Delayed Diagnosis and False Relapse Due to Paternal Testosterone Use in Adrenocortical Carcinoma

abstract

The prognosis of pediatric adrenocortical carcinoma often depends on prompt diagnosis to begin treatment before metastatic progression. We discuss a girl who presented at 8 months of age with virilization, which was thought to be due to exposure to a topical testosterone preparation being used by her father. Her testosterone level did not decrease promptly after her father discontinued the medication, however, and when she followed up with signs of Cushing syndrome 5 months later, metastatic adrenocortical carcinoma was diagnosed. The patient was successfully treated with surgery and multiagent chemotherapy. Nine months after the end of treatment, her testosterone level was again found to be elevated. Testosterone precursors were now absent, however, and there were no imaging signs of recurrence. Further history showed that her father had restarted topical testosterone, and this time, exogenous exposure was correctly diagnosed. As use of topical testosterone becomes more prevalent, exogenous exposure must be considered in the differential diagnosis of childhood virilization. Any persistent testosterone elevation after exposure ceases or signs of hypercortisolism, however, are inconsistent with this diagnosis. We believe that the risk-benefit ratio favors abdominal ultrasound to rule out malignancy in all children presenting with virilization. Pediatrics 2014;133:e1772–e1776

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KEY WORDS
adrenocortical carcinoma, children, delay, diagnosis, exogenous, paternal, recurrence, testosterone, topical, virilization

ABBREVIATIONS
ACC—adrenocortical carcinoma
CT—computed tomography
DHA—dehydroepiandrosterone
dHEAS—dehydroepiandrosterone sulfate

Dr Green is the patient’s oncology attending, formerly her oncology fellow, who compiled the case and references, wrote most of the first draft of the manuscript, and created the figures; Dr Srivatsa is the patient’s endocrinologist and diagnosed her tumor, and reviewed the related endocrinology literature, provided appropriate references, and edited the manuscript; Dr Rodriguez-Galindo is the patient’s former oncology attending, raised the idea of the case report and its teaching points, and edited the manuscript; and all authors approved the final draft as submitted.

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Adrenocortical carcinoma (ACC) is a rare solid tumor in children that most often presents with virilization. The differential diagnosis for virilization in children is broad, however, and has recently come to include exogenous testosterone exposure due to parental use. The treatment and prognosis of ACC change dramatically with progression to metastatic disease, so prompt diagnosis is crucial. Therefore, in virilized children, pediatricians and endocrinologists must be able to efficiently negotiate the differential diagnosis. History, physical examination, measurement of levels of testosterone and its precursors, and targeted imaging are all useful tools in this process. Here we present an instructive case addressing these issues.

**CASE**

The patient is a 3-year-old girl who began to develop pubic hair at the age of 8 months, along with rapid weight gain. Her father was using Androgel 1% (37.5 mg testosterone topically once daily) prescribed by his physician for symptoms including fatigue and moodiness. The family brought her symptoms to her pediatrician’s attention at her 9-month physical, and the patient was referred to endocrinology. At her initial endocrinology visit at 9 months, her parents described her as a happy baby with a big appetite. She was noted to have Tanner II pubic hair on the labia majora, without other signs of puberty or virilization. Her weight at this visit was 11.2 kg (86th percentile), with length 72.1 cm (13th percentile). Her testosterone level was 23 ng/dL, with 17-hydroxyprogesterone 29 ng/dL, DHEAS 32.8 μg/dL (normal 5–40), and androstenedione 34 ng/dL (normal 10–47). Because of the patient’s accelerated weight gain and decelerated linear growth, along with her facial appearance, a dexamethasone suppression test was performed. The early morning cortisol level before dexamethasone was 22.6 μg/dL (normal 5–25), with an undetectable (<5 pg/mL) adrenocorticotropic hormone level; after the dose of dexamethasone, the cortisol level the next morning was 21.8 μg/dL, with adrenocorticotropic hormone still undetectable. With the unsuppressed serum cortisol and a persistently elevated testosterone despite elimination of the potential exogenous source, an abdominal ultrasound was performed and showed a 5 × 6 × 5-cm calcified right suprarenal mass.

The patient subsequently underwent computed tomography (CT) of the chest, abdomen, and pelvis to further characterize the mass; the scan was notable for multiple, bilateral pulmonary nodules. She underwent resection of her right adrenal mass and wedge resections of pulmonary nodules in the right upper and right lower lobes, all of which showed ACC. After recovery from surgery, the patient was treated on the Children’s Oncology Group protocol ARAR0332 with 8 cycles of chemotherapy that included cisplatin (total dose 750 mg/m²), etoposide (2400 mg/m²), doxorubicin (400 mg/m²), and mitotane (given by gastrostomy tube in a lipophilic suspension, with serum levels followed to maintain a level of 14–20 μg/mL throughout therapy). One month postoperatively and 5 days after completing her first cycle of chemotherapy, her DHEAS, DHA, and androstenedione had all become undetectable; the first testosterone level on treatment, checked after 2 cycles, was also undetectable. These markers remained undetectable on checks after every 2 cycles for the remainder of treatment. The patient’s remaining pulmonary nodules stabilized by CT after 2 cycles, improved after 4 cycles, and disappeared after 6 cycles. She completed therapy at 23 months of age.

