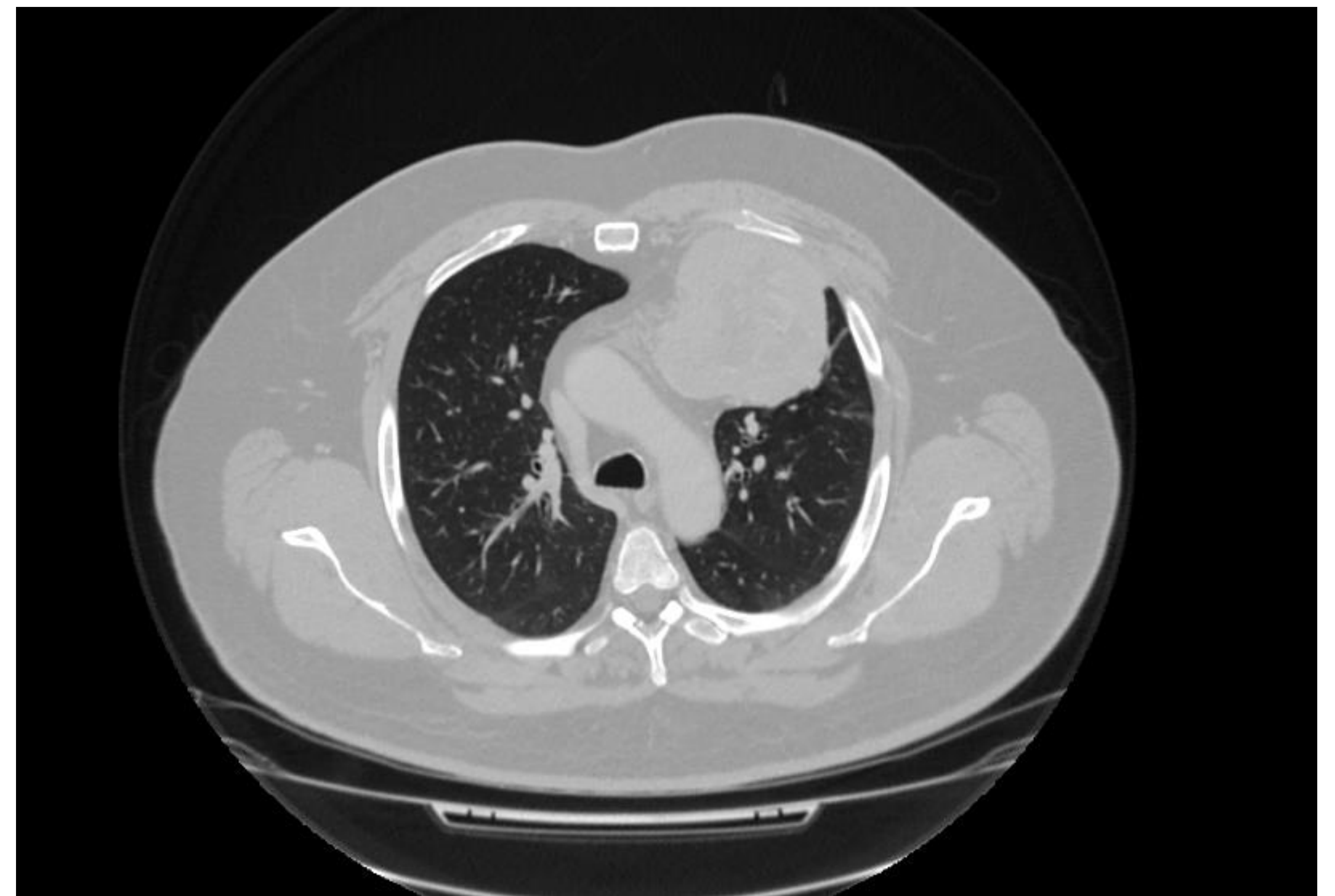
Hypocortisolism is confirmed with a screening test such as; an overnight dexamethasone suppression test (DST), 24 h urinary free cortisol, or late-night salivary cortisol. ACTH levels are measured. In ACTH-independent cases an adrenal CT is performed. In ACTH-dependent cases, MRI of pituitary alongside further biochemical assessments such as high dose DST or corticotrophin releasing hormone (CRH) test. Where these tests are concordant, Cushing's disease is confirmed. If not, then bilateral inferior petrosal sinus sampling is performed. Where pituitary disease is excluded, cross-sectional imaging, octreoscan or PET-CT is used to determine an ectopic source of ACTH.

