Pure aldosterone-secreting adrenocortical carcinoma in a patient with refractory primary hyperaldosteronism

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Summary

We describe a young male patient with longstanding hypertension, who was diagnosed with primary hyperaldosteronism and treated by an attempted retroperitoneoscopic total unilateral adrenalectomy for a left-sided presumed aldosterone-secreting adenoma. Imaging had shown an unremarkable focal adrenal lesion with normal contralateral adrenal morphology, and histology of the resected specimen showed no adverse features. Post-operatively, his blood pressure and serum aldosterone levels fell to the normal range, but 9 months later, his hypertension recurred, primary aldosteronism was again confirmed and he was referred to our centre. Repeat imaging demonstrated an irregular left-sided adrenal lesion with normal contralateral gland appearances. Adrenal venous sampling was performed, which supported unilateral (left-sided) aldosterone hypersecretion. Redo surgery via a laparoscopically assisted transperitoneal approach was performed and multiple nodules were noted extending into the retroperitoneum. It was thought unlikely that complete resection had been achieved. His blood pressure returned to normal post-operatively, although hypokalaemia persisted. Histological examination, from this second operation, showed features of an adrenocortical carcinoma (ACC; including increased mitoses and invasion of fat) that was assessed as malignant using the scoring systems of Weiss and Aubert. Biochemical hyperaldosteronism persisted post-operatively, and detailed urine steroid profiling showed no evidence of adrenal steroid precursors or other mineralocorticoid production. He received flank radiotherapy to the left adrenal bed and continues to receive adjunctive mitotane therapy for a diagnosis of a pure aldosterone-secreting ACC.

Learning points:

- Pure aldosterone-secreting ACCs are exceptionally uncommon, but should be considered in the differential diagnosis of patients presenting with primary aldosteronism.
- Aldosterone-producing ACCs may not necessarily show typical radiological features consistent with malignancy.
- Patients who undergo surgical treatment for primary aldosteronism should have follow-up measurements of blood pressure to monitor for disease recurrence, even if post-operative normotension is thought to indicate a surgical ‘cure’.
- Owing to the rarity of such conditions, a greater understanding of their natural history is likely to come from wider cooperation with, and contribution to, large multi-centre outcomes databases.
Background
Pure aldosterone-secreting adrenocortical carcinomas (ACCs) are extremely rare tumours. Their presentation may be indistinguishable from patients with primary aldosteronism secondary to a benign adrenocortical adenoma. Our case highlights the difficulty of diagnosing this condition and emphasises the need for a careful follow-up of patients who undergo surgical treatment of primary aldosteronism.

Case presentation
A 42-year-old male originally presented with a several-month history of polydipsia, polyuria, palpitations and peripheral paraesthesia on a background of 20 years of unsatisfactorily controlled hypertension despite multiple medications.

Investigation
Biochemical evaluation confirmed primary aldosteronism (serum aldosterone 1899 pmol/l (normal range 135–400 pmol/l) and plasma renin activity <0.2 ng/ml per h (normal range 0.5–2.6 ng/ml per h)). There was no evidence of cortisol co-secretion on a standard low-dose dexamethasone suppression test (LDDST). A CT scan of his adrenal glands identified a 2.1 × 2.3 cm left adrenal mass.

Treatment
He underwent an attempted retroperitoneoscopic total left adrenalectomy, where a 2 × 2.5 × 5 cm left adrenal lesion, histologically confirmed as a benign adenoma, was excised. Post-operatively, he felt well, was normotensive without medication and, reassuringly, his serum aldosterone had normalised (287 pmol/l).

However, 9 months later, his original symptoms recurred and primary aldosteronism was reconfirmed (serum aldosterone 2974 pmol/l and plasma renin activity <0.2 ng/ml per h). A repeat LDDST suppressed the plasma cortisol level to undetectable and urinary catecholamines were within normal limits. He was referred to our centre.

Diagnoses considered at this point were unilateral disease with incomplete excision, or underlying bilateral adrenal hyperplasia. Repeat imaging by CT demonstrated a bulky, nodular left adrenal gland, again with normal right adrenal morphology.

Adrenal venous sampling was performed during a continuous i.v. infusion of synthetic ACTH at a rate of 50 µg/h. Adrenal:peripheral vein cortisol ratios > 5:1 confirmed satisfactory cannulation, and the normalised aldosterone values of 202 575 pmol/l (left) and 25 530 pmol/l (right) provided strong supportive evidence for unilateral aldosterone production. Repeat surgery was recommended.

Pre-operatively, his blood pressure was 140/80 mmHg whilst taking Amlodipine 10 mg and Eplerenone 50 mg once daily. Intra-operatively, a 2 × 2 cm multi-nodular mass was seen and found to be attached to the left renal vein with multiple lobules extending into the retroperitoneal fat, making the operation technically very challenging. His post-operative recovery was uneventful, and although he was initially normotensive without medication, hypokalaemia persisted and hypertension had subsequently recurred.

Outcome and follow-up
Histological examination revealed multi-nodular proliferation of neoplastic cells with capsular invasion and extension beyond the excision markers. Ki-67 expression was up to 20% in ‘hot spots’, and the tumour appeared malignant under the scoring systems proposed by Weiss and Aubert (1, 2). The microscopic and biochemical findings were in keeping with an aldosterone-secreting ACC.

Post-operatively, although temporarily normotensive without treatment, he remained persistently hypokalaemic. Biochemical hyperaldosteronism persisted (serum aldosterone 1354 pmol/l) and he redeveloped hypertension, requiring reintroduction of Eplerenone 50 mg daily. In view of the histological findings, he commenced mitotane therapy, aiming for a target serum level of 14–20 mg/l.

A 3-month follow-up CT scan was suspicious for local metastases in the adrenal bed, without evidence of distant disease. He received external beam flank radiotherapy, which resulted in a notable reduction in the residual tissue (3), and almost 2 years later, he had no evidence of disease recurrence.

Discussion
This case is particularly interesting as there were no notable radiological features suspicious of ACC nor were there any suggestive signs seen on the original histology – even after a repeat retrospective assessment. Although the absence of CT signs indicative of adrenocortical malignancy has previously been noted (4, 5), the absence of characteristic histology is much less common (5).
A combination of clear-cut primary aldosteronism and a focal 2 cm adrenal lesion, in the vast majority of cases, is associated with benign pathology (4). Whilst hypokalaemic hypertension has been seen with ACCs, it is more frequently due to the production of steroids more proximal in the steroidogenic pathway, rather than aldosterone. The long duration (~20 years) of poorly controlled hypertension prior to the diagnosis of primary aldosteronism in our patient and the subsequent review and retrospective confirmation of benign pathology is noteworthy, in that it would suggest malignant transformation rather than the presence of ACC from the outset.

Pure aldosterone-secreting ACCs are exceptionally uncommon and, as a consequence, data on the outcomes of patients with this disease are very limited. By analogy with cortisol-secreting ACCs, it may be that our patient’s prognosis is slightly more favourable than a non-secreting lesion; clearly, diligent follow-up and therapeutic mitotane levels are imperative in improving the long-term outcome.

This report emphasises the need to continually monitor patients who have been surgically ‘cured’ for primary aldosteronism, even when malignancy is not suspected.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
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