Adrenocortical carcinoma (ACC) with massive liver metastases in a 4-year-old female patient: the significance of chemotherapy and imaging studies in treatment and diagnosis – a case report

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ABSTRACT:

**Background:** Adrenocortical carcinoma (ACC) is a retroperitoneal tumour, accounting for less than 0.2% of all malignancies in children. In pediatric patients, the most common clinical presentation is virilisation, either isolated or in combination with hypercortisolism.

**Case report:** A 4-year-old girl was admitted to the hospital for diagnostic evaluation of precocious puberty and features of hypercorticism. Ultrasonography revealed a heterogeneous neoplastic lesion between the left kidney and spleen. Computed tomography (CT) scan confirmed a pathological mass in the left adrenal region. The urine steroid profile was suggestive of adrenocortical carcinoma. The patient was qualified for surgery. Histopathological examination confirmed the diagnosis. A PET scan performed a few months later showed a metabolically active lesion in the left lobe of the liver. Due to the suspicion of a metastatic focus, it was proposed to implement systemic treatment, to which the patient's parents did not agree. After 15 months of no treatment and oncological follow-up, the girl was referred to the ED with symptoms of progression of the neoplastic process. In the face of a renewed lack of consent to the inclusion of treatment, the patient was referred to a home hospice, where she died a short time later.

**Conclusions:** In the pediatric population, adrenocortical carcinoma is a rare neoplasm with a very poor prognosis. Prompt diagnosis enables early identification of the primary tumour and implementation of appropriate treatment. Imaging examinations are crucial in order to assess the size of the tumour, the extent of local invasion and the presence of potential metastases.

**Key words:** adrenocortical carcinoma; Cushing's syndrome; computed tomography

INTRODUCTION:

Adrenocortical Carcinoma (ACC) is a rare malignant tumor with an incidence rate of 0.7-2.0 cases per million population per year. It can occur at any age, with two peaks in incidence: earlier in the first decade of life and later between the ages of 40 and 50. ACC is more common in women (55-60%) (Kebebew et al., 2006) [1, 2]. Large adrenal tumors with a diameter of more than 5 cm are usually easy to detect. Such tumors are usually located above
the upper pole of the kidney and extend to the anterior surface of this organ, sometimes displacing the kidney downward. Adrenocortical carcinoma is often a lesion of considerable size. Computed tomography (CT) and magnetic resonance imaging (MRI) allow precise localization of the tumor and evaluation of its features. Features that suggest malignant character of a lesion are: diameter greater than 5 cm, irregular outlines, areas of necrosis and calcification and strong contrast enhancement [3].

This case report presents the clinical journey of a 4-year-old female patient diagnosed with adrenocortical carcinoma (ACC). The case highlights the importance of early detection, timely imaging, and adherence to suggested treatment protocols in managing ACC, a rare and aggressive malignancy. Understanding the consequences of delayed intervention may provide valuable insights for future clinical decisions and emphasize the significance of patient compliance in improving outcomes.

**CASE REPORT:**

A 4-year-old girl presented to the hospital for diagnostic evaluation for precocious puberty. The symptoms that led the parents to seek medical attention were features of Cushing's syndrome, virilization of external genitalia with the presence of pubic hair, and a palpable, non-mobile mass on the left side of the abdomen. An ultrasound was performed, in which a heterogeneous lesion with slightly increased echogenicity and approximate dimensions of 121 x 100 x 141 mm was found between the left kidney and the spleen. The lesion displaced adjacent organs (Fig.1).

