

ACTH-Independent Macronodular Hyperplasia: Unusual Case of Cushing's Syndrome

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1. Clinical History

61-year-old woman, smoker, with a history of diabetes mellitus, osteoporosis and centripetal obesity, was hospitalized after an acute hypertensive crisis, with blood pressure values of about 180/120 mmHg. Physical examination was unremarkable. Lab investigations showed cortisol level of 108 ng/ml after Liddle test and 48 ng/ml after Nugent test, 2.46 ng/ml of salivary cortisol, 10 pg/ml of ACTH and 6.11 of the potassium.

2. Imaging Findings

A contrast enhanced computed tomography (CT) scan was performed during the hospitalisation, showing hyperplastic multinodular adrenal glands, which still retain their adreniform contour (FIG.1).



FIG.1. Contrast-enhanced CT scan shows massive hyperplasia of both adrenal glands (arrows).

Both glands were characterised by a massive increase in size, the left one measured approximately 48 mm, while the right one measured 28 mm. Magnetic resonance imaging of the adrenal glands showed hypointense signal relative to the liver on T1-weighted images and isointense on T2-weighted images (FIG. 2). Axial in-phase and out-of-phase T1-weighted MR images demonstrates signal drop out within the glands, a finding that indicates the presence of intracellular lipid (FIG. 3). Axial contrast-enhanced fat-saturated spin-echo T1-weighted MR images show specks of contrast uptake predominantly at the periphery (FIG. 4).

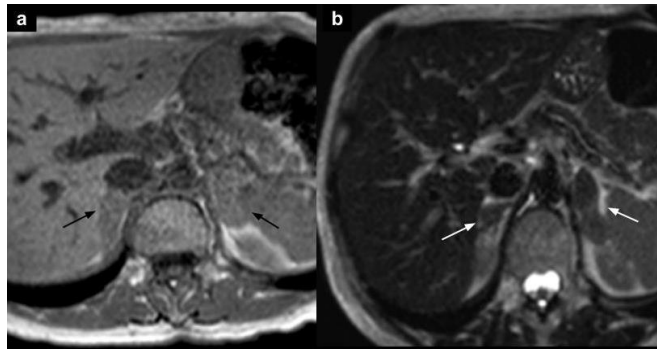


FIG. 2. (a) T1 weighted image and (b) T2 weighted image show enlarged multinodular adrenal glands hyperintense and isointense to liver respectively (arrows).

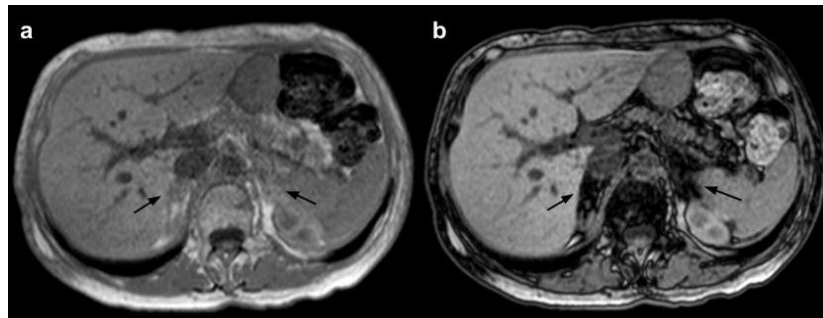


FIG. 3. Axial in-phase (a) and out-of-phase (b) T1-weighted MR images demonstrate signal dropout within the glands due to the presence of intracellular lipid (arrows).

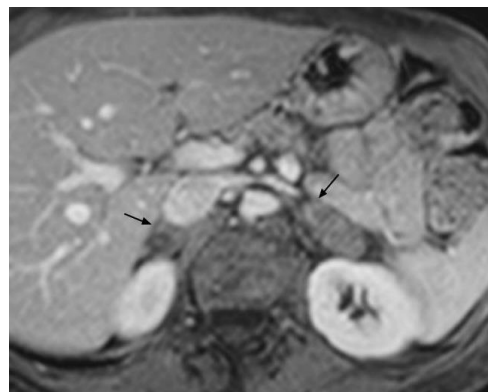


FIG. 4. Axial contrast-enhanced fat-saturated spin-echo T1-weighted MR images shows slight enhancement at the periphery predominantly (arrows).