Subsequent laboratory tests and CT done on therapy completion and every 3 months through 6 months off therapy showed undetectable androgen levels and no evidence of recurrent disease. Nine months off treatment, the testosterone level had increased to 42 ng/dL. CT of the chest, abdomen, and pelvis again showed undetectable androgen levels and no evidence of recurrent disease. The endocrinology and oncology teams were concerned for recurrence. It was noted that DHEAS, DHA, and androstenedione were again undetectable. The patient continued to show no signs of virilization on physical examination. On further questioning, the family stated that the patient’s father had resumed his use of topical testosterone; he again discontinued use of the medication, and on repeat testing 1 month later, the patient’s testosterone level was again undetectable. She continues in remission, now 28 months off therapy.
FIGURE 1
DISCUSSION

In prepubertal children, testosterone is made largely by the adrenal glands. Synthesis of testosterone from cholesterol is a multistep process that includes 17-hydroxyprogesterone, DHA, and androstenedione as intermediate products (Fig 3). More than 99% of DHA is sulfated to form DHEAS before excretion from the adrenal gland; DHEAS is the most abundant steroid in the body and appears to be a circulating precursor that can be desulfated by a variety of peripheral tissues and subsequently converted to various estrogenic and androgenic compounds. DHA and DHEAS tend to be most elevated in ACC with virilization but not hypercortisolism. Because the production of cortisol shunts precursors away from DHA and DHEAS, these are usually less elevated or normal in ACC with virilization and hypercortisolism, which was the situation in our patient. Because androstenedione is the immediate precursor to testosterone, its levels tend to closely mirror testosterone. Because it equilibrates with testosterone via 17β-reductase, however, it is less useful than other precursors in differentiating exogenous from endogenous testosterone production.

ACC in children is a rare occurrence, with approximately 25 new cases occurring annually in the United States, equating to an incidence of 0.2 to 0.3 cases per million. The median age of presentation is 3 to 4 years. Almost all children present with hormonally functioning tumors, most commonly leading to virilization, with a mixed virilization-hypercortisolism pattern somewhat less common. Most children have resectable disease at presentation, with distant metastases present in fewer than one-third. Stage of disease, based on tumor invasiveness and size, is a major predictor of outcome. Long-term survival is expected in >90% of patients with small, completely resectable tumors, whereas in patients with distant metastases, survival plummets to ~10%, emphasizing the need for prompt diagnosis. Historically, surgery has been the mainstay of treatment. Now, clinical trials are investigating the role of intensive, multiagent chemotherapy, including mitotane, in addition to surgery. Mitotane is an insecticide derivative that both inhibits corticoid biosynthesis and causes necrosis of adrenocortical cells; it has been used extensively in adult ACC.

In our case, the paternal use of topical steroids clearly made the diagnosis of ACC more difficult, but a close examination reveals lessons that can be applied to future patients. Virilization in children due to exposure to topical testosterone being used by caregivers has been documented in several case reports and series. In all of the cases in which testosterone levels were reported, however, levels returned to normal on the next measurement after exposure to the exogenous source was

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**Figure 2**
Levels of testosterone and DHEAS over the time course of the case.

**Figure 3**
The steroid pathway, with steps inhibited by mitotane.
removed. With increasing use of topical testosterone, the diagnosis of exogenous virilization in children is likely to become more common. Providers must consider other possibilities carefully, however. Any delay in normalization of testosterone levels after removal of the source is inconsistent with the diagnosis of topical testosterone exposure. Any symptoms of hypercortisolism also rule out exogenous testosterone exposure. In retrospect, hypercortisolism was first suggested in our patient by her decrease in height percentile that accompanied her increase in weight percentile. These inconsistencies must prompt an immediate search for other causes. Measurement of other androgen precursors may be of use in some cases. Although our patient’s initial normal precursor levels could have fit with either exogenous testosterone exposure or ACC, in the more common scenario of purely virilizing ACC, it is likely that DHA and DHEAS would have been elevated in addition to testosterone, ruling out exogenous exposure. Imaging, ultimately, is likely to be necessary to clarify the diagnosis. Even though ACC is rare, we feel that the enormous outcome differences from delayed diagnosis necessitate abdominal ultrasound in any child presenting with virilization. Subsequent exposure to exogenous testosterone in a child with ACC is likely to be an extremely rare occurrence. The contrast in our patient’s androgen markers at diagnosis and false alarm recurrence, though, is illustrative. Our patient’s androgen markers became undetectable immediately on starting mitotane, likely due to effects of the drug on steroidogenesis. With recurrent disease, we would have expected at least detectable levels of testosterone precursors in addition to testosterone, even with the lasting effects of mitotane present. Therefore, an elevation of testosterone alone, to a level higher than was ever produced by her ACC, was clear evidence of exogenous exposure. This was confirmed by normalization after removal of the source. In cases of childhood virilization, providers must differentiate exogenous from endogenous testosterone exposure and promptly evaluate for ACC to minimize morbidity and maximize survival in this rare but deadly childhood cancer.

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