Case Report

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A Rare Paediatric Adrenocortical Carcinoma with Aggressive Clinical Course

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Abstract

Adrenocortical carcinomas are among the rarest and most aggressive paediatric endocrine neoplasms. We report a case of a functional adrenocortical carcinoma in a 6-year and 7-month-old female who initially presented with hypertensive encephalopathy, later progressing to overt Cushing syndrome with refractory hypertension. Given the presence of distant metastases, the patient was commenced on neoadjuvant chemotherapy and mitotane. Genetic testing for *TP53* to evaluate Li-Fraumeni syndrome was declined. Despite initial response to the treatment, the disease remained refractory, and the patient succumbed after seven months of therapy.

Key words: paediatrics, Cushing Syndrome, adrenocortical carcinoma, antineoplastic agents, hormonal, mitotane, ketoconazole

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy of the adrenal gland, associated with an unfavourable prognosis. In paediatric populations, adrenocortical tumours are exceedingly uncommon, representing only 0.2% of all childhood cancers with an annual incidence estimated at 0.3 cases per million individuals.[1] It commonly occurs within the first five years of life, with a median age of diagnosis between 3 and 4 years, and a smaller secondary peak during adolescence. A female predominance is reported, with a reported female-to-male ratio of 1.6:1.[2]

ACC presents with a broad spectrum of clinical manifestations, most commonly virilization, Cushing syndrome or a combination of both. It is strongly associated with constitutional genetic abnormalities, particularly *TP53* gene mutations, which are implicated in approximately two-thirds of cases.[3,4] The fetal zone of the adrenal cortex is thought to be especially vulnerable to adenoma or carcinoma formation due to the loss of *p53* function. Notably, the endemic *TP53* R337H germ line mutation in Southern Brazil significantly increases the incidence of paediatric adrenocortical tumours there, with rates estimated to be at least 15 times higher than in other regions.[5,6]

Distant metastases and large tumour volume remain the most critical adverse prognostic factors, underscoring the poor outcomes often associated with this malignancy.[7]

We present a case of functional adrenocortical carcinoma in a 6-year and 7-month-old female who initially presented with hypertensive encephalopathy and hypokalaemic hypochloraemic metabolic alkalosis. Ten months later, she then presented with overt Cushing syndrome, refractory hypertension, virilization, extensive fungal skin infection and severe back pain caused by multiple vertebral compression fractures. This case underscores the educational value of recognizing early the evolving clinical manifestations of paediatric ACC, as timely diagnosis is crucial for optimizing management and improving prognosis.

CASE

The female patient first presented to a health clinic at age 5 years and 9 months with a chief complaint of worsening facial acne over a period of eight months. During the consultation, she was incidentally found to be hypertensive, with a blood pressure reading of 185/128 mmHg. She was subsequently referred to a district hospital for further evaluation. Her parents denied any history of rapid weight gain or features suggestive of virilisation. On initial assessment, her weight and height were at the 25th percentile. Clinical examination revealed facial acne and hirsutism, but no clitoromegaly. Within the first 24 hours of hospitalization, she developed multiple episodes of seizures, necessitating intubation for airway protection. An urgent brain CT scan was performed, which revealed no evidence of acute intracranial haemorrhage or meningeal enhancement.

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Blood investigations revealed hypochloraemic metabolic alkalosis with hypokalaemia, with a pH of 7.50, HCO3 of 39 mmol/L and potassium of 2.1 mmol/L. The patient was managed symptomatically with oral Captopril (5 mg TDS) and Potassium Chloride. No abdominal ultrasound was performed at that stage. She was successfully extubated after 24 hours and discharged in stable condition. However, she subsequently failed to attend her scheduled outpatient follow-up appointments.

