International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Cushing's Syndrome Revealing Malignant Adrenocortical Carcinoma in a Child: A Case Report with Review of the Literature

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Abstract: ***Malignant adrenocortical carcinoma is a rare tumor in children with a female predominance. Diagnosis is based on a combination of clinical, biological, radiological, and histopathological findings. Complete tumor resection is the treatment of choice, often supplemented by chemotherapy. The prognosis of this tumor is poor due to its advanced stage at diagnosis. This report presents the case of a 15 - year - old girl admitted with Cushing's syndrome, in whom biological, radiological, and histopathological investigations confirmed the diagnosis of malignant adrenocortical carcinoma.***

Keywords: Malignant adrenocortical carcinoma, Cushings syndrome, pediatric oncology, adrenal tumor, surgery

1. Introduction

Adrenal cortical tumors are an infrequent occurrence in children. Unlike adults where histological criteria for malignancy are well - defined, pediatric cases present a diagnostic challenge. The clinical course often serves as the most reliable indicator of tumor behavior.

2. Observation

This is a 15 - year - old girl, born to non - consanguineous parents, with no significant medical history. For the past six months, she has been complaining of left upper quadrant abdominal pain, exacerbated by exertion, along with the onset of hirsutism, facial puffiness, acne, and headaches. Physical examination revealed a left lumbar mass and Cushing's syndrome with blood pressure of 180/90 mmHg, controlled with antihypertensive medication. Laboratory tests showed elevated 8 AM cortisol levels at 82 ng/mL, elevated 24 - hour urinary free cortisol at 621 nmol/24h, elevated 17 - hydroxyprogesterone at 19.8 mmol/L, and elevated testosterone at 64.39 nmol/L. Abdominal ultrasound showed a left adrenal mass, confirmed by a subsequent thoraco - abdomino - pelvic CT scan (Figure 1) revealing a 95x75x95mm heterogeneous left adrenal mass without evidence of distant metastases**.**

The patient underwent surgical resection of the adrenal tumor with regional lymph node dissection. Histopathology confirmed a malignant adrenocortical carcinoma with a high - grade histology (Weiss score 6). Adjuvant chemotherapy with carboplatin and etoposide was initiated.

The patient demonstrated normalization of hormonal levels following surgery. Six - month follow - up imaging and hormonal studies showed no evidence of disease recurrence.

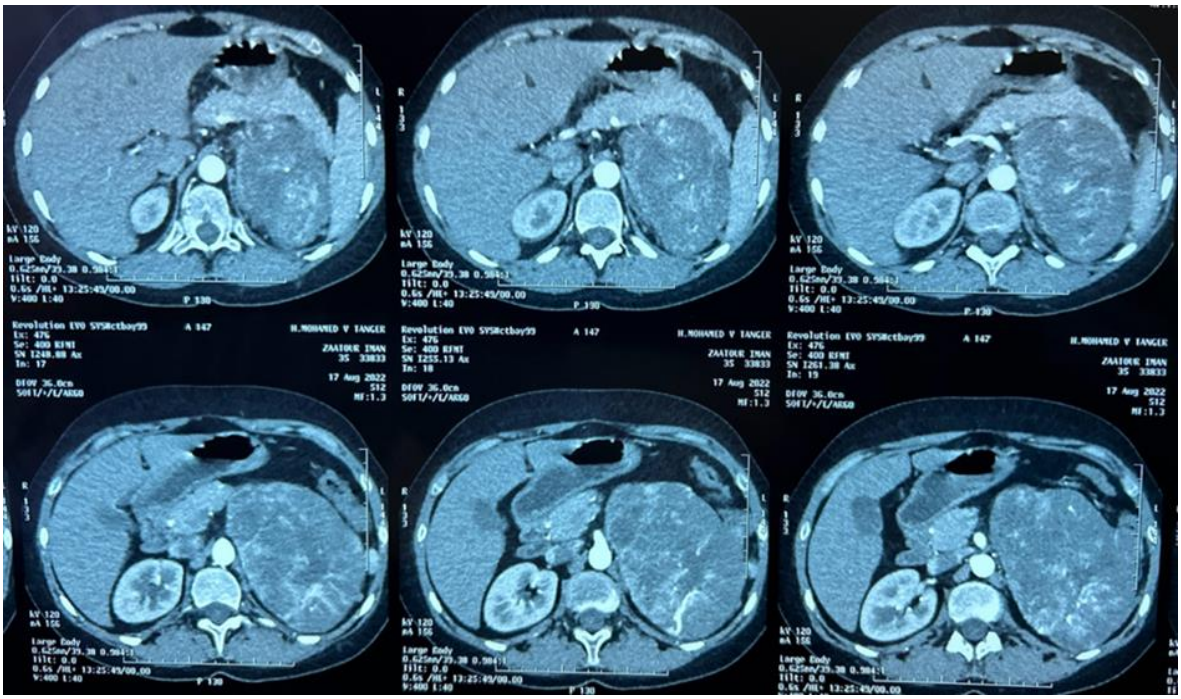

Figure 1: Abdominal CT scan showing a left adrenal mass

3. Discussion

Malignant adrenocortical carcinoma is an uncommon tumor of the adrenal cortex. It accounts for 1.3% of pediatric cancers and 0.2% of all childhood malignancies (1). The annual incidence is estimated at one to two cases per million children. The age distribution is bimodal, with peaks in early childhood and in adults aged 40 - 50 years.

Adrenocortical carcinoma can occur sporadically or be associated with familial cancer syndromes such as Li - Fraumeni syndrome, multiple endocrine neoplasia type 1, or Wiedemann - Beckwith syndrome (2). Clinical manifestations are variable and depend on the hormonal profile of the tumor, with secretory tumors accounting for 90% of cases (4).

