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ORIGINAL PAPER

Cushing's syndrome caused by an ACTH-producing ovarian steroid cell tumor, NOS, in a prepubertal girl

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Abstract Ectopic ACTH syndrome is a very rare cause of pediatric Cushing's syndrome. And if present, bronchial or thymic carcinoids predominate as causes. We hereby demonstrate a first case report of ACTH-producing ovarian steroid cell tumor, NOS, causing ectopic ACTH syndrome in a prepubertal girl.

Keywords Cushing's syndrome · ACTH · Ovarian steroid cell tumor, NOS · Girl

Case report

A 6 4/12-year-old Thai girl presented to the Department of Pediatrics with a 5-month history of rapid weight gain of 7 kg. Two months prior, she developed facial acne, round facie, and hirsutism. She had no history of vomiting, headache, blurred vision, or behavioral change. Her growth rate had declined significantly. Her past medical history was unremarkable. She denied any history of taking herbal medication, steroids, or supplemental drugs.

At presentation, she was moderately obese and cushinoid, with a % weight for height of 141. Her weight was 27.2 kg (>97th percentile) and her height was 114 cms (25th–50th percentile). She had a blood pressure of 146/94 mmHg. Her face was round and hirsutism at upper and lower back, multiple acnes at forehead and both cheeks, and purplish striae at both upper arms and thighs were noted. She had Tanner I breasts and pubic hair. Prominent clitoris was noted. Her neurological examination was unremarkable.

Due to the presence of classic signs and symptoms of Cushing's syndrome, appropriate hormonal investigations were performed and confirmed the diagnosis of hypercortisolism. She had loss of diurnal variation of serum cortisol levels (8 AM serum cortisol 50.36 μg/dl, 1,388 nmol/l, 8 PM serum cortisol 42.55 μg/dl, 1,174 nmol/l), which was consistent with cortisol overproduction. Her serum cortisol, ACTH, and 24 h urine free cortisol were remarkably high. High-dose dexamethasone suppression test showed non-suppressible serum ACTH and serum cortisol levels. Ectopic ACTH-producing tumor was suspected.

High dose dexamethasone suppression test

Day	24 h urine free cortisol (normal range 3–9 μg/24 h, 8.3–24.8 nmol/day)	Serum cortisol (normal range 3–21 μg/dl, 83–579 nmol/l)	Serum ACTH (normal range 10–60 pg/ml, 2.2–13.3 pmol/l)
0	657.45 μg/24 h (1,814 nmol/day)	38.93 μg/dl (1,073 nmol/l)	402.40 pg/ml (89.4 pmol/l)
1	1036.07 μg/24 h (2,858 nmol/day)	44.8 μg/dL (1,234 nmol/l)	N/A
2	Missing specimen	50.42 μg/dl (1,389 nmol/l)	278.40 pg/ml (61.9 pmol/l)

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Hypokalemia (serum K 2.1 mmol/l) and metabolic alkalosis (CO2 29 mmol/l) were noted but her serum aldosterone level was normal (3.94 ng/dl, 109 pmol/l [normal 3–35 ng/dl, 83–972 pmol/l]). Her plasma renin activity was low (35 ng Ang I/ml h, normal 50–385 ng Ang I/ml h). Serum testosterone was high (56 ng/dl, 1.94 nmol/l [normal 3–10 ng/dl, 0.1–0.35 nmol/l]) and serum DHEA-S was slightly high (156 μg/dl, 4.2 μmol/l [normal 19–144 μg/dl, 0.5–3.9 μmol/l]).

CT scan of the abdomen showed a smooth border, well-defined, and heterogeneous enhancing left ovarian tumor without calcification. The size was 5.8 cm in diameter. Initially, ovarian germ cell tumor was suspected. Bilateral adrenal enlargement was also observed (4 × 7–8 cm).

Tumor markers, including AFP, β-hCG, and CA-19-9 were normal. In contrast, CA-125 was very high (95.68, normal 0–35 U/ml) and NSE was slightly elevated (40.48, normal 0-15.2 μg/ml).

During the first week of admission, the girl developed hypertensive encephalopathy characterized by behavioral change, convulsion, and cortical blindness. MRI brain showed generalized brain atrophy with ventriculomegaly. Her blood pressure was controlled with multiple antihypertensive drugs. Subsequently, the patient underwent exploratory laparotomy and a well-circumscribed, twisted left ovarian tumor with intact capsule and hypervascularization was found. Left salpingo-oophorectomy was performed.

The pathological findings were consistent with steroid cell tumor, not otherwise specified (NOS). Macroscopically, the ovary was enlarged measuring 7 × 6 × 5 cm and showed smooth external surface with congested serosal vessels. The cut surface revealed non-homogeneous light brown and pink tan appearance with a small focus of necrosis (Fig. 1). Microscopically, the ovarian tissue was replaced by nests or cords of round to polygonal cells with eosinophilic cytoplasm, mild nuclear atypia, and frequent intranuclear inclusions. Mitotic figures ranged from 2–5/10 high power fields (HPFs). There was no capsular, angiolymphatic, or perineural invasion.

