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RESEARCH ARTICLE

CYCLIC ACTH-INDEPENDENT CUSHING SYNDROME IN AN ADOLESCENT REVEALING MULTINODULAR ADRENAL HYPERPLASIA: A CASE REPORT

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Abstract

Background:ACTH-independent Cushing syndrome is rare in children and adolescents, and multinodular adrenal hyperplasia represents an unusual etiology. When hypercortisolism follows a cyclic pattern, diag nosis may be delayed because hormonal abnormalities can fluctuate over time [1,2].

Case Presentation: We report the case of a 16-year-old girl with Cushing syndrome evolving since the age of 8 years, initially marked by alternating symptomatic phases lasting about 15 days and spontaneo us remissions of nearly 3 months. Over time, the disease became clinically persistent. Hormonal evaluation showed ACTH-independent hypercortisolism with loss of cortisol circadian rhythm, urinary free cortisol elevated to 8.6 times the upper limit of normal, failure to suppress after overnight dexamethasone testing, and low ACTH levels. Adrenal computed tomography revealed predominant enlargement of the left adrenal gland, associated with atrophy and micronodular changes of the right adrenal gland. Initial treatment with ketoconazole resulted in adrenal insufficiency, requiring hydrocortisone replacement, and was later reintroduced at a lower intermittent dose according to a block and replace strategy. Because hypercortisolism remained insuffic iently controlled, left adrenalectomy was performed. Histopathological examination confirmed multinodular adrenal hyperplasia. The postoper ative course was favorable, with progressive clinical improvement and biochemical normalization under hydrocortisone replacement.

Conclusion: This case highlights the diagnostic challenge of cyclic ACTH-independent Cushing syndrome in adolescence and underlines the importance of repeated hormonal assessment, careful imaging interpretation,and histopathological confirmation. Multinodular adrenal hyperplasia should be considered in young patients with atypical or fluctuating adrenal Cushing syndrome [1–4].

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Introduction:-

Cushing syndrome results from prolonged exposure to excessive glucocorticoids and remains an uncommon diagnosis in childhood and adolescence. In pediatric patients, endogenous cases are rare, and after early childhood, ACTH-dependent forms are more frequent than ACTH-independent ones. ACTH-independent adrenal Cushing syndrome in young patients is therefore unusual and may create important diagnostic uncertainty, especially when biochemical activity fluctuates over time [1,5].Cyclic Cushing syndrome is characterized by alternating periods of hypercortisolism and partial or complete remission. The duration of active and inactive phases is highly variable, and this pattern may occur in both ACTH-dependent and ACTH-independent disease. In practice, cyclicity often delays diagnosis because hormonal testing may be performed during a quiescent phase, leading to apparently inconsistent results [2].Among adrenal causes of ACTH-independent Cushing syndrome, unilateral cortisol-producing tumors are the most common, whereas bilateral nodular adrenal diseases are much less frequent. These include primary pigmented nodular adrenocortical disease and bilateral macro- or multinodular hyperplasia. Recent classifications of adrenal cortical proliferations have emphasized the broad spectrum of nodular adrenal disease and the need to correlate pathological findings with clinical and functional data [3,6,7].We report the case of an adolescent girl with ACTH-independent Cushing syndrome that initially followed a cyclic course and 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 essential hypertension, had been followed for Cushing syndrome evolving since the age of 8 years. At disease onset, the course was clearly cyclic, with symptomatic phases lasting approximately 15 days and spontaneous remissions of nearly 3 months. During the last 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 a pendulous abdomen, buffalo hump, and wide striae. There was no melanoderma. Hormonal evaluation supported ACTH-independent Cushing syndrome, showing loss of cortisol circadian rhythm, urinary free cortisol elevated to 8.6 times the upper limit of normal, failure to suppress after the overnight dexamethasone suppression test, and low ACTH levels. These findings were consistent with autonomous adrenal cortisol secretion. The Liddle test was negative.

