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ENDGAMES

PICTURE QUIZ

A collapse with hypertension and hypokalaemia

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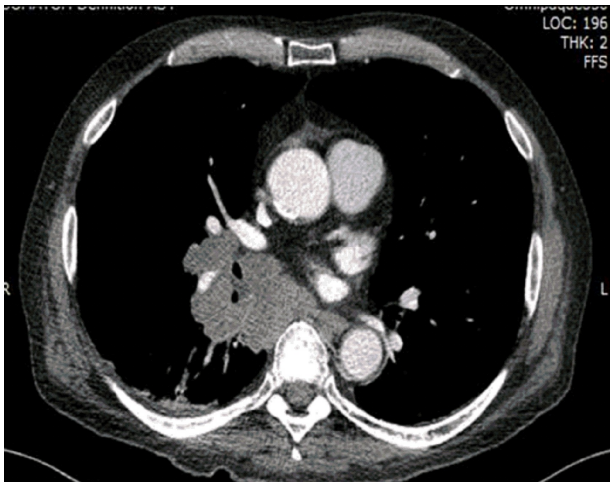
A 60 year old white man was admitted from the emergency department after an unwitnessed collapse and generalised weakness and malaise. He had no medical history of note and was taking no drugs. On clinical assessment he had hypertension, which had not previously been documented, with a blood pressure of 187/91 mm Hg. Blood tests showed severe hypokalaemia (2.1 mmol/L (reference range 3.6-5.0), having been normal (4.7) nine months earlier) and metabolic alkalosis (bicarbonate 38 mmol/L, 22-30). Random blood glucose was 6.0 mmol/L (3.5-7.8).

On the post take ward round, he was noted to have clubbing of the nails and a tanned appearance. A 60 pack year smoking history was elicited. Further biochemical tests were requested and, because his chest radiograph was abnormal, chest computed tomography was performed (fig 1).



Questions

1. What does this axial computed tomogram through the chest show?
2. What is the unifying diagnosis?
3. What is the underlying pathophysiology?
4. What tests would you use to confirm the diagnosis?
5. How would you manage this condition?

Answers

1. What does this axial computed tomogram through the chest show?

Short answer

A large mass in the right hilar and posterior lower lobe with confluent hilar lymphadenopathy.

Long answer

A large soft tissue mass is seen in the right hilum and posterior lower lobe with confluent hilar lymphadenopathy (fig 2). It encases the segmental bronchi of the right lower lobe and the ipsilateral pulmonary vasculature. Additional images showed subcarinal, precarinal, and pretracheal lymphadenopathy but no distant metastases. The radiological stage is T4, N2, M0.

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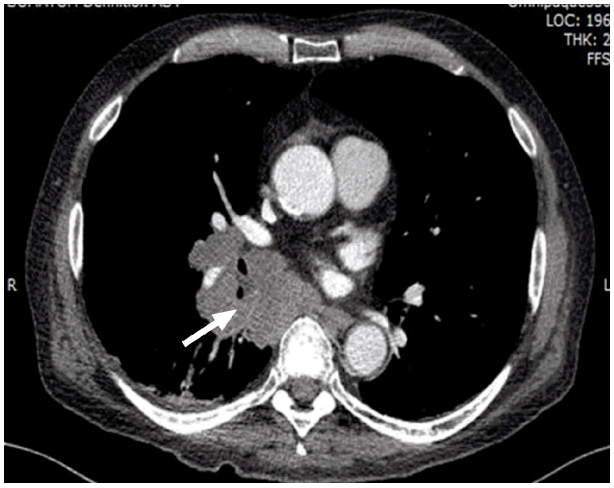

Fig 2 Mass in right hilum and posterior lower lobe (arrow)

2. What is the unifying diagnosis?

Short answer

Cushing's syndrome secondary to ectopic production of adrenocorticotrophin by a primary tumour in the lung.

Long answer

The presence of nail clubbing in a patient with a history of smoking is highly suspicious of primary lung cancer (most commonly bronchial adenocarcinoma). The combination of hyperpigmentation, hypertension, and hypokalaemia is suggestive of adrenocorticotrophin driven Cushing's syndrome.[1] This can occur as a result of ectopic production of adrenocorticotrophin by tumours of the lung, most commonly small cell lung cancer—around 2% of patients with this type of cancer have this complication. Other sources of ectopic adrenocorticotrophin include tumours of the thymus or islet cells, medullary carcinoma of the thyroid, carcinoid tumours, and phaeochromocytoma.

3. What is the underlying pathophysiology?

Short answer

Ectopic secretion of adrenocorticotrophin leads to Cushing's syndrome and apparent mineralocorticoid excess.