Hypocortisolism can be treated with medical therapy such as metyrapone, which selectively inhibits 11 $\beta$ -hydroxylase, or cabergoline (effective in approximately 30% of patients)<sup>1</sup>. Ketoconazole also reduces endogenous cortisol production, but was withdrawn in Europe due to concerns regarding liver toxicity. Surgical treatment should be considered in adrenal, or pituitary-adenomatous disease or in cases of ectopic ACTH.

**Case Presentation:** A 50 year old man was admitted to the Acute Assessment Unit at Glasgow Royal Infirmary on 20/8/2017 with left-sided chest pain. A chest radiograph revealed a left-sided hilar mass. Blood pressure was 164/94. A non-fasting glucose sample was 5.1 mmol/L. He was not on treatment for hypertension. Cross-sectional imaging of the thorax demonstrated a 9.2 cm centrally necrotic mass arising from the anterior mediastinum, abutting the left ventricle, with adjacent lymphadenopathy and multiple bone metastases. A CT-guided biopsy was performed on 04/09/2017, and the pathology was felt to be of an atypical carcinoid tumour.

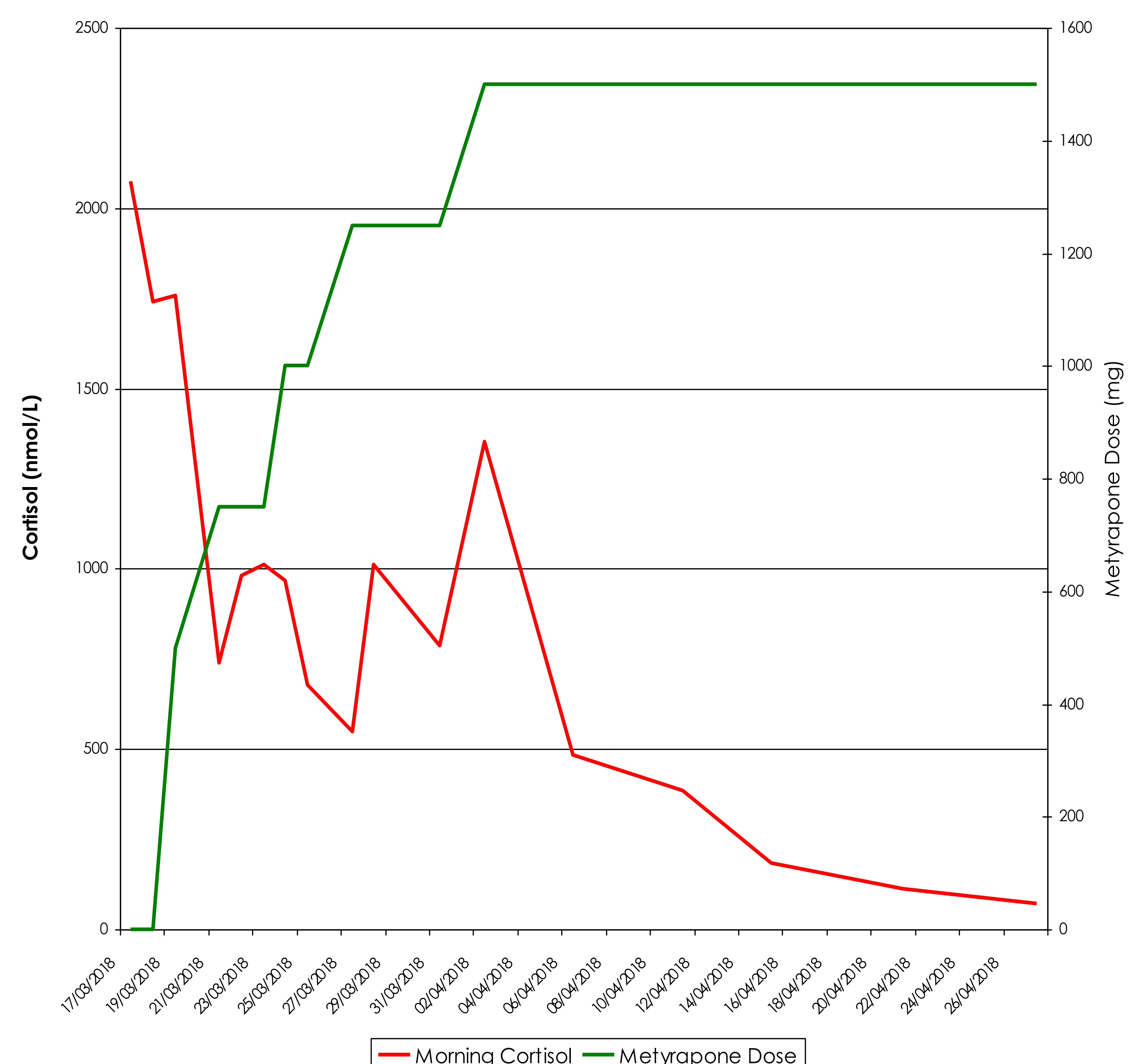
The patient was referred to clinical oncology. An octreotide scan confirmed a left-sided avid lesion within the thorax. Gut hormone profile was normal. He was commenced on octreotide LAR in November. A further CT in February, following 3 doses of octreotide, demonstrated progression of the primary tumour, lymphadenopathy and skeletal metastases and he was commenced on temozolomide. He was reviewed by cardiothoracic surgery who had concerns regarding his suitability for operative intervention due to his weight – BMI was 42.9 kg/m<sup>2</sup>.