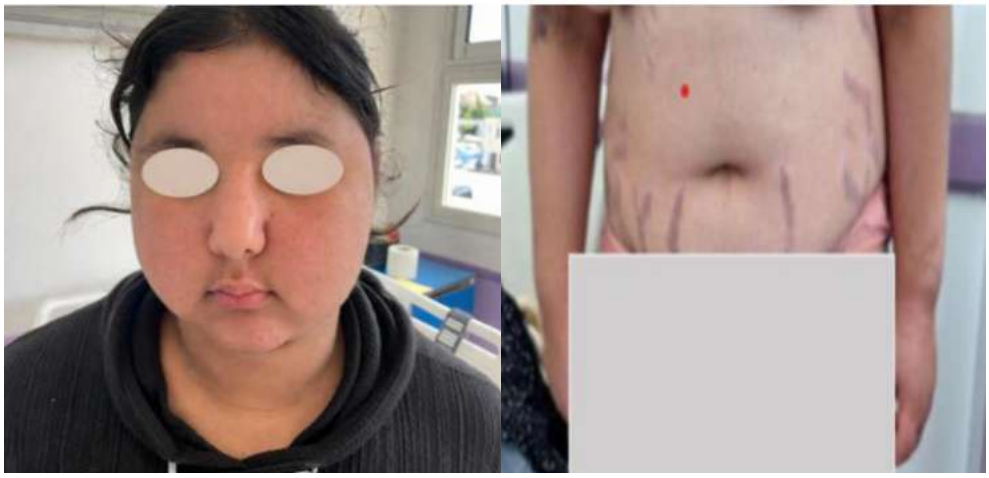

Figure 1:Clinical appearance showing facial plethora and pendulous abdomen.

Adrenal computed tomography revealed left adrenal enlargement suggestive of hyperplasia, associated with atrophy and micronodular changes of the right adrenal gland.

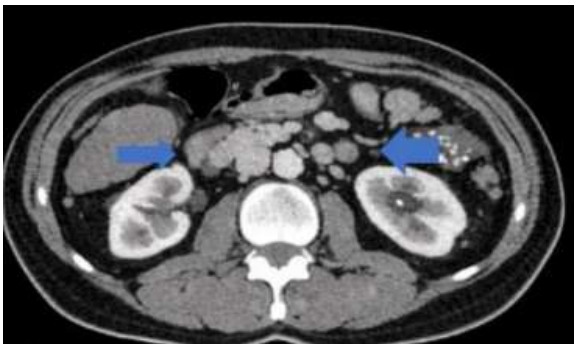

Figure 2:Adrenal computed tomography performed at Hassan II University Hospital in Fez showing enlargement of the left adrenal gland consistent with hyperplasia, along with atrophy and micronodular changes of the right adrenal gland.

Ketoconazole was initially prescribed at 200 mg/day because it was the most accessible steroidogenesis inhibitor in our setting and represented a practical medical option before surgery. After 15 days, the patient developed adrenal insufficiency, with a morning cortisol level of 2.6 µg/dL. Treatment was therefore discontinued and hydrocortisone replacement was introduced at 15 mg/day. Because hypercortisolism remained insufficiently controlled, ketoconazole was subsequently 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 adrenalectomy was eventually performed.Histopathological examination showed multinodular adrenocortical architecture. The lesion was composed of large cells with abundant cytoplasm, clear in some areas and eosinophilic in others, with regular hyperchromatic nuclei. No necrosis or mitotic figures were identified. The overall appearance was consistent with adrenal hyperplasia rather than adrenocortical carcinoma. Quantitative morphometric and immunohistochemical analysis, including Ki-67 index, was not available.

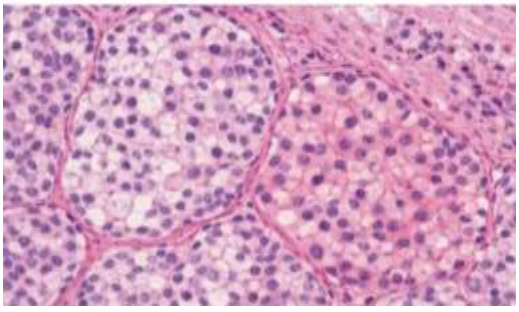

Figure 3: Histopathological examination of the adrenal lesion performed at Hassan II UniversityHospital, Fez

The postoperative course was favorable. Clinically, the patient showed progressive regression of Cushingoid features, including marked improvement in facial plethora and gradual fading of the abdominal and thigh striae. Body weight decreased, and a qualitative improvement in hirsutism was also observed during follow-up. Biochemically, urinary free cortisol progressively normalized under 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. The right adrenal micronodules have not required intervention to date.

