Metastatic Congenital Adrenocortical Carcinoma: A Case Report with Tumor Remission at 3½ Years

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ABSTRACT

We describe a case of metastasizing congenital adrenocortical carcinoma and a follow-up of 3 ½ yr. Treatment with surgery and mitotane was associated with multiple complications. The patient was in remission at 3 ½ yr. Because of the rarity of this condition, we discuss step-by-step problems encountered during management.

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ADRENOCORTICAL CARCINOMA is a rare malignancy, especially in children. The overall incidence is approximately 2 cases per million per year, which accounts for 0.2% of all cancers (1). In children, the incidence is 0.3 cases per million per year except in Southern Brazil, where the incidence is 3.4–4.2 cases per million per year (2). Most series show a female preponderance. It is described in children of all age groups, but it usually appears before the age of 5 yr (3). It is very uncommon in early infancy, and only a few cases have been reported in the newborn period (4–10).

Case Report

The patient was born at 34 weeks gestation, to a 20-yr-old woman, by cesarean section (because of low biophysical profile and decreased fetal movements). A prenatal sonogram at 33 weeks gestation showed an abdominal mass of 6.5 × 4.9 × 5.6 cm. Amniocentesis revealed a normal karyotype, normal α-fetoprotein (AFP), and human chorionic gonadotrophin. Birth weight was 1.7 kg; and length, 40.6 cm. Apgar scores were 9 at 1 and 5 min. Blood pressure was 62/41 mm Hg; pulse, 157/min; temperature, 98.4 F; and respiratory rate, 44/min. Physical examination confirmed a right abdominal mass of 5 × 6 cm, firm in consistency, with a smooth surface. He had no pubic hair, and genitalia were normal for a male infant. An axial computed tomography (CT) scan revealed a large mass in the right abdomen replacing the right adrenal gland. The mass was low in density, with multiple areas of hyperdensity suggestive of necrosis (Fig 1). A small pleural based density, approximately 4 mm at the base of the right lung, was also identified. Magnetic resonance imaging confirmed the right abdominal mass and the pleural based density in the right lung. Serum cortisol was 916 nmol/L; AFP, 204,000 IU/mL (mean, 173,800 ± 53,462 IU/mL for premature infants) (11); human chorionic gonadotrophin, negative; and neuron-specific enolase, 89.5 ng/mL (4.8–19.4 ng/mL in cord blood for full-term infants) (12).

On the second day of life, the patient experienced hypoxia, with a tonic clonic seizure and epistaxis. Mechanical ventilation was required. A chest x-ray revealed diffuse haziness, with an air bronchogram. He became anemic, and pulmonary hemorrhage was suspected. Coagulation studies were normal. A head sonogram revealed grade I intraventricular hemorrhage. His electroencephalogram (EEG) was normal.

The patient was started on hydrocortisone (100 mg/m²/day), and a laparotomy was performed on the third day of life. A large homogenous mass was completely resected from the right side, and the left adrenal gland was biopsied. The tumor was well circumscribed (7 × 7 × 4.5 cm) and weighed 117 g. There was a central area of necrosis, with hemorrhage. Histopathology showed marked nuclear pleomorphism. Mitotic figures were identified (although not numerous, but present in all histologic sections). The neoplastic cells were arranged in a diffuse pattern and had abundant eosinophilic cytoplasm. Foci of coagulative necrosis were identified, in relation to organizing thrombi in small veins. There was no evidence of capsular, venous, or sinusoidal invasion. Immunohistochemical staining was positive for AFP, vimentin, α1-antitrypsin, and Ki-67 (nuclear associated proliferation marker); weakly positive for neuron-specific enolase; and negative for chromagranin and synaptophysin. The diagnosis of adrenocortical carcinoma was made. The biopsy of the left adrenal gland was normal.

A CT scan, 2 weeks after the surgery, revealed an additional 4-mm soft-tissue density in the right lung, located posteriorly and inferiorly. No local recurrence in the right abdomen was noted. A follow-up CT, 1 month after the
surgery showed another 6-mm nodular density in the right basal lung, more centrally located.

At the age of 6 weeks, he underwent a right thoracotomy. Three lesions were identified in the right lower lobe. A lobectomy was performed. The histological features of the lung lesions were consistent with those of the previously resected primary adrenal tumor. Immunohistochemical staining was positive for α1-antitrypsin and weakly positive for AFP.

