The larger doses also produced dyspepsia and a sensation of burning in the mouth which persisted for 24 hours.[13] Despite methylene blue's potential to cause diverse anti-inflammatory and physiologic effects,[14,15] we were unable to detect any significant toxicity in our patient.

Based on the short-term haemodynamic benefits of methylene blue in septic shock, we would encourage investigators to consider more prolonged administration of the drug. Data on benefit and absence of toxicity can only be obtained through increased investigation.

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Cushing's syndrome due to autonomous macronodular adrenal hyperplasia: long-term follow-up after unilateral adrenalectomy

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Summary

This report describes a case of Cushing's syndrome due to autonomous macronodular adrenocortical hyperplasia in which unilateral resection of the right adrenal resolved the Cushing's syndrome.

Keywords: Cushing's sydrome, suprarrenal hyperplasia, adrenalectomy

Endogenous adrenocorticotropin (ACTH)-independent Cushing's syndrome is caused by an autonomous adrenal production of cortisol. In most cases, it is due to a primary adrenal neoplasm, adenoma or carcinoma, usually unilateral. Rare nontumourous primary adrenal processess that can also cause Cushing's syndrome are bilateral. They include pigmented micronodular adrenal dysplasia[1] and autonomous macronodular adrenocortical hyperplasia (AMAH).[2–4] We describe a patient with AMAH who was treated successfully by unilateral adrenalectomy.

Case report

In 1984, a 53-year-old man presented with weakness, weight gain, easy bruising and impotence, which had developed over a period of two years. He had a history of chronic obstructive pulmonary disease, heart failure and mixed angina, and was known to have been hypertensive for 10 years. On physical examination, the patient was found to have cushingoid appearance, with centripetal obesity, atrophic skin and ecchymoses on forearms.

Endocrine assessment is summarised in the table. Computed tomography (CT) of the turcica sella was normal. Abdominal CT revealed a tumour mass occupying the entire right adrenal gland. The contralateral gland was also enlarged and contained a focal nodule localised in its central portion (figure 1). Scanning with ^{131}I-labelled cholesterol demonstrated bilateral but asymmetrical uptake of the tracer, indicating much greater activity on the right arm than on the left gland (figure 2).

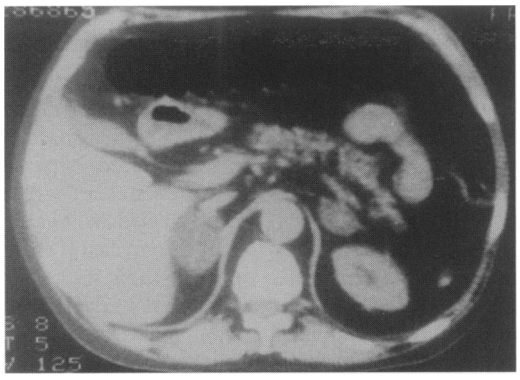

Figure 1 Abdominal CT imaging. Bilateral but asymmetrical diffuse enlargement of adrenal glands. Note a small nodular image inside the left gland

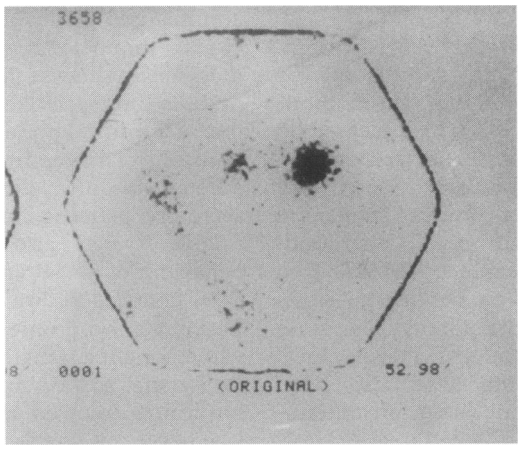

Figure 2 Scanning of the adrenals with ^{131}iodocholesterol. Uptake of the tracer is bilateral but considerably more marked on the right

Cushing's syndrome: classification and management

ACTH-dependent
- Cushing's disease: transsphenoidal surgery
- ectopic ACTH-secreting tumour: surgical resection (medical therapy if surgery not possible)

ACTH-independent
- adrenal tumour: ipsilateral adrenalectomy
- pigmented micronodular dysplasia: bilateral simultaneous adrenalectomy
- AMAH: bilateral adrenalectomy (evaluating unilateral adrenalectomy if adrenals are asymmetrical)

Summary points

Cases of AMAH (especially if asymmetrical hyperplasia occurs) could be treated by removal of the most hyperplastic adrenal, performing a delayed contralateral adrenalectomy only if hypocortisolism recurs

With the diagnosis of AMAH, the patient underwent right adrenalectomy. Owing to the concurrent history of cardiac and pulmonary diseases, bilateral adrenalectomy was considered to entail high risk and resection of the other gland was delayed for a further operation.