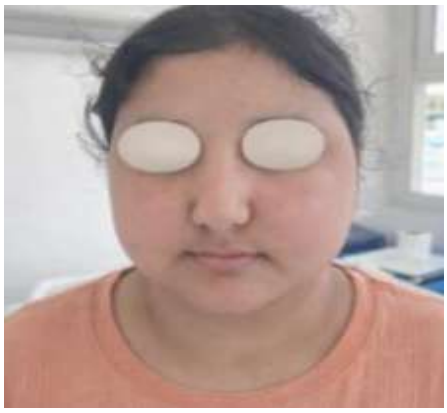

Figure 4: Current clinical appearance after left adrenalectomy

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Discussion:-

The present observation is notable for three reasons: the young age of the patient, the initially cyclic course of hypercortisolism, and the final diagnosis of multinodular adrenal hyperplasia. Pediatric Cushing syndrome is rare, and ACTH-independent adrenal forms account for only a minority of cases in adolescence [1,5]. In this setting, the main differential diagnoses usually include cortisol-secreting adrenal tumors, primary pigmented nodular adrenocortical disease, and, more rarely, bilateral nodular adrenal hyperplasia [1,6,7].The cyclic nature of the disease probably contributed substantially to the diagnostic delay. Cyclic Cushing syndrome is defined by recurrent episodes of hypercortisolism separated by periods of spontaneous remission, and both clinical and biochemical expression may fluctuate widely. This pattern is a well-recognized source of diagnostic difficulty. The history in our patient, with repeated symptomatic phases followed by relatively long remissions, fits closely with this description. During quiescent phases, differential diagnoses may include exogenous causes, pseudo-Cushing states, pituitary-dependent disease with intermittent hormonal secretion, or initially non-contributive adrenal disease. Repeated endocrine reassessment was therefore essential to establish the diagnosis. Although cyclic Cushing syndrome is more often discussed in relation to pituitary disease, it may also occur in adrenal forms, making repeated clinical and hormonal reassessment particularly important [2,4].

Once ACTH-independent hypercortisolism was established, an adrenal origin became highly likely. In this context, imaging is essential to distinguish between a unilateral secreting lesion and bilateral nodular disease. In our patient, computed tomography showed asymmetrical adrenal involvement, with predominant left-sided hyperplasia and contralateral atrophy with micronodules. This pattern raised the possibility of a diffuse nodular adrenal process rather than a simple unilateral adenoma. Nodular adrenal diseases, although rare, should remain part of the differential diagnosis in young patients with ACTH-independent disease [1,6,7].A negative Liddle test made primary pigmented nodular adrenocortical disease less probable, but did not definitively rule it out because of the test's limited diagnostic accuracy. Formal exclusion of PPNAD would require genetic testing, particularly for PRKAR1A mutations [7]. Histopathological examination then played a key role in establishing the diagnosis. It showed multinodular cortical architecture without necrosis or mitotic figures, favoring adrenal hyperplasia over malignancy. These pathological findings were in agreement with the imaging features, notably the nodular adrenal pattern, and supported the diagnosis of ACTH-independent nodular adrenal disease [3,6].

The medical phase of management also deserves comment. Ketoconazole is a recognized steroidogenesis inhibitor and can be effective in controlling hypercortisolism, but it may be difficult to titrate in fluctuating disease. In our patient, treatment rapidly led to adrenal insufficiency, requiring treatment withdrawal and hydrocortisone replacement. This illustrates the narrow therapeutic window that may be encountered in cyclic or variable forms of Cushing syndrome. Because hypercortisolism persisted despite subsequent medical adjustment, surgery became the preferred option. The favorable postoperative course strongly suggests that the left adrenal gland was the major functional source of cortisol excess, even though imaging had also shown abnormalities on the contralateral side [4].

Given the young age at onset, the bilateral nodular adrenal abnormalities, and the history of parental consanguinity, the possibility of an underlying genetic predisposition may reasonably be raised. In rare bilateral adrenal hyperplasias, germline alterations involving genes such as ARMC5, PRKAR1A, or GNAS may be considered depending on the clinical and pathological context. Genetic testing was not performed because of limited availability, which represents a limitation of this report [6–8].

This case underlines an important practical point: multinodular adrenal hyperplasia, although uncommon in adolescence, should not be overlooked when evaluating ACTH-independent Cushing syndrome in a young patient. Careful interpretation 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 and guide treatment.

Conclusion:-

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

Clinical Pearl:

In adolescents with variable or intermittent cushingoid manifestations, repeated endocrine assessment is essential, since cyclic hypercortisolism may conceal an ACTH-independent adrenal etiology and complicate timely diagnosis.

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