Cyclic ACTH-Independent Cushing Syndrome in an Adolescent Revealing Multinodular Adrenal Hyperplasia: A Case Report.

Introduction

Cushing syndrome results from prolonged exposure to excessive glucocorticoids and remains an uncommon diagnosis inchildhood and adolescence. In pediatric patients, endogenous cases are rare, and ACTH-dependent forms are morefrequent than ACTH-independent ones after early childhood. Adrenal ACTH-independent Cushing syndrome in youngpatients is therefore unusual and may create important diagnostic uncertainty, especially when biochemical activityfluctuates over time [1].

Cyclic Cushing syndrome is characterized by alternating periods of hypercortisolism and partial or complete remission. Theduration of active and inactive phases is highly variable, and this pattern can involve either ACTH-dependent or ACTH-independent disease. In practice, cyclicity often delays diagnosis because hormonal testing may be performed during aquiescent phase, leading to apparently inconsistent results [2].

Among adrenal causes of ACTH-independent Cushing syndrome, unilateral cortisol-producing tumors are the mostcommon, whereas bilateral nodular adrenal diseases are much less frequent. These include primary pigmented nodularadrenal disease and bilateral macro- or multinodular hyperplasia. Recent classifications of adrenal cortical proliferationshave emphasized the broader spectrum of nodular adrenal disease and the need to correlate pathology with clinical andfunctional findings.

We report the case of an adolescent girl with ACTH-independent Cushing syndrome that initially followed a cyclic courseand was ultimately found to be associated with multinodular adrenal hyperplasia.

Case Presentation

A 16-year-old girl, born to first-degree consanguineous parents, with a family history of diabetes and essentialhypertension, had been followed for Cushing syndrome evolving since the age of 8 years. At disease onset, the course wasclearly cyclic, with symptomatic phases lasting around 15 days and spontaneous remissions of nearly 3 months. During thelast 3 years, this pattern progressively disappeared and the disease became clinically persistent.

Her clinical presentation was typical of hypercortisolism, with facial plethora, moon facies, central obesity with pendulousabdomen, buffalo hump, and wide striae. There was no melanoderma. The hormonal work-up supported ACTH-independent Cushing syndrome, showing loss of cortisol circadian rhythm, urinary free cortisol elevated to 8.6 times theupper limit of normal, failure to suppress after the overnight dexamethasone suppression test, and low ACTH levels. Thesefindings were consistent with autonomous adrenal cortisol secretion. The Liddle test was negative.

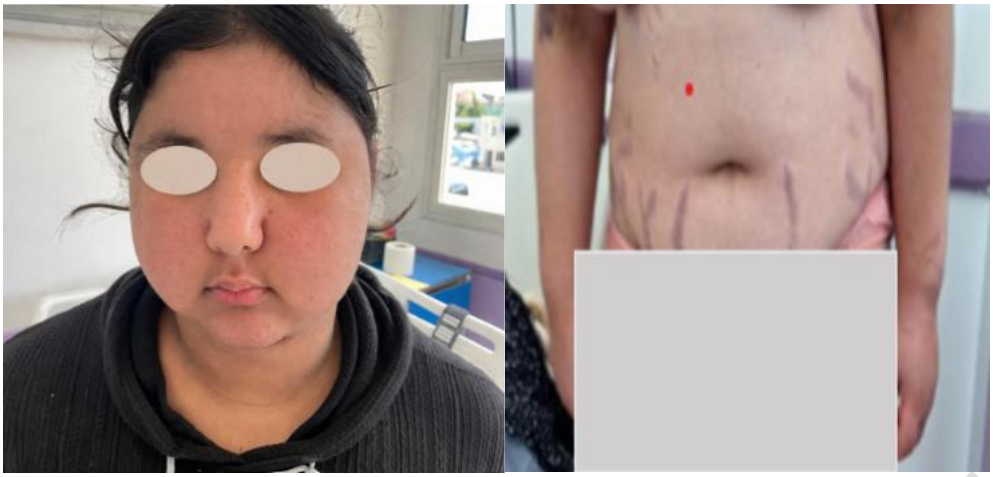

Figure 1: Clinical appearance showing facial plethora and pendulous abdomen

Adrenal computed tomography showed left adrenal enlargement suggestive of hyperplasia, associated with atrophy andmicronodules of the right adrenal gland.