3. Discussion

Cushing's syndrome (CS) is characterized by a composition of clinical, endocrinologic, laboratory and radiological features. Clinical manifestations include hypertension, weight gain, diabetes mellitus, osteoporosis, and easy skin bruising. CS is most frequently iatrogenic and rarely it may be endogenous [1-3]. The etiopathology of endogenous CS may be adrenocorticotropic hormone (ACTH)- dependent (80%-85% of cases) or ACTH-independent (15%-20%). ACTH-dependent CS is often caused by an ACTH-secreting pituitary adenoma 85% and rarely (15%) by an ectopic ACTH-secreting tumor [1]. ACTH-independent CS is always of adrenocortical origin, in the majority of cases (95%) is due to an adenoma or carcinoma. However, in rare conditions it may be caused by pigmented nodular adrenal dysplasia (PPNAD) or ACTH-independent macronodular hyperplasia (AIMAH), approximately <2% [2]. PPNAD is characterised by small bilateral pigmented adrenocortical nodules, while AIMAH by multiple bilateral adrenocortical macronodules leading to massive glandular enlargement [4,5]. In case of ACTH-independent CS, CT scan and MR imaging are used to characterise the lesions, size, presence or absence of calcifications, hemorrhage, necrosis, enhancement pattern and signal intensity change at chemical shift imaging [6]. Unilateral adrenal disease-causing Cushing's syndrome is due to adenoma or carcinoma while bilateral disease is due to PPNAD and AIMAH [1]. Bilateral metastases or multiple bilateral adenoma could manifest with similar morphological appearances, but in the presence of CS, this appearance is practically pathognomonic for AIMAH. The typical imaging features of AIMAH are massively enlarged multinodular adrenal glands with hypoattenuating nodules in size ranging between 1 cm and 5.5 cm [5]. There is also often distortion of the adrenal contour. PPNAD nodules have a signal intensity on T2-weighted images and the total adrenal weight rarely is above 30 g, while in cases of AIMAH the total weight can even reach about 300 mg [5]. Furthermore in patients with AIMAH the internodular cortex is always hyperplastic, while normal, atrophic or uninvolved cortex has been reported in PPNAD. Bilateral adrenalectomy is considered the treatment of choice in patients with AIMAH with profound cortisol excess [1]. However, also unilateral adrenalectomy of the largest adrenal gland represents a safe and viable option in order to get a long-term response [4]. In case of unilateral adrenalectomy, a long-term follow up is mandatory in order to keep the cortisol level under an adequate control. Another option is represented by steroidogenesis inhibitors, which can be a good option in acute situations or before a surgical approach. By the way, bilateral complete adrenalectomy remains the treatment of choice [4].

4. Teaching Points

- ACTH-independent Cushing's syndrome is always of adrenocortical origin, in the majority of cases (95% of patients) is due to an adenoma or carcinoma.
- Unilateral adrenal disease-causing Cushing's syndrome is due to adenoma or carcinoma while bilateral disease is due to PPNAD and AIMAH.
- ACTH-independent Cushing's syndrome in rare conditions it is caused by pigmented nodular adrenal dysplasia (PPNAD) or ACTH-independent macronodular hyperplasia (AIMAH), approximately <2%.
- The typical imaging features of AIMAH are massively enlarged multinodular adrenal glands with hypoattenuating nodules in size ranging between 1 and 5.5 cm. There is also often distortion of the adrenal contour.
- Bilateral adrenalectomy is considered the treatment of choice in patients with AIMAH with profound cortisol excess, when is not viable unilateral adrenalectomy or medical therapy with steroidogenesis inhibitors are other possible options.

5. Final Diagnosis

ACTH-independent macronodular hyperplasia.

6. Differential Diagnosis List

- Pituitary-dependent macronodular hyperplasia.
- ACTH ectopic dependent hyperplasia.
- Bilateral adenoma.
- Bilateral metastases.
- Pigmented nodular adrenal dysplasia.
- ACTH-independent macronodular hyperplasia.

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