The patient was subsequently re-admitted on 19/02/2018 with osmotic symptoms and a laboratory glucose of 21.8 mmol/L consistent with a diagnosis of diabetes mellitus. He was managed with twice daily insulin and metformin. Despite lacking symptoms of Cushing's syndrome, the cortisol following an overnight dexamethasone suppression test was 1878 nmol/L (ref. < 50 nmol/L). ACTH was elevated at 258 mU/L (ref. < 20 mU/L) and urinary cortisol was > 2000 nmol/L. The presumed diagnosis was of ectopic ACTH from the known carcinoid tumour.



The patient was re-admitted on 14/03/2018 with a hypokalaemia of 2.7 mmol/L and was noted to have marked proximal myopathy and peripheral oedema. He was commenced on metyrapone at an initial dose of 250 mg, twice daily, which was up-titrated to 1500 mg per day (see figure below). He was commenced on 20 mg in the morning and 10 mg in the afternoon of hydrocortisone on 28/03/2018. His admission was complicated by respiratory sepsis, and he was converted onto intravenous hydrocortisone for several days. Cortisol levels rose and the hydrocortisone was suspended on 02/04/2018 with his levels being monitored regularly. It was resumed on 06/04/2018.

Since discharge he has continued on insulin therapy, metformin, metyrapone and hydrocortisone, alongside octreotide LAR and temozolamide. A CT on 30/07/2018 has shown a slight reduction in the size of the mediastinal mass. BMI had reduced to 38.3 kg/m<sup>2</sup> in September, and HbA<sub>1c</sub> was 55 mmol/L. He is to be re-discussed with cardiothoracic surgery for consideration of resection of the tumour. If this is felt to be inappropriate, bilateral adrenalectomy will be considered.



#### References:

1. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's Syndrome. *Lancet*. 2015;386:913-27
2. Nieman KL. Cushing's Syndrome: Update on signs, symptoms and biochemical screening. *Eur J Endocrinol*. 2015;173(4):M33-38