![Fig. 1. Abdominal ultrasound. Heterogeneous neoplastic lesion (a) with single vascular flow signals (b) in the immediate vicinity of the left kidney, modelling its upper pole (c) [red arrow].](image-url)
Contrast enhanced CT scans of the chest and abdomen were performed, which confirmed a significantly sized pathological mass in the anatomical location of the left adrenal gland, measuring approximately 10 cm in length, 13.5 cm in anterior-posterior diameter, and 12 cm in craniocaudal diameter (Fig.2). The described tumor slightly exceeded the midline and was adjacent to the aorta, discretely molding its branches - the celiac trunk and upper mesenteric artery, and distinctly molding and displacing the left renal artery. The tumor showed calcification in the lower part. CT contrast enhancement revealed small tortuous blood vessels within the mass and significant heterogeneous enhancement mainly in peripheral areas, leaving large irregular low-density areas inside, probably representing central necrotic areas. The tumor caused significant mass effect on neighboring organs – displacing pancreas, stomach, spleen and left kidney. In segment VI of the liver, a focal hypodense lesion measuring 11 x 13 mm with centripetal fill-in post contrast administration was observed with a suggestion of a hepatic hemangioma (Fig.3). A contrast-enhanced chest CT scan showed no abnormalities.

Fig. 2. Abdominal CT scan. Pathological mass in the anatomical location of the left adrenal gland displacing left kidney. In the central part, areas of necrosis are visualized [red arrow] (a) - frontal plane, (b) - sagittal plane.
Laboratory tests were notable for very high blood androgen concentrations of testosterone, dehydroepiandrosterone sulphate (DHEA-SO4) and androstendione, hypercortisolemia, markedly elevated lactate dehydrogenase (LDH) activity and reduced adrenocorticotropic hormone (ACTH) levels (Table 1). Steroid profile in 24-hour urine collection determined by GC-MS (Gas Chromatography Mass Spectrometry) was indicative of adrenocortical carcinoma, secreting cortisol and androgens, showing pronounced enzymatic disorders - deficiency of 3β-HSD (3β-hydroxysteroid dehydrogenase), 11β-OH (11β-hydroxylase), and 21-OH (21-hydroxylase), and elevated 6β-OHF (6β-hydroxycortisol) excretion.

**Table 1. Laboratory test result**

<table>
<thead>
<tr>
<th>NAME OF TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESTOSTERONE</td>
<td>1 366,00 ng/dl</td>
<td>6-82 ng/dl</td>
</tr>
<tr>
<td>DHEA-SULFATE</td>
<td>1 000,00 µg/dl</td>
<td>0,47-19,4 µg/dl</td>
</tr>
<tr>
<td>PROGESTERONE</td>
<td>2,30 ng/ml</td>
<td>0-0,99 ng/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>0,41 U/l</td>
<td>0,2-11,1 U/l</td>
</tr>
<tr>
<td>LH</td>
<td>&lt;0,100 U/l</td>
<td>0-0,5 U/l</td>
</tr>
<tr>
<td>AFP</td>
<td>2,99 ng/ml</td>
<td>0-4,2 ng/ml</td>
</tr>
<tr>
<td>CORTISOL</td>
<td>21,36 µg/dl</td>
<td>6,2-19,4 µg/dl</td>
</tr>
<tr>
<td>LDH</td>
<td>3 184 U/l</td>
<td>0-615 U/l</td>
</tr>
<tr>
<td>ACTH</td>
<td>3,82 pg/ml</td>
<td>7,2-63,6 pg/ml</td>
</tr>
<tr>
<td>ANDROSTENEDIONE</td>
<td>&gt;30 ng/ml</td>
<td>0,3-3,33 ng/ml</td>
</tr>
</tbody>
</table>
Due to suspected adrenocortical carcinoma, the patient was referred for surgical treatment. The tumor along with the left kidney was resected macroscopically radically. The lesion was removed from the anterior surface of segment VI of the liver. Lymph nodes located between the aorta and inferior vena cava were also taken for histopathological analysis. The result of the examination indicated adrenocortical carcinoma with strongly expressed features of histological malignancy (high mitotic activity, atypical mitoses, necrosis and pleomorphism). Features of angioinvasion were found. The tumor was surrounded by fibrous and adipose tissue, which constituted the resection margin. The kidney adjacent to the tumor showed no abnormalities. No metastasis was observed in the surrounding lymph nodes. Histopathologic evaluation confirmed removed hepatic lesion as cavernous hemangioma. The final diagnosis was adrenocortical carcinoma stage II, T2N0, R0.