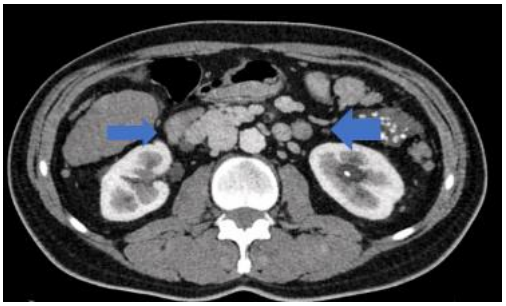

Figure 2: Adrenal computed tomography performed at Hassan II University Hospital in Fez revealed enlargement of theleft adrenal gland consistent with hyperplasia, along with atrophy and micronodular changes of the right adrenal gland.

Ketoconazole was initially prescribed at 200 mg/day, but after 15 days the patient developed adrenal insufficiency, asreflected by a morning cortisol level of 2.6 µg/dL, leading to treatment discontinuation and the introduction ofhydrocortisone replacement at 15 mg/day. Because hypercortisolism remained uncontrolled, ketoconazole wassubsequently reintroduced at a lower intermittent dose in combination with hydrocortisone, according to a block-and-replace strategy, with close clinical and biochemical follow-up. As disease control remained incomplete, left adrenalectomywas eventually performed.

Histopathological examination showed multinodular adrenocortical architecture. The lesion was composed of large cellswith abundant cytoplasm, clear in some areas and eosinophilic in others, with regular hyperchromatic nuclei. No necrosisand no mitotic figures were identified. The overall appearance was consistent with adrenal hyperplasia rather thanadrenocortical carcinoma.

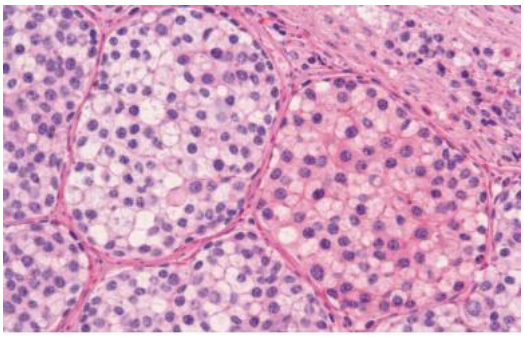

Figure 3: Histopathological examination of the adrenal lesion performed at Hassan II University Hospital, Fez

The postoperative course was favorable. Clinically, the patient showed progressive regression of Cushingoid features,including marked improvement in facial plethora and gradual whitening of the abdominal and thigh striae. Body weightdecreased, and the Ferriman-Gallwey score also improved. Biochemically, urinary free cortisol progressively normalizedunder hydrocortisone replacement. At follow-up, she remained clinically stable, without signs of adrenal decompensation,and continued hydrocortisone at a replacement dose with planned hormonal reassessment.

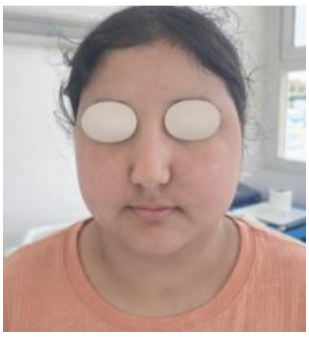

Figure 4: Current clinical appearance after left adrenalectomy

Discussion

The present observation is notable for three reasons: the young age of the patient, the initially cyclic course ofhypercortisolism, and the final diagnosis of multinodular adrenal hyperplasia. Pediatric Cushing syndrome is rare, andACTH-independent adrenal forms account for a minority of cases in adolescence. In this setting, the main differentialdiagnoses usually include cortisol-secreting adrenal tumors, primary pigmented nodular adrenal disease, and more rarelybilateral nodular adrenal hyperplasia [3].