Two weeks after thoracotomy, a CT scan showed three new 2- to 3-mm nodules in the right middle lobe. He was started on chemotherapy with mitotane (ο, p''-DDD; 250 mg, by mouth, every day), and the dose was progressively increased, by 250 mg/week, to a total of 2000 mg/day (approximately 8000 mg/m²-day). Replacement with hydrocortisone (15 mg/m²-day) and fludrocortisone (0.05 mg/day) was started, with chemotherapy. Two months after the start of chemotherapy, repeat CT scans showed three pulmonary nodules within the right lung (the largest measuring 8 mm in the right mid-lower lung; others were 5 mm). During escalation of the dose of mitotane, he became fussy and cranky. His feeding decreased. When the mitotane was increased to 2000 mg/day, he became lethargic, lost appetite, lost weight, and developed twitching of the extremities. EEG and CT scans of the head were normal. Thyroid function tests became progressively abnormal on mitotane (low T₄, normal T₃, normal thyroid stimulating hormone, and normal T₃-binding globulin). He became hyponatremic (Na, 122 milliequivalents/L) and hyperkalemic (K, 6 milliequivalents/L). PRA was elevated (8.3 ng/L/sec). He was started on L-T₄ (23 μg every day). The dose of hydrocortisone was progressively increased to 75 mg/m²/day; and fludrocortisone, to 0.1 mg/day. His feeding improved significantly, but seizure-like activity continued. An EEG showed spike and wave activity. Magnetic resonance imaging of the brain was essentially normal. He was started on phenobarbitol (15 mg, twice a day). Because of persistently low levels of free T₄, the dose of L-T₄ was increased to 50 μg, and then 75 μg, every day. The hyponatremia persisted, and the dose of fludrocortisone was increased to 0.2 mg, and then 0.4 mg, twice a day, with correction of the hyponatremia. He also developed gynecomastia during the course of chemotherapy with mitotane. Follow-up CT scans showed no change in the size or configuration of the three pulmonary nodules.

Because of persistent seizures, carbamazepine was added to the anticonvulsant regimen in doses increasing to 400 mg/day. His developmental assessment at the age of 5 months showed adaptive functioning at a 4- to 8-weeks level; and gross and fine motor skills, at a 4-weeks level.

A CT scan, after almost 6 months of chemotherapy, revealed only two nodules in the right lung, measuring 2 and 4 mm, respectively (an improvement from the prior study). Because of persistent seizure activity and the possibility of permanent toxic effects of mitotane on the central nervous system, the dose of mitotane was gradually decreased. His development progressed slowly on decreasing doses of mitotane. The dose of fludrocortisone and hydrocortisone was also decreased because of suppressed PRA and ACTH levels. A CT scan, at the age of 1 yr, showed only one nodule in the right lung.

After completing 1 yr of chemotherapy, mitotane was discontinued. The patient became seizure free. Gynecomastia resolved. Repeat EEGs were normal. Neurologic development improved significantly. Seizure medication and L-T₄ were discontinued, with subsequent normal thyroid function tests. Developmental evaluation, at the age of 20 months, was at about a 10- to 12-months level. CT scans, at 3, 10, and 16 months after the discontinuation of mitotane, showed no evidence of lung nodules or recurrence of tumor in the abdomen. One and a half years after discontinuing mitotane, he became hypertensive and hypokalemic. Fludrocortisone was discontinued, and both the hypertension and hypokalemia resolved. He remained on hydrocortisone (17 mg/m²-day). The most recent developmental evaluation showed delay in expressive speech, marginal delay in receptive language, and continuous progression in motor skills.

Discussion

The etiology of adrenal tumors is not understood. They may be found in association with Beckwith-Wiedmann and Li-Fraumeni syndromes. Reports in siblings and in families with a strong history of malignancy suggest a genetic predisposition (1, 13). Cytogenetics and an analysis using restriction fragment length polymorphism suggest that a locus on chromosome 11p15 is involved in adrenocortical carcinoma (14). Commonly, these tumors are associated with 11p uniparental disomy and insulin-like growth factor II gene overexpression (15). Loss of heterozygosity at the multiple endocrine neoplasia 1 gene locus at 11q13 is associated with adrenocortical carcinoma (16).

Adrenocortical carcinomas are classified as functional or nonfunctional (3). Most (95%) adrenocortical carcinomas in children are functional, as opposed to 50% in adults. Virilization, with or without hypercortisolism, is the most common associated endocrine syndrome in children with ad-
renocortical tumor. Nonfunctional tumors are rare (5%) in children, occur more commonly in males, and have a high likelihood of malignant behavior and poor prognosis (13).

Endocrine evaluation should include serum cortisol (pre- and post dexamethasone), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione, aldosterone, PRA and 24 h urinary 17 ketosteroids, 17 hydroxysteroids, and free cortisol. Elevation of 17 urinary ketosteroids is the most sensitive tumor marker, and DHEAS provides the most specific assessment of adrenal androgen production (2, 13). All patients should also be screened for pheochromocytoma (3) and neuroblastoma. Although our patient underwent surgery before we could obtain these studies, he was not virilized, cushingoid, or hypertensive. The baseline cortisol concentration of 916 nmol/L could indicate hypercortisolism or may have been attributable to the stress of his associated pulmonary condition. Measurement of DHEAS may have been a useful tumor marker, in retrospect.