The postoperative course was complicated by lymph leakage, symptoms of pancreatitis and pneumonia. Two months later a laparotomy was performed, during which multiple intestinal adhesions were released. Due to the accumulation of fluid in the pleural cavity on the left side, a drainage of the pleural cavity was applied. The patient's general condition improved after the procedure, and the pleural drain was removed without further postoperative complications. It was proposed to implement Mitotan treatment, to which the patient's parents did not agree.

A few months later a PET scan was performed, which showed a metabolically active lesion in the liver. The finding was confirmed by an abdominal MRI showing focal lesion in the left liver lobe measuring approximately 12 x 11 x 11 mm, hypointense on T1-weighted sequence, hyperintense on T2-weighted sequence, showing diffusion restriction on DWI sequence. The lesion showed non-intense, heterogeneous enhancement after contrast agent administration. The image was suggestive of a metastatic change (Fig.4). The parents rejected the proposed treatment and did not report to the Clinic.

Fig. 4. Abdominal MR. Transverse plane. Metastatic focal lesion in the left lobe of the liver - hypointense on T1-weighted sequence (a), showing diffusion restriction on DWI sequence (b).
After 15 months without treatment and oncological follow-up, the patient was referred to the ED (Emergency Department) with symptoms of progression of the cancer process. On readmission to the hospital, she was found to have features of Cushing's syndrome, skin lesions consistent with acne on the face, chest and torso. The patient complained of abdominal pain, and there was a significant deterioration of her well-being. Physical examination described a tumor extending from the left to right midclavicular line, reaching up to about 2.5 cm above the umbilical line.

An abdominal MRI scan showed an enlarged liver with a pathological mass measuring approximately 196 x 112 x 128 mm (RLxAPxCC), encompassing segments 1, 2, 3, 4a, 4b and partially 5. Over the course of 15 months, the lesion's transverse dimension increased from 1 cm to 20 cm (Fig.5). The lesion showed restricted diffusion and heterogeneous, relatively intense contrast enhancement. The MR image supported the presence of a metastatic change with signs of a malignant thrombus in branches of the portal vein. The mass had significant mass effect on adjacent organs.

Fig. 5. Abdominal MR. Transverse plane. Pathological mass in left liver lobe consistent with massive metastasis.

In 15 months, the transverse dimension of the lesion increased from 1 cm (a) to 20 cm (b).

The father was presented with a systemic treatment option, including chemotherapy with mitotane, NN-I (vincristine, ifosfamide, adriamycin) and NN-II (carboplatin, etoposide), but decided not to implement the proposed therapy. The patient was referred to a home hospice, where she died a short time later.

**DISCUSSION:**

The aim of this study is to highlight the importance of postoperative therapy in reducing the risk of recurrence and prolonging patient survival. The natural course of recurrence after surgery remains uncertain, but even in cases of complete resection, the rate of local recurrence
remains significant, ranging from 19% to 34%, depending on the stage of the tumor. For this reason, follow-up treatment, which includes Mitotane and irradiation of the tumor locus, can be used after surgery. Mitotane is a derivative of the insecticide dichlorodiphenyltrichloroethane (DDD) with adrenolytic and cytotoxic effects. Notably, mitotane metabolites inhibit several enzymes in the adrenal steroidogenesis pathway, mainly targeting the cholesterol side-chain cleaving enzymes CYP11A1 and CYP11B1 [2]. Mitotane inhibits steroidogenesis and exerts direct adrenolytic effects, leading to sustained atrophy of the adrenal cortex's zona fasciculata and reticularis [4,5]. Mitotane has been shown to improve treatment outcomes in the pediatric population with intermediate-risk ACC when given for more than 6 months and reaching therapeutic levels (greater than 14 mg/l) [6,7]. Furthermore, it has been shown to improve treatment outcomes in children with stage III and IV ACC, although it is poorly tolerated [8,9]. A review of various studies showed that the objective response rate is at most 24% [(De Francia et al., 2012)(10)]. The first international randomized trial on locally advanced and metastatic adrenocortical carcinoma (FIRM-ACT) included 304 patients with metastatic ACC. It compared the combination of Mitotane with etoposide-cisplatin-doxorubicin (M-EDP) to mitotane-streptozotocin (M-Sz) as first or second-line treatment. M-EDP demonstrated better progression-free survival and objective response rate compared to M-Sz (5.0 vs. 2.1 months, 23.2 vs. 9.2%), although no significant difference in overall survival was observed [(Fassnacht et al., 2012) (11)]. Based on these findings, M-EDP is considered a first-line therapy for patients requiring cytotoxic treatment [2].

