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CASE REPORT
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Ectopic Cushing's Syndrome: A Race Against Time

ABSTRACT

Cushing's syndrome is characterized by a phenotype resulting from cortisol excess. To manage Cushing's syndrome, the etiology must be defined. Cushing's syndrome is broadly divided into adrenocorticotrophic hormone-dependent and adrenocorticotrophic hormone-independent Cushing's syndrome. Adrenocorticotrophic hormone-dependent Cushing's syndrome is further subdivided as pituitary adrenocorticotrophic hormone-secreting Cushing's disease and ectopic Cushing's syndrome where adrenocorticotrophic hormone is secreted from a location outside the pituitary. Ectopic adrenocorticotrophic hormone syndrome can be a challenging situation as the patients are often sick and the adrenocorticotrophic hormone source is not always obvious. The challenge is even tougher in case of infants and children. Here, we present one such case of ectopic adrenocorticotrophic hormone syndrome we encountered recently, had difficulties in managing her, and unfortunately lost the child. The source of adrenocorticotrophic hormone was a sacrococcygeal teratoma.

Keywords: ACTH-dependent, Cushing's syndrome, ectopic, schwannoma, teratoma

Introduction

Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH) secretion can be associated with a wide variety of tumors. Since its first recognition in 1929 by Brown, there has been a plethora of tumors associated with ectopic ACTH secretion.[1] According to various estimates, ectopic ACTH comprises 5%-10 % of all cases of ACTH-dependent Cushing's syndrome.[2] Ectopic adrenocorticotrophic hormone syndrome generally has a rapidly progressive course, more sick presentation, and poor outcome. This can be due to a high cortisol load and associated complications or due to the ominous nature of the ACTH-secreting tumor, which can be malignant and metastatic. The management is difficult and sometimes the search for the source of ACTH can be difficult.

Case Presentation

A 16-month-old girl was brought to our endocrinology outpatient department with a swelling on the left buttock for last 3 months. At the same time, the child started to gain weight and was also feeding voraciously. She grew so plump that it was difficult for her parents to manage her and she also developed excoriations at the folds and creases of her skin. Born out of a non-consanguineous marriage, this first-born child had an uneventful birth and initial developmental history. An endocrinologist who saw the patient initially ordered a set of investigations that revealed hypokalemia (K+ = 3.4), normal thyroid function tests, and hypercortisolism (8:00 AM serum cortisol = 63.44 µg/dL). A provisional diagnosis of pediatric Cushing's syndrome was made and the child was referred to us.

On initial examination, the child weighed 13 kg (>95th centile for age and sex), had a round face, central obesity, reddish skin, and poor muscle tone (Figure 1). She was also unable to sit without support. Her blood pressure was 100/90 mmHg (>95th percentile for age and sex). Routine investigations conducted after admission revealed elevated liver enzymes at aspartate transaminase = 41 IU/L (N < 35) and alanine transaminase = 89 IU/L (N < 35) along with mild hypokalemia with a serum potassium of 3.4 meq/L (N = 4.1-5.3). Her fasting plasma glucose during the admission was 145 mg/dL (N < 126). The hormonal evaluation performed at baseline gave the following results: 8 AM serum cortisol was greater than 50 µg/dL (N = 5-25), serum dehydroepiandrosterone sulphate (DHEAS) was 41 µg/dL (N < 35), plasma ACTH was 79 pg/mL (N = 0-46), serum testosterone was <20 ng/dL (N < 20), and serum androstenedione was 3.53 ng/mL (<0.15). Bone age was corroborative with the chronological age.

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Figure 1. Child at presentation showing moon face, swelling of body, and poor muscle tone.

Considering the initial findings and high ACTH value, a provisional diagnosis of ACTH-dependent Cushing was reached. In the meantime, hypertension was managed with tablets spironolactone and amlodipine, which was difficult to control. Realizing the urgency of the situation, we straight away embarked on a high-dose dexamethasone suppression test for etiological diagnosis. After obtaining basal serum cortisol levels, the child was administered oral dexamethasone tablet at 20 µg/kg/dose for a total of 8 doses over 48 hours at the end of which another serum cortisol level was obtained. The baseline and post dexamethasone values of cortisol were >100 µg/dL.

MAIN POINTS

- Cushing's syndrome is a rare disease and even rarer in children and infants.
- Ectopic Cushing's syndrome (ECS) is characterized by a severe phenotype, fulminant course, and overdose of complications.
- The source of adrenocorticotrophic hormone in ECS sometimes can be very difficult to locate and if located, may not be amenable to treatment.
- Sacrococcygeal teratoma is an extremely rare cause of ECS seen in young children.
- Treatment of ECS is often delayed because of difficulty in diagnosis and mortality is high because of the high cortisol load, low potassium, opportunistic infections, and comorbidities.