Distinguishing an adrenal cortical adenoma from adrenal cortical carcinoma on the basis of histologic findings is most problematic, especially in children. The distinction between benign and malignant tumors is usually made after careful consideration of clinical, gross and microscopic features (17). In general, most adenomas are less than 100 g and are usually encapsulated, whereas carcinomas are usually greater than 500 g and may or may not be encapsulated (13). Three systems for assessing the malignant potential of an adrenal cortical tumor, based (in part) on histologic findings, have been suggested (17–19). Based on these classification systems, our patient’s tumor would be classified as clearly malignant in the Van Slooten and the Weiss systems and probably malignant in the Hough system. The significance of histological features in children has been questioned by many authors, who conclude that the morphologic criteria for biologic behavior are different in pediatric and adult tumors (20, 21). At present, a tumor can be clearly labeled as malignant only if there is distant metastasis or apparent local invasion present at the time of presentation.

On immunohistochemical staining, normal adrenal cortex expresses intermediate filaments, cytokeratin predominantly, and vimentin minimally. In contrast, most adrenal cortical carcinomas show no-to-minimal reactivity for cytokeratin but express vimentin intensely (22). Similarly, Hoak noted that neuroendocrine protein synaptophysin and neuron-specific enolase was focally present in the normal cortex, whereas extensively positive in adrenal tumors, suggesting neuroendocrine differentiation of the adrenal cortical cell after neoplastic transformation (23). Our patient’s tumor was positive for vimentin, weakly positive for neuron-specific enolase, and negative for keratin (suggesting malignant potential).

Four stages, I-IV, have been proposed for adrenocortical carcinoma, depending on the tumor size, extent of involvement, presence or absence of nodal involvement, and distant metastasis (24, 25). Patients with stage I or II disease have the best chance of cure, whereas patients with stage III-IV have poor prognoses (1, 2, 24). Our patient’s tumor would be classified as stage IV.

Surgery is the treatment of choice, even in patients with extensive metastasis. Radical excision with en bloc resection of any local invasion offers the best chance for cure (13). Continued surveillance is required, even after apparent cure, because recurrence even after 10–12 yr has been reported (3).

Adjuvant chemotherapy has been used, but the experience with cytotoxic agents other than mitotane (o- p′-DDD) is limited, especially in children. Mitotane blocks 11-β hydroxylation and decreases cortisol production. Chronic administration results in adrenal atrophy and glucocorticoid and mineralocorticoid deficiency. Mitotane also affects the peripheral metabolism of steroids. This often necessitates greater-than-normal replacement doses of adrenal steroids (26, 27). Our patient required three to four times the usual recommended doses of hydrocortisone and fludrocortisone while on mitotane.

Improved survival with mitotane is controversial and is reported in only a few series (28, 29). There are isolated cases of cure with mitotane therapy, even in metastatic disease (30, 31), and some suggest its use in all patients after surgery (28). Mitotane is lipid-soluble, has a very long half-life, and remains in the tissue for an extended time (probably months) after discontinuing the therapy (27), perhaps explaining the disappearance of pulmonary densities after the cessation of chemotherapy in our patient. Therefore, replacement of exogenous glucocorticoid and mineralocorticoid should be discontinued slowly and cautiously while observing the patient’s weight, blood pressure, potassium level, and adrenal functions.

The side effects of mitotane have reduced its tolerance. The side effects are largely dose-related and include anorexia, diarrhea, vomiting, rashes, gynecomastia, arthralgia, and leukopenia. Neurotoxicity, manifested by lethargy, somnolence, weakness, confusion, seizures, headache, ataxia, or dysarthria, can occur (3, 29). The toxic effects of mitotane are reversible after its discontinuation (31), as noted by the improvement in the seizures, progression of development, and normalization of EEG after the discontinuation of mitotane in our patient. In Van Slooten’s series (28), a low T4 level was seen in all patients who received mitotane. This was associated with an increase in T3 resin uptake, suggesting a decrease in T3-binding globulin. However, we did not observe low T4-binding globulin in our patient. The low free T4 level with normal TSH in our patient reflects either central hypothyroidism or euthyroid sick syndrome.

Conclusion

Considering the rarity of congenital adrenal carcinoma, it is understandable that few long-term follow-up reports are available in the literature. Most of these patients died by a few months of age. We are aware of one patient who had surgery at the age of 24 days, followed by local recurrence and a second surgery at the age of 4 yr, and was well at the age of 5 yr (4). To the best of our knowledge, no neonate has been described in the literature who received mitotane after surgery. Our patient had metastasis twice after surgery but responded well to mitotane and was alive and disease-free at the age of 3½ yr. The toxic effects of mitotane, although serious, were largely reversible after the discontinuation of the drug. This observation supports the suggestion that mi-
totane should not be discontinued prematurely, even if serious side effects occur, because (in selective patients) it may have a beneficial effect on survival.

References