Immunohistochemistry stains showed neoplastic cells marked with vimentin, and calretinin, focally marked with alpha-inhibin and AE1/AE3. They do not mark with chromogranin A, synaptophysin, CD56, Melan-A, and HMB 45. Faintly positive ACTH-immunoreactivity was found. The latter was performed simultaneously on two blocks of paraffin embedded tissue, one obtained from formalin fixed tissue within 12 h after fixation and the other had been fixed for more than 24 h. The former yielded faintly positive and the latter negative results. The ultrastructural study was performed from the fresh tissue immediately fixed in 4% glutaraldehyde. Secretory granules of irregular shapes were found ranging from 100–400 nm compatible with ACTH secretory granules (Fig. 2).

The final diagnosis in this girl was ectopic Cushing's syndrome secondary to ACTH-producing ovarian steroid cell tumor, NOS. Metastatic work up consisting of CT chest and bone scan were normal. This tumor was classified as stage I disease. Within 2 weeks after tumor removal, the patient had normalization of blood pressure without further requirement for antihypertensive medication. At 6 weeks, her serum testosterone and CA-125 became normal (9 U/ml). Serum NSE remained slightly elevated (29.94 μg/ml). At 6 months, her serum ACTH level normalized and a CT whole abdomen revealed no definite mass at surgical base and no hyperplasia of both adrenal glands. The girl's Cushing features had subsided with 4 kg of weight loss within 8 months. She also was noted to have catch-up growth and improvement of her vision.

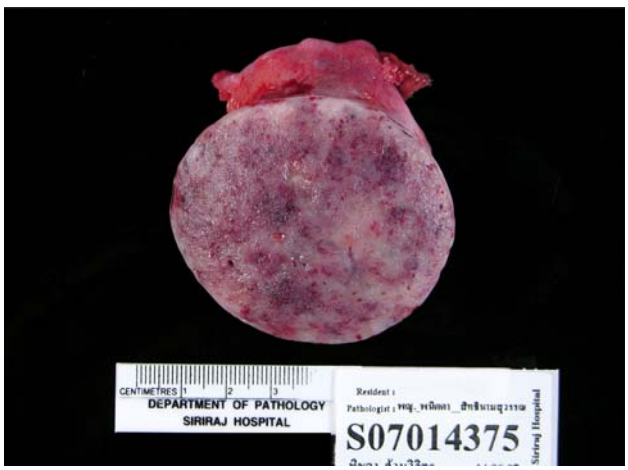

Fig. 1 Nonhomogeneous light brown and pink tan cut surface with a small focus of necrosis

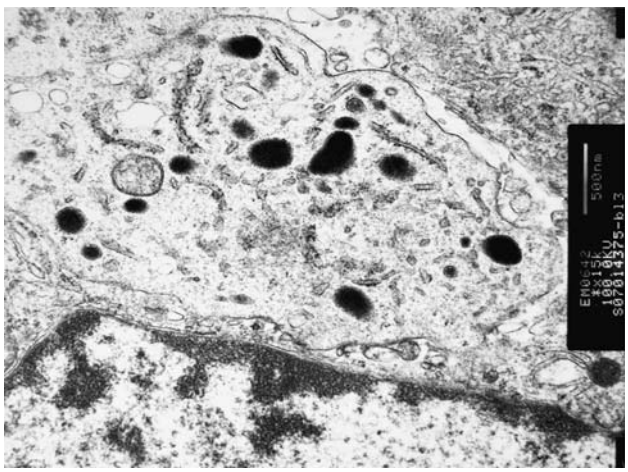

Fig. 2 Numerous irregular shaped ACTH secretory granules varying from 100 to 400 nm in neoplastic cells

Discussion

Cushing's syndrome is rare in children but presents a diagnostic and therapeutic challenge. It is a clinical syndrome caused by excessive circulating glucocorticoid concentrations resulting from either endogenous secretion or exogenous administration [1]. The most common cause of endogenous Cushing's syndrome in children is Cushing's disease, which is caused by an ACTH-secreting corticotroph adenoma [2].

Ectopic ACTH syndrome is extremely rare in the pediatric age range. It accounts for less than 1% of the cases of Cushing's syndrome in adolescents [3]. Carcinoid tumors, mostly bronchial or thymic in origin predominate as causes of pediatric ectopic ACTH syndrome [1]. We hereby report, to our knowledge, a first case of ACTH-producing ovarian steroid cell tumor, NOS, causing ectopic ACTH syndrome in a girl. Cushing's syndrome resulting from an ovarian tumor is extremely rare in children. Only two cases of adrenal rest cell and hilus cell tumors of ovary have been reported in children so far [4, 5].

Our patient presented with classic signs and symptoms of Cushing's syndrome. She also developed severe complications of excess serum cortisol which were brain atrophy [6] and hypertensive encephalopathy leading to cortical visual impairment. Loss of diurnal variation of serum cortisol levels confirms hypercortisolemia. High-dose dexamethasone suppression test showed non-suppressed serum cortisol and ACTH levels, which indicated ectopic ACTH syndrome. Although 10–20% of individuals with Cushing's disease do not suppress, serum ACTH concentrations of >300 pg/ml strongly suggest ectopic ACTH production [7].