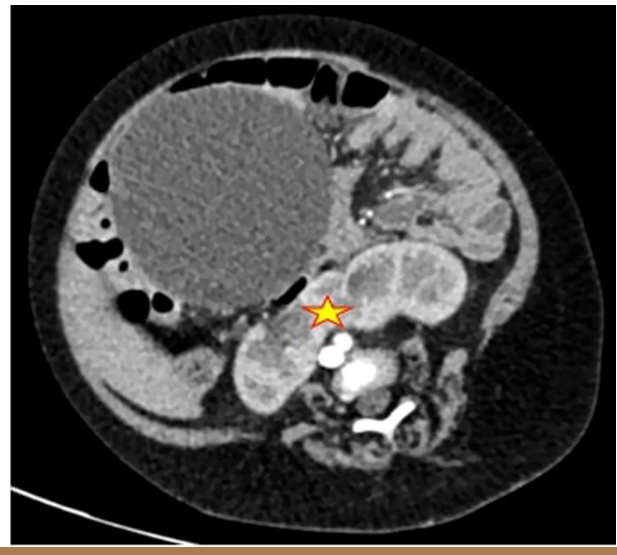

Figure 2. Computed tomography scan of abdomen showing horseshoe kidney (star).

During her in-hospital stay, she had worsening hypertension and blood glucose levels, which were managed with increasing doses of antihypertensives and insulin. Then, imaging investigations were ordered to locate a culprit source for ACTH. A contrast-enhanced computerized tomography (CECT) of the abdomen revealed the following (Figure 2):

1. horseshoe kidneys;
2. 78 mm large mass involving left posterior pelvis, sacrococcygeal area, and posterior gluteal region—sacrococcygeal teratoma;
3. nodular masses in both lungs, likely metastasis.

Magnetic resonance imaging (MRI) of the hypothalamo-pituitary area demonstrated a normal pituitary with diffuse cortical atrophy as a sequelae of hypercortisolemia (Figure 3). The CECT abdomen findings prompted us to perform a focused MRI of the pelvic area which showed a large, heterogeneous, mixed signal mass (showing both cystic and solid components) within the left paramedian pelvis, with asymmetrical bulging within the left gluteal region suggestive of teratoma/schwannoma/peripheral nerve sheath tumor (Figure 4).

We considered a diagnosis of ectopic ACTH syndrome likely due to the gluteal teratoma/schwannoma. The pediatric surgery team was called in to help with a histopathological diagnosis and excision of the mass. A panel of tumor markers was obtained in the meantime. The reports revealed a serum alpha-fetoprotein level of 928 ng/mL (N < 12), serum beta-human chorionic gonadotrophin level of 6159 mIU/mL (N < 5.3), and serum lactate dehydrogenase level of 1528 U/L (N = 120-300). The elevated tumor markers pointed toward the diagnosis of a tumor of germ cell origin.

The infant gradually became drowsy and breathless. At that point of time, the total leucocyte count was 28.4×10^9/L and the serum potassium was 2.9 meq/L. She was shifted to the pediatric critical care unit (PICU) and treated for these complications. Unfortunately, after a total stay of 3 weeks, the infant succumbed before definitive therapy could be offered. While in the PICU, liver dysfunction

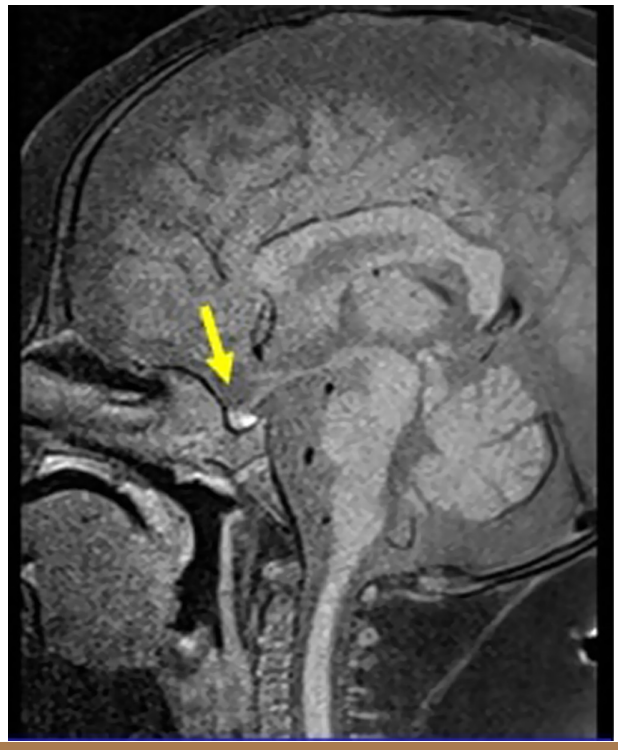

Figure 3. T1-weighted magnetic resonance imaging showing normal pituitary (arrow) and gross cortical atrophy.

had also set in and parenteral access was also difficult. The probable cause of death could be sepsis or arrhythmia due to hypokalemia. A hypercoagulable state and its consequences could also have contributed to the infant's death. The parents did not consent to a medical autopsy. Though the diagnosis was obvious, a tissue diagnosis could not be done. Written informed consent was obtained from the patient's guardian to share the figures and information of this case report.

