

# Macronodular adrenocortical hyperplasia in a postmenopausal woman

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## ABSTRACT

This case report describes the diagnosis of Cushing's syndrome due to macronodular adrenal hyperplasia in an elderly woman who presented with fatigue, muscle weakness and oedema, and recent excessive bruising. Long-standing disease and comorbidity precluded adrenalectomy. Despite treatment with metyrapone and diuretics, the patient died after two months hospitalisation. Postmortal examination revealed overexpression of luteinising hormone (LH) receptors in the adrenal glands, suggesting that the postmenopausal rise in LH may have a role in adrenal hyperplasia and hypercortisolism.

## CASE REPORT

A 79-year-old woman with a history of ischaemic stroke, pulmonary embolism and a recent deep venous thrombosis of the right leg, was admitted to our hospital because of extensive bruising under anticoagulant use. During the last two years, she had been mentally depressed and walking had been increasingly impaired by fatigue, muscle weakness and leg oedema. Physical examination revealed centripetal adipositas with a buffalo hump (*figure 1*), thoracic kyphosis, muscle atrophy, a thin, easily bruisable skin and generalised oedema. There was no normal diurnal cortisol rhythm, urinary cortisol excretion was high (581 nmol/24 h), a 4 mg overnight dexamethasone suppression test was abnormal (cortisol 535 and 590 nmol/l before and after, respectively) and serum cortisol level was 465 nmol/l after 7 mg dexamethasone intravenously in seven hours. Plasma ACTH

levels were repeatedly low (1.2 pmol/l). An abdominal CT scan showed enlarged adrenal glands. Somatostatin receptor scintigraphy, performed in search of ectopic ACTH-producing source(s), showed increased uptake in the pituitary region. Adrenalectomy had to be postponed because of the patient's poor cardiopulmonary condition. Despite treatment with metyrapone and diuretics, she died after two months hospitalisation.

Autopsy revealed huge adrenal glands of 145 and 150 g, containing multiple large nodules (*figure 2*). The tissue showed malignant transformation. This means that on several locations in both adrenals there were broad fibrous bands with a trabecular pattern, areas with a diffuse growth pattern including nests of more compact cells with eosinophilic cytoplasm and vesicular nuclei, with significant cellular polymorphism. Focally there was vascular invasion. In one of the adrenal glands capsular invasion was seen as well as solitary areas with necrosis. The mitotic activity was 3 per 50 high-power fields.

Interestingly, islands of ACTH-positive cells were present in the adrenal glands. Stains for glucose-dependent insulinotropic peptide (GIP), vasopressin, serotonin and  $\beta$ -HCG were negative. However, staining for luteinising hormone (LH) was strongly positive, indicating adrenal expression of LH receptors. The somatostatin scan appeared false-positive due to an olfactory meningioma (diameter 3 cm), which was positive on somatostatin staining. There was no evidence of infection. Taken together, this patient died of Cushing's syndrome due to ACTH-independent macronodular adrenal hyperplasia (AIMAH).



**Figure 1**  
*Patient with an apparent buffalo hump and thoracic kyphosis*



**Figure 2**  
*Adrenal glands of the patient on autopsy, weighing 145 and 150 g and containing multiple large nodules, consistent with bilateral macronodular adrenocortical hyperplasia*

## DISCUSSION

Bilateral macronodular hyperplasia is a rare (<1%) cause of Cushing's syndrome. The disease is characterised by enlarged adrenal glands weighing from 24 to >500 g, containing multiple nodules >5 mm, and may be associated with McCune-Albright syndrome. The pathogenesis of AIMAH is unknown. The diagnosis, usually made in elderly patients, is often delayed (from 1 to 20 years). In our case, obvious signs of hypercortisolism were present years before diagnosis. This illustrates that recognition of cortisol excess may be difficult in the elderly, possibly because symptoms are easily considered 'age-related'. Laparoscopic bilateral adrenalectomy is the treatment of choice for AIMAH. However, when long-standing disease and comorbidity preclude immediate surgery in elderly patients, medical treatment with steroidogenesis inhibitors such as metyrapone can be a temporary alternative.

The presence of ACTH-positive cells in the adrenals suggests that intra-adrenal ACTH production may be responsible for the autonomous cortisol production. Two recent cases describe the expression of ACTH receptors and production of ACTH in adrenocortical adenomas and AIMAH,<sup>1,2</sup> regulated by the ACTH precursor proopiomelanocortin (POMC) gene. Locally produced ACTH has paracrine effects on cortisol secretion and adrenocortical cell proliferation, and does not lead to elevation of plasma ACTH.<sup>2</sup> This observation shows that Cushing's syndromes with suppressed plasma ACTH levels may be dependent upon ACTH production within adrenocortical tissue. In this case, the term 'ACTH-independent' is inappropriate.<sup>2</sup> It was recently determined that aberrant expression and function of adrenal receptors for various hormones cause the secretion of cortisol in several cases with AIMAH.<sup>3,4</sup> These aberrant receptors include ectopic receptors for gastric inhibitory polypeptide (GIP), LH, HCG or catecholamines and abnormally active eutopic receptors, such as vasopressin V<sub>1</sub> and serotonin 5-hydroxytryptamine<sub>4</sub> (5-HT<sub>4</sub>) receptors. In our patient, there was adrenal overexpression of LH receptors. Cortisol secretion can be controlled by LH, as described in three postmenopausal and one premenopausal women with AIMAH.<sup>5,7</sup> Two patients responded to suppression of LH with leuprolide acetate therapy.<sup>5,6</sup> We hypothesise that LH-controlled adrenal hyperplasia might be a process that especially develops after menopause, induced by the rise in serum LH.

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