Ten months later, the patient presented to the same health clinic with complaints of worsening facial acne and, on this occasion, was referred to our tertiary centre for evaluation of suspected Cushing syndrome. Following her earlier discharge from the district hospital, antihypertensive medications had not been continued, and blood pressure monitoring was not performed, likely due to a limited understanding of her illness. During this period, she had gained 12 kg without any documented increase in height. She had no pubic hair development or clitoromegaly. There was no history of exogenous steroid use. Family history was notable only for breast carcinoma in her maternal aunt, with no other relevant hereditary conditions.

On examination, she was found to be hypertensive with a blood pressure of 180/127 mmHg and a heart rate of 124 beats per minute. She exhibited central obesity with disproportionately thin limbs. Her BMI was 30.2 kg/m^2, with a height of 106 cm (<3rd percentile) and a weight of 34 kg (>97th percentile). She appeared plethoric with extensive pustular acne lesions and hirsutism, but there was no evidence of clitoromegaly (Figure 1). Additional findings included multiple purplish striae, generalised fungal skin infections and a vague palpable mass in the left abdomen. She also demonstrated proximal muscle weakness and tenderness of the spine.

Table 1. Investigations at diagnosis

Investigations	Results	Normal Range [Age Specific]
Serum cortisol (diurnal)	1045.0 nmol/L (6 am), 1057.0 nmol/L (12 mn)	250 – 550 nmol/L <50 nmol/L
24Hour urine cortisol	689.55 nmol/24Hr	<50 nmol/24Hr
Serum ACTH	0.3 pmol/L	1.6 – 13.9 pmol/L
Testosterone	33.41 nmol/L	<0.24 – 0.69 nmol/L
Serum DHEA-S	>27 umol/L	<1 umol/L
Renin	>550 mU/L	5.4 – 30 mU/L (Supine)
Aldosterone	983.50 pmol / L	<1108 pmol/L (Supine)
Thyroid function test	TSH 0.075 mIU/L Free T4 16.19 pmol/L	0.47 – 3.41 mIU/L 11.4 – 17.6 pmol/L
HbA1c	5.2%	<5.7 %

Hormonal investigations demonstrated a non-ACTH-dependent hypercortisolism with hyperandrogenism (Table 1). The abdominal ultrasound revealed a large heterogeneous mass in the left suprarenal region, multiple liver lesions and bilateral medullary nephrocalcinosis. Subsequent computed tomography of the thorax, abdomen and pelvis (CT TAP) confirmed the above findings. The large lobulated, heterogeneously enhancing left adrenal mass (8.1 x 9.3 x 8.7 cm) caused significant mass effect, including inferior displacement of the left kidney and resulting in left renal vein thrombosis (Figure 2). Additional findings included multiple lung nodules and liver lesions, consistent with distant metastases. Her lateral spine X-ray demonstrated multiple vertebral compression fractures and generalised osteopenia (Figure 3). A formal echocardiogram revealed left ventricular hypertrophy. However, the patient had no evidence of hypertensive retinopathy and she remained euglycaemic. Her blood pressure was controlled with four antihypertensive medications (Captopril, Prazosin, Amlodipine and Spironolactone) at near-maximal dosages.

