

A CASE OF CHILDHOOD ADRENOCORTICAL CARCINOMA

Colombage DDE¹, Muthukuda DT², Bulugahapitiya U³, Ranasinghe LD³

¹National Hospital of Sri Lanka, ²Provincial General Hospital, Ratnapura, Sri Lanka, ³Colombo South Teaching Hospital, Sri Lanka

ABSTRACT

We describe a one year and seven months old baby girl who presented with a short history of pubic hair growth. The child was otherwise healthy and there were no other features of virilization. Her axillary hair and breast development were pre-pubertal (Tanner 1). Hormonal evaluation revealed markedly raised androgen levels. There were no features of hypercortisolism or hyperaldosteronism. USS abdomen revealed a left sided adrenal mass measuring 6.8cm x 6cm. A left sided adrenalectomy was performed and the histology revealed features of an adrenocortical carcinoma with areas of necrosis, lymphatic and vascular invasion. Child was treated with adrenalectomy followed by mitotane therapy. This case highlights the importance of suspecting ACC in a young child presenting with pubarche in order to avoid delay in making the diagnosis.

Key Words: Adreno cortical carcinoma, Paediatric

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 1-2/ million (1). It has a bimodal age distribution with a peak in the below 5 year age group and in the 4th and 5th decades of life. These tumours are generally more aggressive in adults (2).

Paediatric ACC occurs mostly in children below 5 years of age with a peak incidence at 3.5 years (3). It is commoner in girls and frequently (80-90%) produces adrenocortical hormones (4). Majority of the younger children (>90%) present with virilizing features, whereas adolescents and young adults tend to have Cushing syndrome or non-functional tumours at presentation (5).

CASE REPORT

A one year and seven months old girl was referred to the Endocrine department for evaluation of pubic hair growth, which was noticed by her grandmother 2 weeks prior to the initial presentation. She was otherwise healthy and had an uneventful perinatal period and age appropriate growth and development. There was no consanguinity, history of ambiguous genitalia or recent pigmentation. On examination, her height was 77cm and her weight was 11kg. She had Tanner 2 pubic hair growth without axillary hair development and clitoral hypertrophy. Breast development was Tanner 1. There were no features of Cushing syndrome and she was normotensive. The abdomen was distended but no distinct masses were felt on palpation.

The hormonal analysis of the patient revealed very high

serum testosterone level of 405 ng/dl (2-10) along with elevated Dehydroepiandrosterone sulphate (DHEA-S) of 375µg/dl (<30µg/dl). Her baseline 17-hydroxyprogesterone (17-OHP) level was normal (1.98 ng/dl). Over-night dexamethasone suppression test showed suppressed serum cortisol. Basal serum cortisol was also normal.

Her haematological and other biochemical markers were unremarkable. Ultrasound scan of the abdomen showed a 6.8 cm x 6 cm well defined, solid, hypo-echoic mass in the right supra renal region consistent with a supra renal mass. Contrast enhanced CT revealed a fairly well-circumscribed, rounded lesion in the right supra renal region measuring 5.8 x 6.7 x 7.2cm without any invasion into the inferior vena cava, liver or right kidney. It was hypodense and inhomogeneously enhancing without intra-lesional calcifications. Radiologically, this appearance was suggestive of a neuroblastoma arising from the right supra renal gland. Patient underwent right sided adrenalectomy and the histology confirmed the diagnosis of adrenocortical carcinoma arising from the zona glomerulosa. There were 5-10 mitotic figures per 50 high power fields examined. The resection margins were clear. However, intra-capsular lymphatics and blood vessels contained tumour emboli. Necrotic areas were also noted (<5% of the tumour). Ki 67 proliferation index and P 53 mutation analysis were not available. Following surgery, the patient was referred to an oncologist for adjuvant therapy with mitotane and further follow up.

DISCUSSION

Unlike in most other carcinomas, the children with

ACCs appear generally healthy due to the anabolic effects of the increased amounts of androgens and/or other steroid and the diagnosis is often delayed. The median interval between the first clinical manifestations of ACC and its diagnosis is about 10 months (6).

Most of the young children present with virilization and the common manifestations include deepening of the voice, acne, hirsutism, increase of muscle mass and secretion and proliferation of the sebaceous glands with characteristic adult odor. In females, clitoral enlargement, facial and pubic hair with male escutcheon, amenorrhea and rarely temporal balding may occur (7). Penile enlargement and precocious isosexual pseudo-puberty occur in males and it is usually adrenal in origin when the testes are small (8). Cushing syndrome (CS) is very rare in children and in the absence of iatrogenic steroid ingestion, it is highly indicative of ACC. (9). Less commonly, ACC co-secretes glucocorticoids and androgens. Rarely patients with ACCs present with feminization and features of hyperaldosteronism (10). Our patient's tumour was considerably large (>200cm³) with very high androgen levels by the time of diagnosis. However, the only clinical feature that our patient has was the pubic hair growth indicating a short duration androgen exposure due to the rapidity of the tumour growth.

In young children, ACCs may arise from the fetal zone of the fetal adrenal cortex, whereas in adolescents and adults, may originate from the definitive adrenal cortex (5). Young children with ACC frequently demonstrate mutations of the *p53* gene, while these mutations are relatively rare in adults (11, 12). It is likely that the presence of a constitutional *p53* mutation may increase the penetrance of ACCs in the fetal adrenal cortex but not in the definitive adrenal cortex. For this reason, individuals with constitutional *p53* mutations (Li-Fraumeni syndrome), adrenocortical tumours usually occur only during the first decade of life (13). Various other genetic predispositions and tumour syndromes such as Beckwith-Wiedemann syndrome, MEN 1, Carney Complex are also associated with paediatric ACC (8).

In paediatric ACCs, abdominal ultrasound should be the first line of imaging, which is also sensitive enough in detecting caval extension of tumour thrombus. If it is negative, Magnetic resonance imaging (MRI) or Computerized tomograph (CT) scan is recommended. MRI is preferred as it lacks ionising radiation. It also gives a better definition of tumour extent and invasion into adjacent structures. Exposure to repeated X-ray radiation should be minimized in view of the likely genetic predisposition and propensity to second tumours (14). And suspected ACCs should not be biopsied because of the risk of tumour seeding (3).

The tumour staging system used in paediatric age group is slightly different from adults. The size, weight and amount of resection of the tumour are vital factors that are considered in staging these tumours (3). The

histopathological distinction between adrenal adenoma and carcinoma is difficult and the tumor size is considered as the best available predictor of biological behaviour of these tumours. The tumours of >100g/200cm³ are associated with a worse prognosis (15) and older age at presentation, increased urinary steroid DHEA-S and glucocorticoid hormone levels, hypertension, peri-operative tumour rupture and delay in diagnosis (16) are the other poor prognostic factors.

Treatment for ACCs includes en block tumour removal and chemotherapy. Because of the high likelihood of a genetic cancer predisposition and risk of occurrence of secondary tumours within the radiation field, radiotherapy is not advised in children (3). Postoperative adrenocortical hormone replacement may be required in selected patients. Mitotane is an adrenolytic agent that is usually effective in controlling the endocrine symptoms and tumour regression. Some studies have shown that it has a greater effectiveness in children than adults, especially if the neoplasm is hormonally active (17). Mitotane has a cytotoxic effect especially on the zona reticulosa and also zona fasciculata to a lesser extent. In contrast, its effect on the zona glomerulosa is negligible. Other effective chemotherapeutic agents include cisplatin, etoposide, doxorubicin, 5-Fluorouracil and cyclophosphamide (3).

In conclusion, paediatric ACCs are very rare and quite different from adult ACCs in terms of origin and its' behavior. These are mostly virilizing tumours especially in children below 5 years of age. In order to avoid delay in the diagnosis, any child less than 4 years with pubarche should be considered to have an adrenocortical tumour, until proven otherwise.

REFERENCES

1. Andre' Lacroix. Approach to the Patient with Adrenocortical Carcinoma. *Journal of Clinical Endocrinology and Metabolism*. 2010; **95**: 4812-4822.
2. Fassnacht M, Allolio B. Clinical management of adrenocortical carcinoma. *Best Practice and Research Clinical Endocrinology and Metabolism*. 2009; **23**: 273-289.
3. Spoudeas HA, Harrison B. Paediatric endocrine tumours: A multi-disciplinary consensus statement of best practice from a working group convened under the auspices of the British society of paediatric endocrinology and diabetes (BSPED) and the UK children's cancer study group (UKCCSG). 2005; 47-63.
4. Ribeiro RC, Sandrini R, Schell MJ, Lacerda L, Sambaio GA, Cat I. Adrenocortical carcinoma in children: A study of 40 cases. *Journal of Clinical Oncology*. 1990; **8**: 67-74.
5. Michalkiewicz E, Sandrini R, Figueiredo B,

- Miranda ECM, Caran E, Oliveira-Filho AG, et al. Clinical and Outcome Characteristics of Children With Adrenocortical Tumors: A Report From the International Pediatric Adrenocortical Tumor Registry. *Journal of Clinical Oncology*. 2004; **22**: 838-845.
6. Sandrini R, Ribeiro R & DeLacerda L. Extensive personal experience: childhood adrenocortical tumors. *Journal of Clinical Endocrinology and Metabolism*. 1997; **82**: 2027-2031.
 7. Ribeiro RC, Michalkiewicz EL, Figueiredo BC, Delacerda L, Sandrini F, Pianovsky MD et al. Adrenocortical tumors in children. *Brazilian Journal of Medical and Biological Research*. 2000; **33**(10): 1225-1234.
 8. Ajanthan R, Lamabadusuriya SP. Assortment of adrenocortical tumours. *Sri Lanka Journal of Child Health*. 2002; **31**: 9-13.
 9. Gilbert MG, Cleveland WW. Cushing's syndrome in infancy. *Pediatrics*. 1970; **46**: 217-229.
 10. Leditschke JF, Arden F. Feminizing adrenal adenoma in a five-year-old boy. *Australian Paediatric Journal*. 1974; **10**: 217-221.
 11. Wagner J, Portwine C, Rabin K, Leclerc JM, Narod SA, Malkin D. High frequency of germline p53 mutations in childhood adrenocortical cancer. *Journal of the National Cancer Institute*. 1994; **86**: 1707-1710.
 12. Stojadinovic A, Ghossein RA, Hoos A, Nissan A, Marshall D, Dudas M et al. Adrenocortical carcinoma: Clinical, morphologic, and molecular characterization. *Journal of Clinical Oncology*. 2002; **20**: 941-950.
 13. Kleihues P, Schauble B, Hausen A, Esteve J, Ohgaki H. Tumors associated with p53 germline mutations: A synopsis of 91 families. *American Journal of Pathology*. 1997; **150**: 1-13.
 14. Varley JM, Mc Gowan G, Thorncroft M, James LA, Margison GP, Harris M et al. Are there Low-Penetrance TP53 Alleles? Evidence from Childhood Adrenocortical Tumors. *American Journal of Human Genetics*. 1999; **65**: 995-1006.
 15. Slooten HV, Moolenaar AJ, Seters APV, Smeenk D. The treatment of adrenocortical carcinoma with o, p¹-DDD: the prognostic implications of serum monitoring. *European Journal of Clinical Oncology*. 1984; **20**: 47-53.
 16. Cobb WS, Kercher KW, Sing RF, Henifrod BT. Laparoscopic adrenalectomy for malignancy. *American Journal of Surgery*. 2005; **189**: 405-411.
 17. Hogan TF, Gilchrist KW, Westring DW, Citrin DL. A Clinical and pathological study of adrenocortical carcinoma. *Cancer*. 1980; **45**: 2880-2883.