According to Leblond et al., the clinical manifestations of adrenocortical carcinoma in the pediatric population include:

- Virilisation or pseudopuberty (76%),
- Cushing's syndrome (15%),
- Gynecomastia and pseudopuberty (5%).
- An abdominal mass can be palpated in approximately 50% of cases.
- Hypertension is also observed in 20 - 50% of cases, according to different series, and may be related to the overproduction of steroid hormones or secondary to potential compression of the renal vessels by the tumor. (5.6)

The following hormonal blood tests should be performed in patients suspected of adrenal cortical tumor (7):

- Cortisol (post - dexamethasone suppression, free urinary)
- Plasma ACTH
- Sex steroids (testosterone, estradiol, 17 - hydroxyprogesterone, DHEA - S, delta - 4 - androstenedione)
- Aldosterone/renin ratio (in hypertensive patients with hypokalemia)

These hormonal tests confirm the origin of the lesion and its malignant potential. Preoperative evaluation with these tests is essential to prevent inadequate management of adrenal insufficiency during surgery.

Urinary hormone measurements, including 17 - ketosteroids, 17 - hydroxycorticosteroids, and free cortisol, are essential for establishing a pretreatment baseline and for monitoring for disease recurrence (8).

Abdominal CT and MRI, with or without contrast, are the primary imaging modalities used to characterize adrenal masses. These studies help to identify features suggestive of malignancy, assess disease extent, and monitor treatment response. However, neither modality can reliably differentiate adenomas from carcinomas.

Typically, the tumor is large and heterogeneous, with areas of hemorrhage, necrosis, or calcification. It demonstrates a density greater than 10 HU and peripheral enhancement (Figure 2).

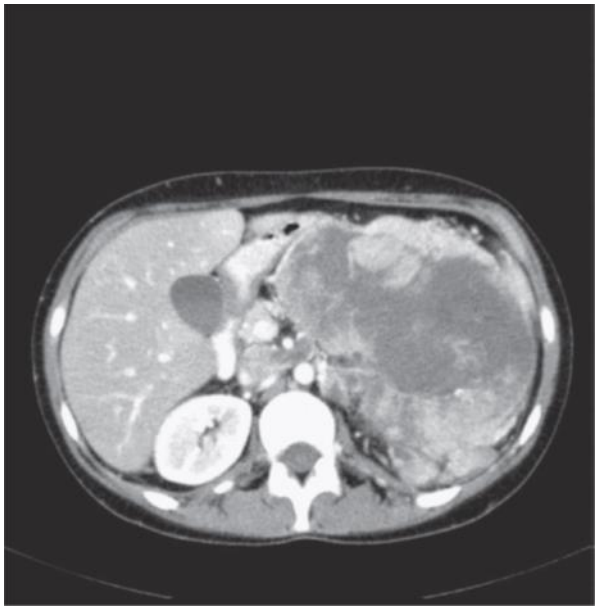

Figure 2: Axial CT scan obtained after intravenous contrast administration in a 16 - year - old girl with metastatic adrenocortical carcinoma. The scan demonstrates a large, heterogeneous retroperitoneal mass, measuring 15×10×18 cm, with areas of necrosis. The mass is displacing adjacent organs. (5)

Positron emission tomography using 18F - fluorodeoxyglucose (FDG - PET) allows for differentiation between benign and malignant tumors (9) and can detect distant metastases. FDG - PET is also valuable in monitoring patients (8).

Histopathological examination, utilizing the Weiss score and immunohistochemistry for markers such as Ki - 67, IGF II, α - inhibin, calretinin, synaptophysin, melan - A, and SF1 (steroidogenic factor 1), is crucial for diagnosis. However, unlike adult tumors, the various proposed multiparametric systems have limited ability to predict the prognosis of pediatric tumors (10, 11, 12).

Complete surgical removal of the tumor is the primary treatment, usually performed via laparotomy in children given the tumor's friable nature. The incidence of intraoperative tumor rupture has been reported as high as 20% in initial pediatric surgeries, and can exceed 40% for local recurrences. (4, 13).

Zancanella et al. conducted a prospective study involving 11 children treated with a combination of cisplatin, etoposide, doxorubicin, and mitotane, resulting in two complete responses and five partial responses (14). This therapeutic regimen is the standard of care in pediatric patients.

Radiotherapy has been considered ineffective against adrenocortical carcinomas for a long time. It is indicated in patients at high risk of local recurrence following incomplete resection, and for palliative care, at doses above 40 Gy. However, this is not recommended in young children due to potential side effects. Moreover, radiotherapy can induce radiosensitive tumors in children with a TP53 gene mutation (5).

The evolving field of targeted therapies has led to the investigation of novel agents for the treatment of adult adrenocortical carcinoma. These include IGF - 1R - targeted antibodies, tyrosine kinase inhibitors such as sunitinib, and radiolabeled agents like iodine - 131 - labeled mitotane. While these therapies have shown some promise in adult populations, there is a paucity of clinical data evaluating their efficacy and safety in pediatric patients with adrenocortical carcinoma. (15)

The most significant prognostic factors for pediatric adrenocortical tumors are primarily clinical, with biological factors contributing to a lesser extent. Analysis of multiple patient cohorts, such as the IPACTR study of 254 children, has revealed several prognostic indicators. Favorable prognostic factors include younger age at diagnosis (less than three years), smaller tumor size (less than 200g), presence of virilization, and complete surgical resection with subsequent normalization of hormonal levels. (4).

4. Conclusion

Malignant adrenocortical carcinoma is a rare entity with a poor prognosis. Diagnosis is often based on a combination of clinical, biological, radiological, and histopathological findings. Radical adrenalectomy remains the gold standard for localized disease, often complemented by chemotherapy, while targeted oncogenic therapies are awaited.

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