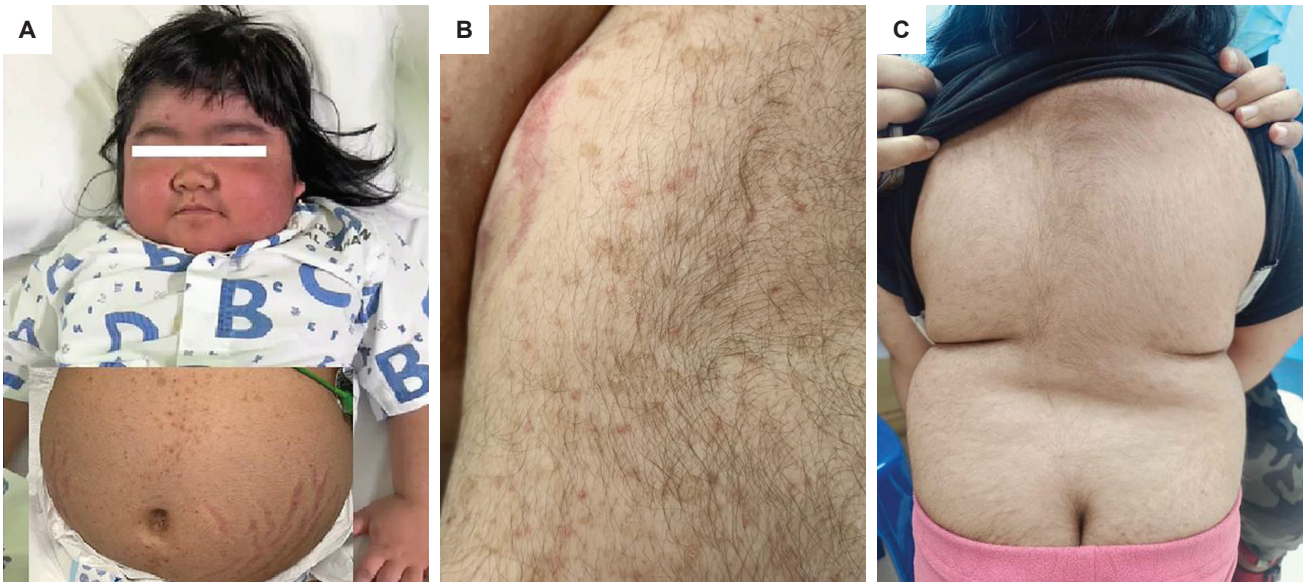

Figure 1. (A) Clinical features of the patient include a plethoric face with extensive pustular acne lesions, hirsutism, **(B)** multiple purplish striae, and **(C)** central obesity.

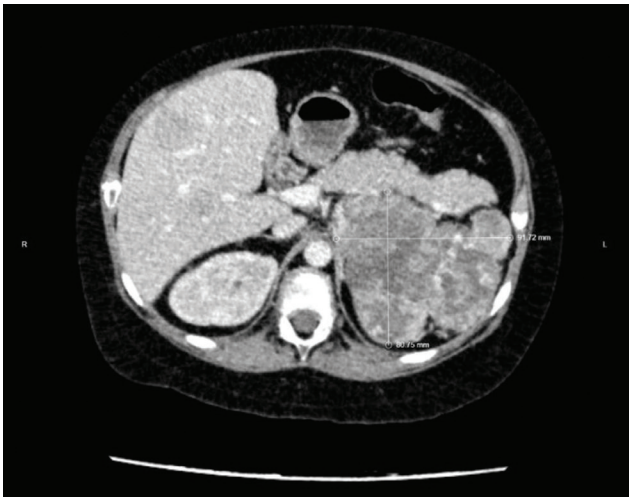

Figure 2. Thoracic, abdominal and pelvic CT revealed a large lobulated, heterogeneously enhancing left adrenal mass (8.1 x 9.3 x 8.7 cm) causing significant mass effect, including inferior displacement of the left kidney.

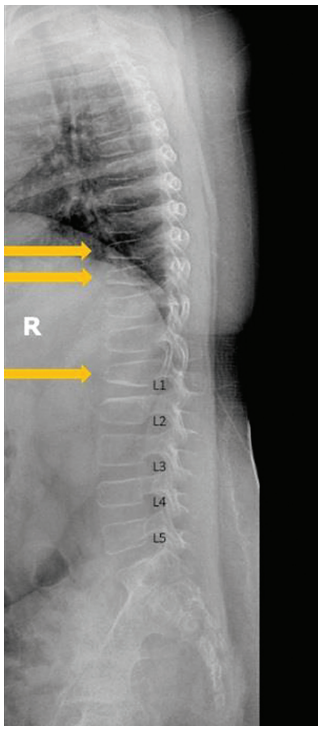

Figure 3. Lateral spine X-ray demonstrated multiple vertebral compression fractures at T9, T10 and L1 *(yellow arrows)* with generalized osteopenia.