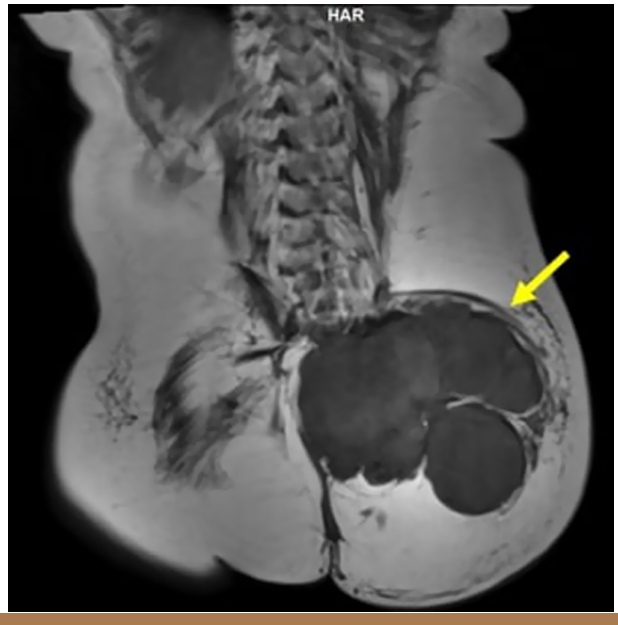

Figure 4. Magnetic resonance imaging of pelvis showing large heterogeneous mass in left gluteal region suggestive of teratoma/schwannoma (arrow).

Discussion

Cushing's syndrome is rare in children.[3] Endogenous Cushing's can be ACTH-dependent or independent.[4] A very high cortisol level, unsuppressed cortisol after high-dose dexamethasone, and raised plasma ACTH level in our patient clearly point to an ACTH-dependent etiology of Cushing's syndrome. The raised DHEAS level also supports a diagnosis of ACTH-dependent Cushing's syndrome. Dehydroepiandrosterone sulfate levels are expected to be undetectable in normal infants. Adrenocorticotrophic hormone-secreting non-pituitary tumors may lead to preferential stimulation of androstenedione secretion through an unidentified proopiomelanocortin (POMC)-derived peptide, which explains the raised androstenedione in our case.[5]

During infancy, Cushing's syndrome is usually associated with McCune–Albright syndrome while adrenocortical tumors are the most common cause of Cushing's syndrome in children under 7 years of age.[6] Tumors outside the normal pituitary–adrenal system can produce ACTH which affects the adrenal glands and is termed ECS or paraneoplastic Cushing's syndrome. Ectopic Cushing's syndrome has been reported in literature to be caused due to variety of tumors, mostly small cell carcinoma of the lung, carcinoid tumors, or neuroendocrine tumors, and less frequently, phaeochromocytoma, pancreatic carcinoma, thyroid neoplasms, adenocarcinomas of gall bladder, salivary gland, colon, and prostate.[7] The causes of ectopic Cushing's are so varied that it may be difficult to localize the offending lesion.

Teratomas are known to produce several hormones, mainly human chorionic gonadotrophin but may cause Cushing's syndrome[8,9] Sacrococcygeal teratoma as a rare source of ectopic ACTH has been rarely documented in the past.[10] There is 1 case report of an ACTH-secreting mature teratoma in sacro-coccygeal region in a 33-year-old woman.[11] If associated with malformations of rectum or anal canal and agenesis of scrum, this may be part of Currarino syndrome, a rare autosomal-dominant disorder.[12,13]

In our case, we clinched the diagnosis of ectopic Cushing's due to a large sacrococcygeal teratoma that was also extending inside the abdomen. The fulminant course of the illness in our case further strengthens a diagnosis of ECS.

Conclusion

Ectopic Cushing's syndrome can be a difficult-to-treat condition for the endocrinologist. The fulminant course of the illness due to high cortisol load leading to severe hyperglycemia and hypertension, extensive metastatic disease, and opportunistic infections make this an emergent situation. This rare source of ECS and subsequent course of the illness can be a learning for all who deal with such patients.

Informed Consent: Written informed consent was obtained from the patient's guardian to share the figures and information of this case report.

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Declaration of Interests: The authors have no conflict of interest to declare.

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