The cyclic nature of the disease probably contributed substantially to the diagnostic delay. Cyclic Cushing syndrome isdefined by recurrent episodes of hypercortisolism separated by periods of spontaneous remission, and both the clinical andbiochemical expression may fluctuate widely. This pattern is well recognized as a major source of diagnostic difficulty. Thehistory in our patient, with repeated symptomatic phases followed by relatively long remissions, fits closely with thisdescription. Although cyclic Cushing syndrome is more often discussed in relation to pituitary disease, it may also occur inadrenal forms, making repeated clinical and hormonal reassessment particularly important [4].

Once ACTH-independent hypercortisolism was established, the adrenal origin became highly likely. In this context, imagingis essential to distinguish between a unilateral secreting lesion and bilateral

nodular disease. In our patient, computedtomography showed asymmetrical adrenal involvement, with predominant left-sided hyperplasia and contralateral atrophywith micronodules. This pattern raised the possibility of a more diffuse nodular adrenal process rather than a simpleunilateral adenoma. Current reviews of adrenal Cushing syndrome in children emphasize that nodular adrenal diseases,although rare, should remain part of the differential diagnosis in young patients with ACTH-independent disease.

The negative Liddle's test argued against primary pigmented nodular adrenal disease, in which a paradoxical increase inurinary free cortisol can sometimes be observed. Although this test has more limited use in contemporary practice, it maystill be informative in selected cases of nodular adrenal disease. In our patient, the absence of a paradoxical responsesupported the possibility of another form of nodular adrenal hyperplasia rather than pigmented micronodular disease.

Histopathology played an important role in consolidating the diagnosis [5]. The adrenal specimen showed multinodularcortical architecture without necrosis or mitotic activity, favoring hyperplasia rather than malignancy. Recent WHOpathological classifications have emphasized the wide spectrum of adrenal cortical nodular proliferations and the need forcareful clinicopathological correlation in their interpretation. In this case, the pathological findings matched the clinical,hormonal, and imaging profile of ACTH-independent nodular adrenal disease.

The medical phase of management also deserves comment. Ketoconazole is a recognized steroidogenesis inhibitor and canbe effective in controlling hypercortisolism, but it may be difficult to titrate in fluctuating disease. In our patient, treatmentrapidly led to adrenal insufficiency, requiring withdrawal and hydrocortisone replacement. This illustrates the narrowtherapeutic window that may be encountered in cyclic or variable forms of Cushing syndrome. Because hypercortisolismpersisted despite subsequent medical adjustment, surgery became the preferred option. The favorable postoperativecourse strongly suggests that the left adrenal gland was the major functional source of cortisol excess, even though imaginghad also shown abnormalities on the contralateral side [6-7].

This case also underlines an important practical point: multinodular adrenal hyperplasia, although uncommon inadolescence, should not be overlooked when evaluating ACTH-independent Cushing syndrome in a young patient. Carefulinterpretation of the clinical history, especially when cyclicity is reported, combined with repeated biochemical testing,high-quality imaging, and histopathological confirmation, remains the most reliable way to reach an accurate diagnosis andguide treatment.

Conclusion

This case illustrates the diagnostic challenge of ACTH-independent Cushing syndrome in an adolescent, particularly whenthe disease initially follows a cyclic course. It shows the value of a careful and methodical approach based on closecorrelation between clinical presentation, endocrine testing, imaging findings, and histopathology. It also reminds us thatmultinodular adrenal hyperplasia, although rare at this age, should be considered in adolescents with adrenal Cushingsyndrome, especially when the radiological pattern is nodular and the disease course is atypical.

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