The diagnosis of ACC was made based on the non-ACTH-dependent hypercortisolism and hyperandrogenism in the context of a large adrenal mass that demonstrated malignant behaviour. While complete surgical removal of the tumour is the gold standard, it was not feasible due to its substantial size and distant metastases. Neoadjuvant chemotherapy was initiated following the ARAR0332 Stage III/IV protocol,[8] which consisted of IV Cisplatin: 50 mg/m²/day (Days 1–2), IV Etoposide: 100 mg/m²/day (Days 1–3) and IV Doxorubicin: 25 mg/m²/day (Days 4–5). Oral mitotane, an adrenolytic agent, combined with oral ketoconazole, a fast-acting steroidogenesis inhibitor, was started on Day 8 of chemotherapy. Mitotane tablets were crushed and mixed with 10 mL of milk and administered before feeding, starting at 1 g/m²/day. Ketoconazole was initiated at 100 mg daily and increased by 100 mg/day every 3-5 days if liver enzymes remained normal, up to 800 mg/day.

The patient experienced severe complications from her 1st cycle of chemotherapy. She developed nosocomial pneumonia requiring intubation, as well as profuse diarrhoea after initiating mitotane. Additionally, transient transaminitis was observed when the oral ketoconazole dose reached 400 mg/day. Due to severe gastrointestinal symptoms, mitotane was temporarily withheld and later reintroduced at a lower dose with a more gradual titration.

Following two cycles of chemotherapy and while on oral mitotane at 3 g/m²/day, the patient demonstrated a positive response. Her antihypertensive medications were reduced to two medications, and the persistent hypokalaemia was resolved. Given the adrenolytic effects of mitotane, oral fludrocortisone and hydrocortisone supplementation were initiated. Before the third cycle of chemotherapy, cortisol, testosterone and DHEAS levels had normalised.

The patient was scheduled for the 3rd cycle of chemotherapy followed by tumour resection in accordance with the ARAR0332 Stage III/IV protocol. However, her parents were not keen on further chemotherapy and requested discharge. When she was eventually readmitted to the hospital, her condition had significantly deteriorated, with biochemical parameters indicating recurrent hypercortisolism and hyperandrogenism.

She also experienced severe back pain due to the progression of multiple vertebral compression fractures. Disease re-evaluation revealed further progression, including an increased number of lung nodules, along with a mixed response in her original adrenal and liver lesions.

Following repeated discussions with the patient and her family, they opted for symptomatic and palliative care. Her respiratory status further worsened, requiring non-invasive ventilation support. Eventually, she succumbed to her illness.

DISCUSSION

The patient presented with a typical functional adrenocortical tumour phenotype, characterised by virilisation and hypercortisolism, the latter manifesting as endocrine hypertension noted on initial presentation. A retrospective cohort study involving 41 paediatric patients[9] indicates that mixed symptomatology is the most common presentation. In particular, virilisation in a prepubertal female is an alarming feature that warrants extensive investigation to identify the underlying cause,[10] and in this context,

should raise a strong suspicion for an adrenal tumour. Despite the dramatic clinical presentation, delayed diagnosis is not uncommon, which is often attributed to physicians' unfamiliarity with this disease entity.[11]

Hyperandrogenism and ACTH-independent hypercortisolism are pathognomonic of adrenocortical tumours, making it crucial to exclude adrenocortical carcinoma (ACC). In our patient, biochemical evidence of mineralocorticoid excess was observed, as indicated by hypokalaemia and hyperchloraemic metabolic alkalosis. However, there was no evidence of hyperaldosteronism; instead, the aldosterone levels were suppressed, likely due to excessive cortisol exerting a mineralocorticoid effect. Additionally, the elevated renin level detected in our patient was suggestive of left renal vein thrombosis secondary to tumour invasion, a common occurrence in locally advanced ACC.

