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CASE REPORT

Malignant aldosterone-producing adrenal tumour: reoccurrence with glucocorticoid excess without hyperaldosteronism

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ABSTRACT

We describe a case of hypokalaemic hypertension due to hyperaldosteronism caused by a unilateral adrenocortical tumour with unfavourable histopathology suggestive of malignancy. After removal, the aldosterone excess disappeared. The patient's clinical course was uneventful, until she presented with extensive metastases of adrenal carcinoma four years later. Biochemical abnormalities were now consistent with glucocorticoid excess without hyperaldosteronism. She died four months later. Although malignant aldosterone-producing adrenal tumours are very rare, the present case underscores that clinicians should be aware that primary hyperaldosteronism can occur in the context of adrenocortical carcinoma.

KEYWORDS

Adrenal carcinoma, aldosterone, hypertension, hypokalaemia

INTRODUCTION

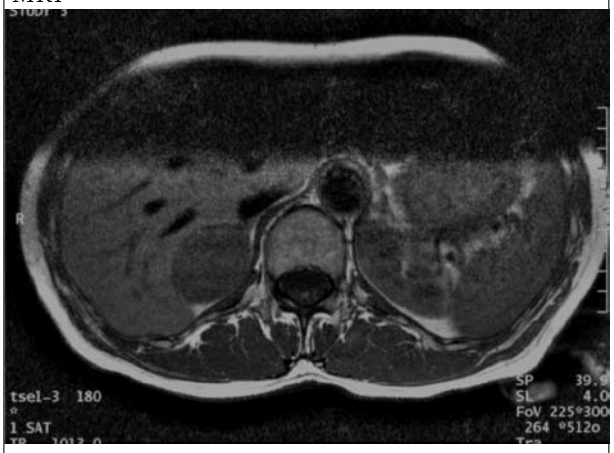
As the criteria for evaluation of hyperaldosteronism are being broadened, aldosterone excess is increasingly diagnosed as the cause of hypertension.[1] Hyperaldosteronism is generally due to an aldosterone-producing adenoma of the adrenal gland (APA) or to bilateral adrenal hyperplasia.[1] Adrenocortical carcinomas are rare with an estimated incidence of only 0.5 to 2 per one million people per year,[2,3] and the occurrence of hyperaldosteronism due to a malignant adrenal tumour is even less frequent. In a large series of adrenocortical carcinomas, only 2.5% had developed hyperaldosteronism.[3] Conversely, it has been estimated that hyperaldosteronism is due to adrenocortical carcinoma in only 1% of patients.[1] When a malignant adrenocortical carcinoma is suspected, surgical removal should be performed as early as possible, and postoperative adjuvant medical therapy may be warranted in case of malignancy.[2]

We describe a case of hyperaldosteronism due to a unilateral adrenocortical tumour with unfavourable histopathology. The aldosterone excess disappeared postoperatively, but the patient subsequently presented with metastatic adrenocortical carcinoma and biochemical signs of glucocorticoid excess without reoccurrence of hyperaldosteronism. The case presented here underscores that clinicians should be aware that aldosterone-producing adrenal tumours can bear malignant potential.

CASE REPORT

A 52-year-old woman without clinical signs suggestive of Cushing's syndrome was referred for evaluation of hypokalaemic hypertension. Her blood pressure was 190 mmHg systolic and 100 mmHg diastolic. Laboratory investigation showed hypokalaemia (3.0 mmol/l), increased urinary potassium and elevated serum aldosterone (0.80 (normal: <0.60) nmol/l) with suppressed plasma renin activity (0.14 nmol/l/h). Urinary aldosterone-glucuronide excretion after salt loading was increased (51 nmol/24 h; normal <34 nmol/24 h). Morning serum cortisol as well as urinary excretion of cortisol metabolites and metanephrines were not elevated. Magnetic resonance imaging showed a 4 cm inhomogeneous mass of the right adrenal (*figure 1*). APA was suspected.

Figure 1. *Appearance of right-sided adrenal tumour on MRI*



T1 weighed MRI sequences showing a 4 cm tumour with low signal intensity compared with the liver parenchyma surrounding it. On a T2 weighed image the signal intensity increased significantly.