In children with ACC, the 5-year survival rate ranges from 30% to 70%, depending on the disease's form [12-14]. Outcomes for patients with metastatic disease are poor, with a 5-year survival rate estimated at less than 20% [6,15,16,12,17]. Prognosis in pediatric ACC is highly variable and challenging to predict in clinical practice [9,18]. Current guidelines for adrenocortical carcinoma treatment in children are based on adult guidelines. The European Cooperative Study Group for Pediatric Rare Tumours has published consensus guidelines for the diagnosis and treatment of pediatric adrenal cortex tumors, based on adult guidelines and data [12]. Surgery is the primary form of therapy, with aggressive surgical approaches recommended when feasible [19]. Mitotane is a commonly used adjunctive therapy after complete ACC resection in the adult population and is approved for ACC treatment [9,20]. Furthermore, a retrospective analysis of 177 adrenal cortex cancer patients showed significant
improvement in recurrence-free survival among those who received adjuvant Mitotane therapy [20].

Michalkiewicz et al. established a pediatric ACC registry and provided a descriptive analysis of 254 patients registered in the International Paediatric Adrenal Tumour Registry. The registry included patients under 20 years of age with recently diagnosed or previously treated ACC. The most common symptom (84.2%) was virilisation. Cushing's syndrome without virilisation was rare (5.5%). Tumours were completely removed in 83% of patients. Patients with metastatic or residual disease received mitotane, cisplatin, etoposide and/or doxorubicin and, less frequently, radiotherapy. After a median follow-up of 2 years and 5 months, 157 patients (61.8%) survived without disease and 97 patients (38.2%) died. The estimated 5-year event-free survival was 54.2%. Childhood ACC occurs predominantly in females and almost always presents with clinical symptoms. Complete resection is required for cure. Residual or metastatic disease is associated with a poor prognosis [12].

Massimo Terzolo et al. conducted a retrospective analysis involving 177 patients who underwent radical surgery for adrenocortical carcinoma at 8 centres in Italy and 47 centres in Germany between 1985 and 2005. The adjuvant Mitotane was given to 47 Italian patients after radical surgery (Mitotane group), while 55 Italian patients and 75 German patients (control groups 1 and 2, respectively) did not receive adjuvant treatment after surgery. In summary, it was found that recurrence occurred in 23 patients in the mitotane group (48.9%), 50 in control group 1 (90.9%) and 55 in control group 2 (73.3%). Mitotane treatment was associated with longer recurrence-free survival compared to both control groups. Median recurrence-free survival was 42 months in the mitotane-treated group, 10 months in control group 1 (p<0.001) and 25 months in control group 2 (p=0.005) [20,21].

**CONCLUSIONS:**

1. The prompt diagnosis and immediate implementation of appropriate treatment are of paramount importance.
2. Imaging studies enable the assessment of tumor size, extent of local invasion, and the presence of potential metastases.
3. Treatment options vary based on the disease stage and may include surgical tumor resection, mitotane, cisplatin/doxorubicin/etoposide combination therapy.
4. Current treatment algorithms for pediatric patients with adrenocortical carcinoma (ACC) are based on studies conducted in adult populations, which necessitates the development of distinct criteria for the pediatric patient group.

5. Postoperative mitotane therapy can be an effective treatment method that extends the survival period after surgery and reduces the risk of disease recurrence.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.
REFERENCES:


