

Adrenocortical Carcinoma in a 2 Years Old Girl, a Rare Cause of Clitoridomegaly: A

Case Report

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1. Abstract

1.1. Background: Adrenocortical carcinoma (ACC) in childhood represent about 0.2% of all pediatric malignancies. Children had a higher incidence of virilization in 72% as common presenting symptom. The prognosis in children who have ACC appears to be better than that of adults, at least for early stage disease. The aim of this study was to evaluate the case of child with a low grade of ACC and to confirm the role of the margins free resection in ACC prognostic factors.

1.2. Case Presentation: We present a 2 year old girl with progressive virilization since the neonates' period. The symptoms were including deepening of the voice, clitoromegaly, growth acceleration and premature pubic hair development associated with the low cortisolemia and hyper androgenemia. Abdominal CT scan concluded to the right adrenal tumor mass. She got the complete excision of 150 g of the mass. The histology concluded to ACC grade 2. Patient had an uneventful at 10 months postoperatively.

1.3. Conclusion: ACC is rare in children. Only complete surgical excision is sufficient in the case of low grade of ACC in pediatric population. Clinical examination, hormonal and imaging follow up remain necessary to any recurrence.

2. Introduction

Adrenocortical carcinoma (ACC) is an extremely rare malignancy in childhood and most commonly reported in adult patients [1,2].

ACC occur with a worldwide incidence of 0.2–0.3 cases per million [3]. There is a bimodal age distribution in the first and fourth decades of life and most children present before the age of 5 years [4]. Girls are more affected than boys and this apparently increases from early childhood [5]. Most children with adrenal tumors (80%) have secreting tumors with signs of virilisation [6]. They may occur sporadically or be associated with hereditary cancer syndromes including Li-Fraumeni and Beckwith-Wiedemann syndromes [7,8]. Current treatment protocols are derived from adult ACC and consist of surgery and/or chemotherapy [2]. Complete resection is required for cure, but residual or metastatic disease carries a poor prognosis [5].

3. Case Report

A 2 years old girl of Twareg ethnicity and nonconsanguineous parents was referred to Pediatric Surgery Service. She was visited with the complaints of congenital enlargement of the clitoris, gradual deepening of the voice for 13 months and appearance of the pubic hair (Figure 1). She had no history of breast enlargement, no history of headache, vomiting, convulsion or ingestion of any offending drug. Her height was 95 cm (upper than 95% percentile of height) and weight was 21 kg (on 95% percentile of weight) and blood pressure was 90/60 mmHg, and pulse was 100 beats/min. In physical examination, she had clitoromegaly (length was 4 cm and its width was 2cm), vaginal orifice intact and urethral orifice in normal position, features of virilization (Figure 1) included pubic

hair stage 4 of Tanner classification (pseudoprecocious puberty) and breast was stage 1.

Examinations of other systems did not revealed any abnormality. The report of lab test was normal Sodium [138 mEq/L], normal Potassium [4.1 mEq/L], Testosterone (RIA) was increased [3.54. ng/mL (normal 0.07-0.65)], Estradiol was raised [normal 10-25], LH was low [1.72 U/l (normal 2.5-21. U/l)], FSH was normal [1.62 μ U/ml (normal 0.25-5)], Cortisolemia (8 AM) was decreased [172.60 nmol/dL (normal 260-720)]. The 24h urines test found Vanil Mandelic Acid was normal [2.72 μ mol/mmol (normal <11.00)], Homo Vanillic Acid was normal [4.86 μ mol/mmol (N<17.00)]. The cytogenetic study found a chromosomal complement of the female type: 46 XX, without any anomaly, of number, nor of structure of the chromosomes was highlighted. Abdominal ultrasound showed a solid hypo echogenic mass measuring about 6.95 \times 6.29 cm in the right side and concluded to right nephromegaly. While, abdominal CT scan study with contrast enhanced, found a heterogeneous mass concerned the right adrenal region. Measuring was 46mm \times 35mm with clear and regular contours. CT scan concluded to an adrenal tumor (Figure 2).

An indication of surgery was planned and the patient underwent complete removal of the mass by lumbotomy. The mass weight was 150 grams. The patient was hospitalized for postoperative

monitoring, where she received treatment with intravenous hydrocortisone and then by the enteral route. The postoperative course was simple, she was discharged on day 5 with a schedule of clinical, biological and imaging follow-up (Figure 3 and 4).

The results of the macroscopic examination found a nodular sample of 150g, with a smooth external surface, measuring 10 \times 7 \times 5 cm (Figure 3). Histological examination concluded to the appearance of a high-grade adrenocortical carcinoma with the presence of tumor emboli and capsular rupture, stage 2: (pT2Nx UICC, 8th edition) (Figure 4a, 4b, 4c and 4d). After histological results, the patient was referred in the pediatric oncology unit and endocrinology for the multidisciplinary follow up. The conservative treatment was instituted and follow-up concomitantly with the surgery pediatric department. Post-operatively monitoring follow up was: day 7 (D7), day 21 (D21), month 3 (M3), month 6 (M6) and month 10 (M10) and will be then annually. It was based on examination clinical examination, androgenic hormones dosage and 24-hour urinary free cortisol assay and/or thoracoabdominal CT scan. Gradual decrease in voice hoarseness, persistence of suprapubic hair, normalization of androgens at M1 and M3, persistence of hypocortisolemia at M1 and M3. Abdominopelvic CT scan at M3 was normal. The evolution was favorable, without recurrence, local or metastases, with a follow-up of 10 months postoperatively.



Figure 1: Image of a 2-year-old girl presenting the virilisation symptoms including pubic hair and clitoromegaly due to the secreting adrenocortical carcinoma.

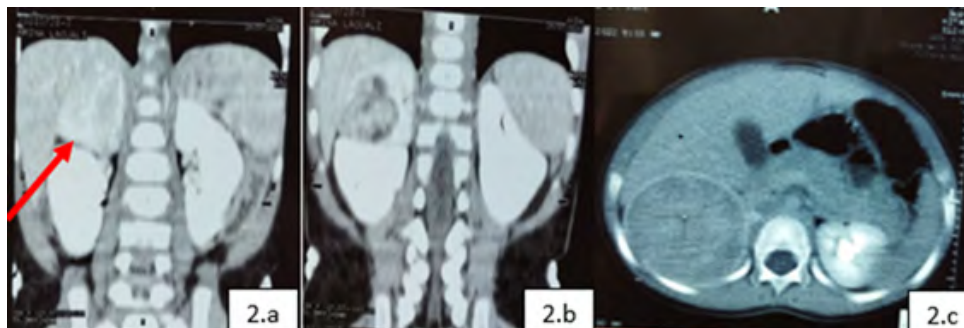


Figure 2a, 2b and 2c: Abdominal CT scan showing a right adrenocortical tumor in a 2year-old girl.



Figure 3: On cutting, an encapsulated, necrotic solidocystic appearance with a brownish color and a crumbly consistency.

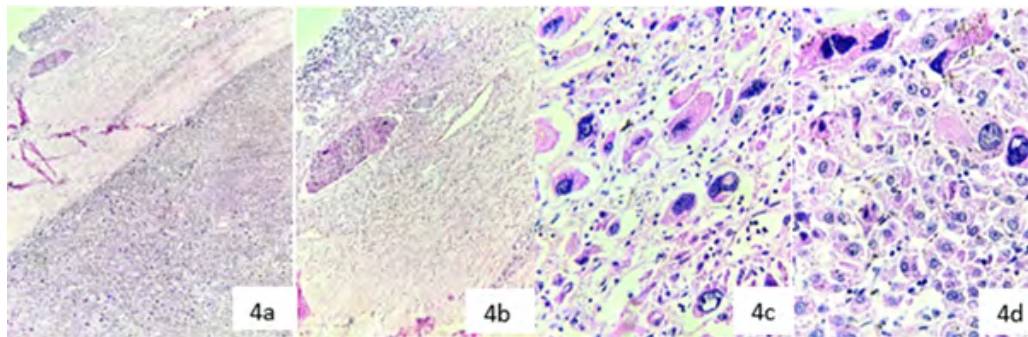


Figure 4: (4a, 4b, 4c, and 4d): Microscopic examination showed a neoplastic proliferation composed of adrenocortical cells and concluded to adrenocortical carcinoma stage: pT2Nx (UICC, 8th edition).

4. Discussion

Here, we described a classical presentation of childhood ACC. ACC is a very rare malignancy tumor in the pediatric population [4]. Incidence of ACC has a bimodal distribution with two peaks in the first and fifth decades of life [5,9]. The frequency of ACC is 0.4 cases per million persons during their first 4 years of life, and it decreases to 0.1 cases per million persons during their subsequent 10 years [5,10]. However, 79.5% of them originated from southern Brazil, where the ACC incidence is 10–15 times higher than in the rest of the world due to the high prevalence of the P53 mutation in the first 4 years [2,11]. Pediatric ACCs are most commonly associated with Li-Fraumeni Syndrome, an autosomal dominant familial cancer syndrome associated with a number of malignancies including sarcoma, breast cancer, brain tumors, leukemia, lymphoma, and adrenocortical carcinomas [2,7,12]. In this case, diagnosis of adrenocortical tumor were established at 21 months. There is a striking predominance of female patients. Gender did not prove to be a statistically significant predictor of an adverse patient outcome [5,13,14]. International Pediatric Adrenocortical Tumor Registry (IPATR) has reported that approximately 90% of pediatric ACCs are functional [6]. The clinical features of adrenocortical tumors can vary widely from abdominal pain and fatigue to hormonal symptoms. The patients present virilization alone (84.3%) or in combination with signs of overproduction of other adrenal hormones and pseudoprecocious puberty with or without Cushing syndrome [4,5,15]. Pseudoprecocious puberty is accompanied

by accelerated growth, while Cushing syndrome by arrest growth; breast development may appear in both males and females [16]. ACC can also be diagnosed incidentally during the evaluation of abdominal pain, fatigue or other non-specific symptoms. Rarely, patients can present with abdominal palpable mass [6,11]. Nidhi G. and al. [5] found mixed symptomatology representing more than one hormonal abnormality was the most common presentation (54%) followed by virilization alone (17%); precocious pubarche was noted in 36% patients, of which 18% of them were less than 1 year of age. In his comparative study, Mendonca B. and al. [14], confirmed that in most pediatric patients, there is a predominance of virilization (72%) over Cushing's syndrome in comparison to adults of whom 60% presented with Cushing's syndrome and 35% with virilization. As described by others authors, our case had virilisation associated with precocious pubic hair clitoromegaly and deepening voice. In contrast to the adult population, tumors in children more often are hormonally functional. Further, feminizing tumors in adults are fatal, a fate not shared in pediatric patients, although death from tumor in this population has been reported [13]. Diagnosis could be challenging in the absence of hormonal secretion, non-functional tumors (<10%) tend to occur in older children and adolescents [5,13]. For Ribeiro C. and al. [10], about 40% of adult patients have nonfunctional adrenocortical tumors. A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017 [5] founds fifteen percent of patients older than 12 years had nonfunctional presentation, compared to only

0.1% nonfunctional tumors in less than 4-year-olds. However, the possibility of a neuroblastoma, particularly in young children, and of a pheochromocytoma should be investigated and excluded by analysis of urine and plasma catecholamines and their metabolites [17]. In our case the urine catecholamines were normal. Increased concentrations of cortisol, dehydroepiandrosterone-sulfate, urine 17-ketosteroid, and urine 17-hydroxycorticosteroid before surgery may indicate carcinoma rather than adenoma, with a positive correlation between tumor stage and hormone concentration level [18,19]. There is variability in clinical presentation; in the present case, we found the increased androgenemia concentrations with low cortisolemia. Fine-needle aspiration (FNA) or core biopsy is not recommended for establishing the diagnosis of ACC due to the risk of complication of needle tract metastases and tumor spillage due to capsular breach [4]. Imaging studies help to the diagnosis, and then surgical planning. They also provide information in the staging of the disease and in the features of resectability such as tumor size, invasion of adjacent structures [20,21]. Ultrasonography (US) is the initial imaging technique to examine the adrenal glands; consequently, they are much more difficult to specify with US. Computed tomography (CT) or magnetic resonance imaging (MRI) are used as a problem-solving tool for lesion characterization, to determine the relationship to adjacent tissues, and to differentiate benign from malignant masses after initial US evaluation [21,22]. Open surgery remains the gold standard and laparoscopic surgery is discouraged in view of excess locoregional recurrences. The aim of surgery should be to achieve margin negative that is R0 resection of the tumor. The complete excision of the tumor at diagnosis may actually cure the patient. Even after this, the recurrence rate can be as high as 80% [4,6]. Staging in childhood ACC involves the size, weight, and amount of resection of the tumor, local spread to lymph nodes, vascular/vein invasion or incomplete resection and the distant metastases (Figure 5). Based on adult criteria, specifically with Weiss criteria, and patient outcomes; the correlation between high Weiss score and worse clinical outcomes was not observed in children; however, stronger correlation was noted with application of the Wieneke index. The Wieneke index was more accurate in predicting clinical outcomes at least in younger children with good significance. The Wieneke criteria are emerging as the gold standard for pathological prognostication in childhood adrenocortical tumors [6,8,23,24].

Surgery remains the cornerstone of treatment in stages I – III of ACC. Despite surgery, recurrence rate can be as high as 80%. The role of chemotherapy in the management of childhood ACT has not been established although occasional tumors are responsive to mitotane or cisplatin-containing regimens [1,25-27]. A complete surgical excision should also be obtained after chemotherapy, removing part of organs, if involved by the tumor, and after the occurrence of relapse and some authors even suggest repeated resections of recurrent local or distant lesions [6,18]. In IPACTR,

for localized disease, surgery alone was recommended. However, 12% of patients with stage I or II received adjuvant chemotherapy including. Stage III or IV tumors were treated with intensive chemotherapy [5,23]. For metastatic unresectable ACC, treatment is based on mitotane monotherapy or triple chemotherapy. Palliative cisplatin-based chemotherapy and / or radiotherapy can be an alternative to surgical debulking. Ketoconazole or metyrapone is used to control hypercortisolemic symptoms [4,26]. Our patient had complete excision; she was classified Wieneke index 1 and there was no necessity of chemotherapy. She got steroid substitution by hydrocortisone administration due to low cortisolemia. Patient was uneventful and had no recurrence 10 months later postoperatively and hormonal exams, abdominal CT scan was normal. Limitations of our study included the nature of a single case and the short follow-up period which limits assessments of prognosis. Genetic testing was not performed due to local unavailability. Therefore, no conclusion regarding association of TP53 mutations with ACC could be made.

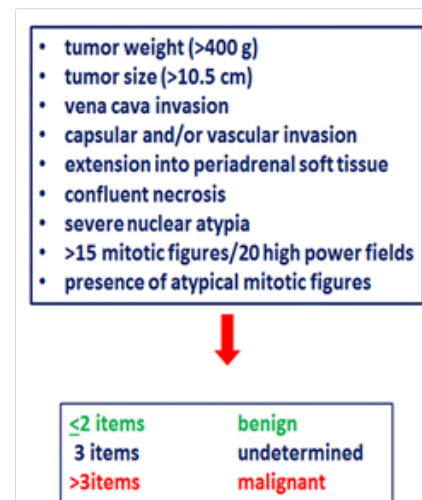


Figure 5: Wieneke criteria [24].

5. Conclusion

Age less than 4 years is an important predictor of survival. Complete surgical excision remain the mainstay of treatment of the local ACC. We recommended clinical, hormonal and imaging follow up, because of a high risk of recurrence of ACC after surgery.

6. Authors' Contributions

NL designed, drafted the study and wrote the manuscript. MO designed and revised the manuscript. BE did histology diagnostic and some figures. SM and MK collected data. MA for data and follow up protocol. YI, AD, MH, and AH designed critically revised the manuscript. The authors received no specific funding for this study.