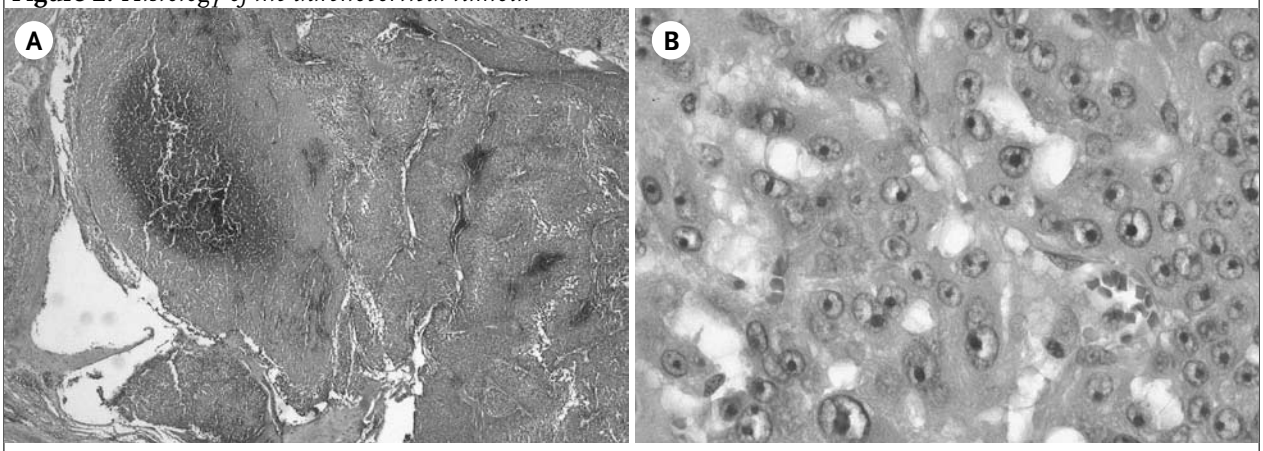
At surgery, an adrenal mass (51 grams) was removed, which was encapsulated and lobulated, with a small margin of normal adrenal tissue. Histopathological examination showed fields of tumour cells, separated by strands of fibrovascular stroma with focal necrosis and calcification. Completely diffuse (40%) areas were present. The tumour infiltrated its capsule and sinusoidal invasion was present. Generally, 13 to 16 mitotic cells/50 high power fields were seen (*figure 2*). The hypokalaemia resolved postoperatively and her blood pressure decreased. The serum aldosterone normalised. One year later, an abdominal ultrasound did not reveal any abnormalities. After two years, the patient appeared healthy and was then referred to her primary physician.

Four years postoperatively, she developed hepatomegaly and her blood pressure had increased. There were no signs of virilisation. Serum potassium, aldosterone (0.2 nmol/l) and plasma renin activity (1.4 nmol/l/h) were normal. Serum cortisol at 8 a.m. was rather high (740 nmol/l), as were serum levels of the cortisol precursor 11-deoxycortisol and testosterone. Plasma ACTH was low. Urinary free cortisol (864 (normal <270) nmol/ 24 h) and androgen metabolite excretion were increased, and abnormal steroid metabolites were present. These findings were consistent with glucocorticoid and androgen excess without hyperaldosteronism. Computer tomography demonstrated a large right-sided adrenal tumour growing into the liver and possibly the right kidney, multiple metastases in the liver and lungs and mediastinal lymphadenopathy. Histopathological investigation showed hepatic metastasis of adrenal carcinoma. Palliative therapy with mitotane was initiated, which was poorly tolerated and not effective. Ascites developed which had to be removed. There were no malignant cells on cytological investigation. The patient died four months later.