The adrenal gland weighed 26.8 g and measured 5.5 × 4.5 × 3 cm. Light microscopic examination revealed well-delimited benign hyperplastic nodules, which ranged in size from microscopic clusters of cells to 2 cm in diameter. The internodular areas of the cortex did not show atrophy, but were also occupied by diffusely hyperplastic tissue.

Postoperatively, baseline plasma cortisol was 377.3 nmol/l (08.00 h) and 470.9 nmol/l (23.00 h), urinary free cortisol was 126.9 nmol/24 h and serum ACTH levels were undetectable. Signs and symptoms of hypercortisolism resolved some months later.

Although baseline plasma cortisol and urinary free cortisol always ranged within normal limits, studies of adrenocortical function at three, six and 12 months postsurgery, and annually thereafter, continued to demonstrate persistent loss of cortisol rhythm, without suppression by high doses of dexamethasone. When last seen at the follow-up clinic, 10 years after adrenalectomy, basal plasma cortisol was 198.2 nmol/l (08.00 h) and 187.6 nmol/l (23.00 h), plasma ACTH was 1.23 pmol/l (08.00 h) and 1.07 pmol/l (23.00 h) and urinary free cortisol was 96.5 nmol/24 h. After overnight 16 mg oral dexamethasone administration, the morning plasma cortisol level was 204.1 nmol/l. Baseline plasma 11-deoxycortisol was 79.1 nmol/l and, 8 h after metyrapone administration, only rose to 329 nmol/l.

Discussion

Bilateral macronodular enlargement of the adrenals develops in 20–40% of patients with Cushing's disease[5] and is thought to be caused by chronic hypersecretion of ACTH. However, a few cases of AMAH without a previous history of Cushing's disease have been convincingly documented.[2–4]

In our patient, dynamic tests of adrenal function, suppressed ACTH levels and scintigraphic image suggested an autonomous adrenal hyperfunction. A diagnosis of AMAH was confirmed at pathological examination.

Table Pituitary-adrenocortical functional assessment

	Baseline levels	*2 mg dexamethasone suppression***	*8 mg dexamethasone suppression†*	*Metyrapone test (pre/post)‡*
Plasma cortisol (nmol/l)	510.4–499.3*	620.7	786.3	–
Urinary free cortisol (nmol/24 h)	804.2	662.4	1445.7	–/190.9
Urinary 17-hydroxycorticosteroids (μmol/24 h)	65.7	44	69.8	65.1/48.3
ACTH (pmol/l)	undetectable	–	–	–

*Samples at 08.00 h–23.00 h. **0.5 mg/6 h, for eight doses. †2 mg/6 h, for eight doses. ‡750 mg/4 h, for six doses

Since AMAH affects both glands, bilateral adrenalectomy appears to be the most appropriate and, to date,[3] the only procedure to achieve surgical cure. Unexpectedly, in our case, a single adrenalectomy proved to be a successful treatment: cortisol secretion was reduced and the physical features of the patient regressed over subsequent months. During long-term follow-up hypercortisolism has never recurred and he is presently doing well. Postoperative outcome has revealed the remaining gland works autonomously, but it is not able to cause hypercortisolism. This striking functional profile persists 10 years after adrenalectomy.

It has been speculated that AMAH originates from a long-lasting stimulation by ACTH, ultimately becoming autonomous and suppressing pituitary ACTH release, on the basis of cases of single adrenal macronodules and coexisting pituitary lesions.[6] We can find no evidence of this 'transition hypothesis' to explain our case. Other non-corticotropin factors can induce AMAH. Two cases have been shown to be due to inappropriate sensitivity of the adrenal glands to gastric inhibitory polypeptide.[7,8] Likewise, local growth promoting factors have also been reported to exert a mitotic effect on adrenocortical cells in vitro.[9]

Whichever the responsible growth factor in our case (systemic or paracrine), it prompted different reactions in each gland. It produced a more intense proliferative response in the right gland, with maintenance of autonomous, differentiated hypersecretion. In contrast, the left adrenal progressed to autonomous but normal-to-low secretion, perhaps suggesting that hyperplastic cells from that gland had lost part of their functional capacity.

Clonal analysis in several macronodules from a patient with AMAH, demonstrated that all the nodules of a gland had a monoclonal composition, whereas those removed from the larger contralateral gland had an intermediate polyclonal–monoclonal pattern.[10] Moreover, studies *in vitro* showed that one of the monoclonal nodules only secreted cortisol precursors, while one of the mixed nodules was still able to secrete cortisol.[10] This report showed that, in AMAH, adrenal nodules display not only variable secretory patterns, but also different genetic origin. It may also explain the discordant behaviour of the adrenal glands in our patient.

In conclusion, we describe a patient with Cushing's syndrome caused by AMAH in whom a right adrenalectomy removed the most important source of corticoids. Cushing's syndrome resolved and replacement therapy was never necessary.

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