References

1. Tabatabaei F, Sharif MR, Reisi N. Adrenocortical carcinoma in a 8 years old child: a Case Report. *Iran J Ped Hematol Oncol.* 2017; 7(3): 193-197.
2. Ilanchezian M, Varghese DG, Glod JW, Reilly KM, Widemann BC, Pommier Y, et al. Pediatric adrenocortical carcinoma. *Front. Endocrinol.* 13: 961650.
3. Li J, Zhang W, Hu H, Zhang Y, Wen Y, Huang D, et al. Adrenocortical Carcinoma in Eight Children: A Report and Literature Review. *Cancer Management and Research.* 2021; 13: 1307-1314.
4. Gundgurthi A, Kharb S, Dutta MK, Garg MK, Khare A, Jacob MJ, et al. Childhood adrenocortical carcinoma: Case report and review. *Indian J Endocr Metab.* 2012; 16: 431-5.
5. Gupta N, Rivera M, Novotny P, Rodriguez V, Bancos I, Lteif A, et al. Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017. *Horm Res Paediatr.* 2018; 90 :8-18.
6. Dall'Igna P, Virgone C, De Salvo G and al. Adrenocortical tumors in Italian children: Analysis of clinical characteristics and P53 status. Data from the national registries. *Journal of Pediatric Surgery.* 2014; 49: 1367-1371.
7. Jouinot A, Bertherat J. Diseases Predisposing to Adrenocortical Malignancy (Li-Fraumeni Syndrome, Beckwith-Wiedemann Syndrome, and Carney Complex). *Experientia supplementum.* 2019; 111: 149-169.
8. Jehangir S, Nanjundaiah P, Sigamani E. Pathological prognostication of paediatric adrenocortical tumours: Is a gold standard emerging? *Pediatr Blood Cancer.* 2018; e27567.
9. Grisanti S, Cosentini D, Laganà M, Turla A, Berruti A. Different management of adrenocortical carcinoma in children compared to adults: is it time to share guidelines? *Endocrine.* 2021; 74: 475-477.
10. Ribeiro RC, Neto RS , Schell MJ, Lacerda L, Sambaio GA, Cat I. Adrenocortical Carcinoma in Children: A Study of 40 Cases. *Journal of Clinical Oncology.* 1990; 8(1): 67-74.
11. Naotunna P, Siriwardana H, Gamage D, Gunarathna S, Samarasinghe M, Gunasekara S, et al. Adrenocortical tumors in children: Sri Lankan experience from a single center, and a mini review. *Journal of Medical Case Reports.* 2023; 17: 137.
12. Bernstein L, Gurney LG. Carcinomas and other malignant epithelial neoplasms. National Cancer Institute SEER Pediatric Monograph. ICCX XI 139. 1999.
13. Wieneke JA, Thompson LD, Heffess CS. Adrenal Cortical Neoplasms in the Pediatric Population. A Clinicopathologic and Immunophenotypic Analysis of 83 Patients. *Am J Surg Pathol.* 2003; 27(7): 867-881.
14. Mendonca B, Lucon AM, Menezes C, Saldanha LB. Clinical, hormonal and pathological findings in a comparative study of adrenocortical neoplasms in childhood and adulthood. *Journal of Urology.* 154: 2004-2009.
15. Yadav SK, Jha CK, Mishra SK, Verma R, Krishna A. Pediatric Mixed Functioning Adrenocortical Carcinoma. A Case Report and Review of Literature. *Middle East Journal of Cancer.* 2019; 10(4): 372-377.
16. Sandru F, Petca RC, Petca MC, Dumitrascu MC, Ghemigian A. Adrenocortical carcinoma: Pediatric aspects (Review). *Experimental and therapeutic medicine.* 2022; 23: 287.
17. Azzi AS, Driessens N. Adrenal disease diagnosis: management of adrenal incidentaloma. *Rev Med Brux.* 2017; 38: 325-33.
18. Cho MJ, Yeon DK, Seong CK, Tae HK, In KK. Adrenocortical tumors in children 18 years old and younger. *Korean Surg Soc.* 2012; 82: 246-250.
19. Savoie PH, Murez T, Fléchon A, Sèbe P, Rocher L, Camparo P, et al. French Cancerology Comity of AFU guidelines — Update 2018—2020: Adrenal cancer. *Prog Urol.* 2018; 28: S175-S193.
20. León M, Chaparro R, Larab B, Pinos D, Ruiz C, Cerrato F, et al. Adrenocortical tumors in children: Imaging adenomas and carcinomas. *Radiología.* 2012; 54(4): 342-349.
21. Özcan HN, Tan AA, Ardicli B, Berna Oguz B, Saniye Ekinici S, Kutluk T, et al. Imaging findings of primary adrenal tumors in pediatric patients. *Diagn Interv Radiol.* 2021; 27: 811-815.
22. Mackie G, Shulkin B, Ribeiro R, Worden F. Use of [18F] fluorodeoxyglucose positron emission tomography in evaluating locally recurrent and metastatic adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2006; 91(7): 2665-71.
23. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda E, Caran E, Oliveira-Filho A, et al. Clinical and Outcome Characteristics of Children With Adrenocortical Tumors: A Report From the International Pediatric Adrenocortical Tumor Registry. *Journal of Clinical Oncology.* 2016.
24. Riedmeier M, Decarolis B, Haubitz I, Müller S, Uttinger K, Börner K, et al. Adrenocortical Carcinoma in Childhood: A Systematic Review. *Cancers.* 2021; 13: 5266.
25. Cecchetto G, Ganarin A, Bien E, Vorwerk P, Bisogno G, Godzinsky J, et al. Outcome and prognostic factors in high-risk childhood adrenocortical carcinomas: A report from the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT). *Pediatr Blood Cancer.* 2016; 1-8.
26. Krege S, Falhammar H, Lax H, Roehle R, Claahsen-van der Grinten H, Kortmann B, et al. Long-Term Results of Surgical Treatment and Patient-Reported Outcomes in Congenital Adrenal Hyperplasia—A Multicenter European Registry Study. *J. Clin. Med.* 2022; 11: 4629.
27. Riedmeier M, Thompson L, Molina CF, Decarolis B, Härtel C, Schlegel P, et al. Prognostic value of the Weiss and Wieneke (AFIP) scoring systems in pediatric ACC – a mini review. *Endocrine-Related Cancer.* 2023; 30: e220259.