In this case, the histopathology including immunohistochemistry of positive calretinin and alpha-inhibin but negative chromogranin supported a steroid cell tumor and excluded adrenocortical tumor and even pituitary neoplasm as apart of germ cell tumor. By morphology and location, it could be readily distinguished from stromal luteoma and Leydig cell tumor. These indicated that this young patient had ovarian steroid cell tumor, NOS [8]. Taken together the findings of abundant ACTH secretory granules in the tumor with high serum ACTH levels and lack of high-dose dexamethasone suppression, we conclude that this ovarian steroid cell tumor, NOS, in this girl produced ACTH. Though we found abundant ACTH secretory granules ultrastructurally, the ACTH immunoperoxidase staining was rather weak and even lost in the prolonged formalin fixed tissue; this might be postulated that the antigenic property was much lost from the compromised vascular supply due to the ovarian torsion.

Hypokalemia and metabolic alkalosis despite normal serum aldosterone levels reflect the metabolic effect of cortisol excess. Excess cortisol can bind to aldosterone receptor and cause aldosterone effects [9], which are hypertension, hypokalemia, metabolic alkalosis, and suppressed plasma renin activity presented in this patient.

The patient had high serum testosterone levels manifesting with signs and symptoms of androgen excess, which were acne, oily face, hirsutism, and clitoromegaly. Increased serum testosterone level was most likely due to the effect of ACTH stimulation to the adrenal glands. However, we could not totally exclude the possibility that the tumor itself also produced testosterone. The increased serum ACTH level also caused bilateral adrenal gland enlargement in this patient as evident by CT scan.

Steroid cell tumors of the ovary have been classified into three groups: stromal luteomas, Leydig cell tumors, and steroid cell tumors, NOS. Steroid cell tumor, NOS, is a group of steroid cell tumors that cannot be readily classified as either stromal luteomas or Leydig cell tumors [10, 11]. Ovarian steroid cell tumors, NOS, usually occur in adults with an average age at diagnosis of 47 years. Hirsutism and virilization resulting from androgen secretion are the most common symptoms occurring in 56–77% of patients [12, 13]. Estradiol secretion occurs in 6–23% of patients [12, 13]. Twenty-five percents of ovarian steroid cell tumors, NOS, do not produce hormones [13]. Steroid cell tumors, NOS, have been associated with Cushing's syndrome due to ovarian cortisol production in only 6–10% of cases [13–15]. There has been only one previous case report of an ACTH-producing ovarian steroid cell tumor, NOS, in a young woman [16].

The majority of steroid cell tumors, NOS, have either benign or low grade behavior. Most of these tumors are usually diagnosed at an early stage and do not recur or metastasize. If metastasis is present, about 20% of metastatic lesions usually occur within the peritoneal cavity and rarely at distant sites [13, 17].

The most accurate predictor of malignant behavior of tumors reported by Hayes and Scully [13] is the presence of $\geq$2 mitotic figures per 10 HPF. The majority of malignant tumors also demonstrate grade 2–3 nuclear atypia, necrosis, hemorrhage, and a tumor diameter of $\geq$7 cm. The presence of mitotic figures of 2–5/10 HPF, focal necrosis, and tumor diameter of 7 cm in our patient raises the probability of malignant behavior of her tumor.

The mainstay of ovarian steroid cell tumors, NOS, is surgery. Conservative surgery with unilateral salphingo-oophorectomy to preserve fertility is recommended in young patients with stage IA disease since the frequency of bilateral occurrence is only 6% [13, 18, 19]. Proper staging should be performed. Postoperative follow up of hormonal levels and tumor surveillance is essential. The necessity of adjuvant chemotherapy should be based on histological appearance of the tumor and its surgical staging.

However, the therapeutic value of chemotherapy and radiation therapy in the treatment of ovarian steroid cell tumor, NOS, is poorly understood due to the rarity of this tumor and the early stage of diseases in the majority of cases [20]. There are some studies that showed efficacy of combination chemotherapy (bleomycin, etoposide, and cisplatin) for stage II primary malignant ovarian stromal tumors, metastatic, and recurrent diseases [21, 22].

Although the tumor's pathological characteristics favored malignancy in our patient, the tumor was stage I without evidence of capsular, angiolymphatic, or perineural invasion. Therefore, she did not receive any adjuvant treatment with either chemotherapy or radiation. Since her serum tumor markers (CA-125 and NSE) and hormonal levels including serum testosterone, ACTH, and cortisol were elevated before tumor removal, she would be followed up closely for these markers and also imaging studies for any recurrence and metastasis.

In conclusion, we hereby demonstrate a first case report of ACTH-producing ovarian steroid cell tumor, NOS, causing Cushing's syndrome in a prepubertal girl. Although, bronchial or thymic carcinoids predominate as causes of ectopic ACTH syndrome in children, ovarian steroid cell tumor, NOS, should be included in the differential diagnosis of Cushing's syndrome in these young children.

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