Definitive diagnosis is based on the gross and histological appearance of surgically obtained tissue, as per the Wieneke criteria. Where feasible, early surgical removal of the tumor is vital for both treatment and diagnostic purposes. Successful tumor removal is associated with better outcomes. Fine needle adrenal biopsy is not recommended due to the friability of the tumor, capsule rupture leading to tumour spillage or needle tract metastases following fine needle biopsy, which are associated with a poorer prognosis.[8] Consequently, the diagnosis of ACC in this patient was initially established based on typical clinical, biochemical and imaging findings.

Given the advanced disease stage, we initiated combination chemotherapy with etoposide, doxorubicin, cisplatin and mitotane as per the ARAR0332 protocol.[8] An important goal is rapid normalisation of cortisol levels, which is crucial for controlling refractory hypertension, managing electrolyte imbalances and reducing infection risk. Mitotane, an irreversible and potent adrenolytic agent, requires approximately 14 weeks to reach therapeutic levels. To bridge this gap, we opted for oral ketoconazole, an imidazole antifungal agent widely used 'off-label' for treating hypercortisolism in Cushing's syndrome due to its rapid anti-cortisol effects. Unlike mitotane, there is no standardised ketoconazole dose for anti-cortisol therapy. However, Castinetti *et al.* reported a final median dose of 200–1200 mg/day in a cohort of 200 patients aged 8–87 years.[12] Liver dysfunction, typically mild and reversible, was observed in approximately 10% of patients, while serious hepatic injury, though rare, can be fatal.[12] Therefore, close monitoring of liver function is warranted.

Due to mitotane's cytotoxic effects on adrenocortical cells, substitutive doses of hydrocortisone and fludrocortisone should be initiated 1–2 weeks after mitotane initiation. The recommended hydrocortisone dose is 2–3 times higher than that used in primary adrenal insufficiency. The ARAR0320 protocol suggests an equivalent hydrocortisone dose of 40–45 mg/m^2/day, considering its significant alteration of steroid hormone metabolism.

Genetic testing for germline *TP53* mutations is essential, even in the absence of a family history suggestive of Li-Fraumeni syndrome. The lifetime penetrance for individuals with this mutation approaches 90%.[13] If a mutation is detected, genetic screening should be considered for family members. However, in this case, the patient's parents declined genetic testing due to financial constraints and concerns regarding potential implications.

The presence of metastases at the time of ACC diagnosis is an independent factor associated with poor prognosis in paediatric patients. The reported two-year survival rate is 39% in patients with metastases at diagnosis, significantly lower than the 93% survival rate observed in patients without metastases.[9] This creates a particularly challenging situation in balancing parental autonomy with the child's best interest, especially when the prognosis is poor and the chances of treatment success are limited.

Our patient experienced significant distress and severe side effects with each cycle of chemotherapy, including neutropenic fever, refractory thrombocytopenia, extensive mucositis and profound fatigue, often requiring at least 2-3 weeks to recover. Her parents perceived that she was suffering with a markedly reduced quality of life and requested discontinuation of chemotherapy, while continuing oral mitotane. This raised an ethical dilemma, prompting extensive discussion on her best interest – carefully weighing the limited potential benefits of further chemotherapy against its high burden of toxicity, in a context of a reported five-year survival rate of less than 20%.

These findings underscore the importance of early detection and timely diagnosis in improving overall survival outcomes in paediatric ACC. The rapid and aggressive clinical course demonstrates the need for clinicians to be alert to the constellation of presenting features, to undertake comprehensive endocrine assessments and to perform targeted imaging at the first presentation.

CONCLUSION

Paediatric ACC is an extremely rare but aggressive malignancy with high morbidity and mortality if not diagnosed and treated promptly. A high index of suspicion is warranted for any child presenting with prepubertal virilisation and Cushing's syndrome, as early detection and intervention can significantly improve prognosis.

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Ethical Consideration
This study was registered and approved by the Malaysia Medical Research and Ethics Committee (MREC), with NMRR ID: 24-02177-RUX.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KYL: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **PPT:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project administration.

Data Availability Statement

No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

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