DISCUSSION

Consequent to more frequent use of abdominal imaging techniques, adrenocortical tumours, including those bearing malignant potential, are increasingly recognised. Nonetheless, adrenocortical carcinomas are not yet being diagnosed earlier, nor has their survival improved.[4,5] Adrenal carcinomas producing excess aldosterone are very rare, with only 58 patients being reported.[6] Adrenocortical carcinomas have a bi-modal age distribution,[3] and occur more frequently in women.[2,3] In a review comprising 602 cases of adrenocortical carcinomas, Ng stated that 62% of these tumours are functional.[3] Glucocorticoid excess was found most frequently.[3] In 114 sporadic adrenal tumours,

Figure 2. *Histology of the adrenocortical tumour*



A. Overview with necrosis, sinusoidal invasion and a solid growth pattern (2 x).
B. Area with hepatoid appearance. The tumour cells have very large nuclei and nucleoli and abundant somewhat granular eosinophilic cytoplasm. In between the tumour cells many thin walled vessels are present (40 x).

mineralocorticoid excess as the only sign of hormonal overproduction was observed in none of 18 malignant tumours.[7] In the patient presented here hyperaldosteronism was demonstrated at presentation. There were no clinical signs of Cushing's syndrome initially, and limited laboratory studies did not show glucocorticoid excess. Upon recurrence of the tumour, serum aldosterone was not elevated and plasma renin activity was not suppressed. Urinary excretion of free cortisol and glucocorticoid metabolites were now increased, whereas plasma ACTH was low. Furthermore, high plasma and urinary levels of abnormal glucocorticoid metabolites were demonstrated, as were increased concentrations of androgens and urinary androgen metabolites. These findings are consistent with the possibility that the type of adrenal hormonal overproduction can change during the course of the disease. This phenomenon has only been described a few times before, and could be due to modifications in the expression of specific steroidogenic enzymes during tumour dedifferentiation, together with (relative) blocks of enzymes involved in adrenal hormonogenesis.[8-10]

Whether an adrenal cortical tumour is malignant can only be ascertained unequivocally in case of metastases. Of the histological classification systems,[11,12] the (modified) Weiss criteria have been used most widely. Using this classification, three findings were only found in malignant tumours: venous invasion, mitotic rate >5 per 50 HPFs and atypical mitotic figures, two of three criteria being present in the current tumour. The Weiss score was found to be a prognostic factor for disease-free survival, independently of tumour size and functional status. This system has been modified, resulting in a sensitivity of 96% for malignancy.[12] According to these criteria, the present tumour had a very high score (*table 1*). Tumour size is also helpful to predict malignancy. Adrenal carcinomas are larger,[11,12] and a cut-off size of 4 to 6 cm has been proposed as criterion for removal in incidentally discovered tumours.[13] At presentation, mean size of adrenocortical carcinoma has been reported to be 11.8 to 14 cm,[4,12] and 84% of these tumours weigh >100 g.[14] In comparison, mean maximal tumour diameter is 7.0 cm in aldosterone-producing adrenocortical carcinomas,[6] whereas in APA mean tumour size is 2.2 cm. Thus, in general malignant aldosterone-producing tumours appear to be larger than APAs and smaller than adrenal cortical carcinomas. Finally, an algorithm has been proposed using tumour density to ascertain the likelihood of malignancy.[15] An irregular shaped tumour >4 cm, with intermediate to high-signal intensity on T2-weighted MRI or high unenhanced CT attenuation values is most likely malignant. Benign tumours are usually <4 cm in diameter, have a smooth, round appearance, are homogeneous and have a low density value.

The patient reported here corroborates that clinicians should be aware that primary hyperaldosteronism can occur in the context of adrenocortical carcinoma.

Table 1. *Modified Weiss classification system with scoring for the tumour of the present patient*[16]

	Weight of criteria (value 0-2 points)	Present case	Present case score
Mitotic rate >5/50 HPF	2	13 mitotic cells per 50 high power fields	2
≤25% clear cells	2	<5%	2
Abnormal mitoses	1	Absent	0
Capsular invasion (tumour capsule)	1	Present	1
Necrosis	1	Present	1
Nuclear grade Fürhmann III/IV	-	Grade IV	-
> 1/3 diffuse architecture	-	Present	-
Venous invasion	-	Absent	-
Sinusoidal invasion	-	Present	-
Total score	0-7*		*6*

*Malignancy threshold: value ≥3 points.

Remarkably, metastases may develop without re-occurrence of hyperaldosteronism. Whether postoperative adjuvant medical treatment and close long-term follow-up beneficially affect prognosis is still uncertain.

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