Long answer

Tumours that secrete adrenocorticotrophin arise from neuroendocrine cells within the primary tissue type—for example, distal bronchioles in lung cancer. The overproduction of adrenocorticotrophin leads to Cushing's syndrome through stimulation of the adrenal glands to produce excess cortisol. The clinical features of Cushing's syndrome may be evident, with proximal muscle weakness, central adiposity, striae, diabetes mellitus, and a Cushingoid appearance. However, these features may not have time to develop because of the rapidity of onset of the condition and may also be masked by manifestations of the underlying cancer (such as weight loss rather than weight gain).

Adrenocorticotrophin is a cleavage product of the prohormone pro-opiomelanocortin. This prohormone is also the precursor to α-melanocyte stimulating hormone. At high concentrations, adrenocorticotrophin can cross react with and stimulate the α-melanocyte stimulating hormone receptor on melanocytes, causing excess melatonin production and hyperpigmentation. Hyperpigmentation may also result from secretion of other pro-opiomelanocortin precursors by the tumour.

In addition to its glucocorticoid effects, cortisol also has mineralocorticoid activity. However, it is normally prevented from binding to the mineralocorticoid receptor due to its paracrine inactivation by the renal enzyme 11β-hydroxysteroid dehydrogenase type 2 (which converts cortisol into inactive cortisone). When excess cortisol is present, enzyme activity is saturated and cortisol can bind to and activate the mineralocorticoid receptor. The clinical manifestation of this is an apparent mineralocorticoid excess, manifested as hypertension, hypokalaemia, and metabolic alkalosis.

4. What tests would you use to confirm the diagnosis?

Short answer

Measurement of serum and urinary cortisol together with adrenocorticotrophin concentrations (both baseline values and after a low dose (and sometimes high dose) dexamethasone suppression test).

Long answer

It is important to diagnose ectopic adrenocorticotrophin production correctly, and the diagnosis of Cushing's syndrome is full of potential pitfalls. Investigation usually requires measurement of diurnal cortisol and adrenocorticotrophin concentrations, often followed by a low dose dexamethasone suppression test. Where clinical uncertainty remains, a high dose dexamethasone suppression test is performed. In the case of ectopic adrenocorticotrophin production, adrenocorticotrophin concentrations are not suppressed even by high doses of dexamethasone (usually 8 mg orally) in about 90% of cases. Adrenocorticotrophin concentrations will be suppressed (50% decrease from baseline) in a high dose dexamethasone suppression test in about 80% of patients with a pituitary source of adrenocorticotrophin. However, bronchial and carcinoid sources can exhibit feedback regulation and may be exceptions to this rule. Once it has been shown that the patient has ectopic adrenocorticotrophin production, appropriate imaging is needed to locate the primary tumour: computed tomography or magnetic resonance imaging (or both) of the chest and abdomen are usually performed initially, but more specialised modalities such as somatostatin scintigraphy may be helpful if the source is not identified by initial structural imaging.

5. How would you manage this condition?

Short answer

Definitive treatment of ectopic adrenocorticotrophin production is by resection of the causative tissue. However, as in this case, if resection is not possible, a multifaceted approach including metyrapone, electrolyte replacement, spironolactone or amiloride (or both), together with oncological input should be used.

Long answer

Initial management involves correction of the electrolyte and acid base disturbances (hypokalaemia and metabolic alkalosis). Spironolactone is often used. This is a direct competitive mineralocorticoid antagonist that acts in the cortical collecting ducts of the renal tubules to reduce kaliuresis and thereby correct the hypokalaemia.

Metyrapone is a competitive inhibitor of 11β-hydroxylation in the adrenal cortex, which therefore blocks the final step in adrenal cortisol production. It is used for symptom control to

reduce hypercortisolaemia. Other unlicensed drugs to reduce hypercortisolaemia include ketoconazole (availability is limited since a Medicines and Healthcare Products Regulatory Agency alert about the risk of hepatotoxicity), and etomidate.

Chemotherapy can be used in patients with tumours that secrete adrenocorticotrophin to reduce disease burden and thus the production of adrenocorticotrophin.

Patient outcome

Biochemical investigation confirmed the diagnosis of Cushing's syndrome, with greatly raised serum and urine cortisol concentrations (and no diurnal variation in serum concentrations) and an extremely high serum adrenocorticotrophin concentration, which is highly suggestive of ectopic rather than pituitary secretion. Biopsy of the lung lesion showed small cell carcinoma. The patient was started on chemotherapy but his general condition declined and he died two months after his initial presentation.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: none.

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Patient consent obtained.

1 Nieman LK. Cushing's syndrome. In: UpToDate, Lacroix A, ed. UpToDate.

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