CLINICAL VIGNETTE

Adrenocortical Carcinoma: A Rare Endocrine Malignancy with Variable Clinical Behavior, Review of Case Series

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Introduction

Adrenocortical carcinomas (ACCs) are rare endocrine tumors that occur in only one in one million population per year in the United States. In contrast, a more common cancer, breast cancer, occurs in about 1,300 in one million population in the United States[1].

The natural history of more common cancers such as breast cancer has been well-described, which illustrates the heterogeneity of that disease. Biomarkers such as estrogen receptor, HER-2/neu gene status, are both prognostic and predictive of a cancer's behavior, as well as response to therapy[1]. Furthermore, patterns of metastases also reflect another layer of biologic complexity. For example, breast cancers that are metastatic to the bone tend to have a more favorable prognosis than metastatic visceral disease to the lung, liver, and brain[1]. Because of adrenocortical carcinoma's rarity, along with its less-established treatment algorithms, the natural history of these tumors is less well understood. It is observed that adrenocortical tumors can be benign or malignant, and functioning (hormone-secreting) or nonfunctioning. Yet, the disease behaves variably in different people. The following cases will be illustrative of some of the biologic heterogeneity of this rare tumor.

Case Report One

At age 5, this female patient was exposed to radiation during the Chernobyl incident in Russia. There were no immediate health issues related to this exposure. Then in 2000, at age 20, she presented with hirsutism and abdominal pain and was subsequently found to have an adrenal mass at surgery. A 16-cm left adrenal mass was removed as well as partial left nephrectomy and partial left diaphragm resection. A liver nodule was also noted and an intraoperative liver biopsy was performed. The pathology from the surgical specimens demonstrated primary adrenocortical carcinoma with metastatic disease to the liver. She was monitored expectantly and in January 2001 she developed a liver recurrence. She was then treated with radiofrequency ablation (RFA) and palliative mitotane but did not tolerate the mitotane well because of dyspepsia and neuropathy. By May of 2001, three new liver lesions were found as well as bone disease. A bone scan confirmed multiple sites of bony disease. The patient was then treated with a course of chemotherapy (etoposide, cisplatin, doxorubicin) from May 2001 to September 2001. An incidental inferior vena cava/right atrial mass was noted and subsequently resected and found to be mural thrombus. Her bony disease then took clinical precedence in terms of symptoms of pain, requiring systemic therapy as well as local treatments to various parts of her body. Notable sites of bony disease included shoulder, rib, hip, pelvic region, thoracic and cervical spine, femur, scapula, pubic bone, knee, and humerus (most of the axial and appendicular skeletons). Despite receiving multiple therapies (local and systemic), such as RFA, mitotane, bevacizumab, and other chemotherapies and radiation, the bone disease eventually progressed. Her various treatments appeared to offer periodic stabilization of disease, allowing a prolonged disease course. In addition, other medical complications occurred which included Klebsiella bacteremia, pneumonitis, and hypertensive encephalopathy (likely related to bevacizumab therapy). Nearly 8 years after diagnosis, she died of complications related to progressive bony disease and severe pain syndrome necessitating extremely high levels of narcotics.

Case Report Two

Patient Two, a 20-year-old previously healthy female, was diagnosed in June 2007 with Cushing's syndrome and was found to have a 10-cm right adrenal mass that had invaded the right renal hilum and encroached upon the liver and extended into the inferior vena cava and right atrium. The patient underwent a right adrenalectomy and nephrectomy as well as tumor thrombectomy of the right atrium and inferior vena cava. Postoperatively the patient was placed on adjuvant mitotane therapy because of the high-risk nature of her underlying disease. Within 4 months, the patient presented again with chest discomfort and shortness of breath and was found to have significant

bulky intrathoracic disease including 3 large lesions, one causing significant partial obstruction of the right bronchial airway. Also noted were multiple liver metastases. She received combined aggressive chemo-radiotherapy. Radiation therapy was administered to the mediastinum and right hilar mass in an effort to relieve pulmonary obstruction. She received 3 cycles of cisplatin and etoposide, and responded with decrease in the bulky lung disease. However, she experienced complications of neutropenic sepsis and severe asthenia. Her fourth treatment was delayed because of severe deconditioning and general lethargy. She was hospitalized for failure to thrive and was also found to have numerous asymptomatic compression fractures. Further complications included cranial nerve VI palsy, which was most likely caused by a clivus metastasis. Ultimately this patient died within 10 months of diagnosis from progressive lung disease and secretory hormonal dysfunction (refractory Cushing's disease).

Case Report Three

In 2004, a previously healthy 58-year-old Caucasian female was being evaluated for carotid vascular disease and was incidentally noted to have a large abdominal mass. She underwent a left adrenalectomy with a 19cm x 15cm x 8cm tumor weighing 1,803 grams. On staging workup, she was found to have four suspicious liver lesions as well as multiple pulmonary micronodules. She received systemic chemotherapy as well as local therapy in the form of chemoembolization, bevacizumab, mitotane, and erlotinib therapies. Consideration for systemic active chemotherapy was aborted because of the patient's poor clinical performance status. Despite the therapies utilized, the liver masses continued to progress and encompassed a significant proportion of the patient's abdomen. As a result of this progressive bulky liver/abdominal disease, early satiety, and progressive malnutrition, she was transferred to hospice care, where she ultimately died of liver failure within 2 years of her diagnosis.

Case Report Four

In June 1996, a 52-year-old previously healthy Caucasian female presented with gallstones. She had a cholecystectomy and was incidentally found to have a right 6.5cm x 4cm adrenal mass on ultrasound. A right adrenalectomy was performed with a pathologic impression of adrenal adenoma versus well-differentiated adrenocortical carcinoma. She recovered well postoperatively but developed complications from an incisional site hernia, which was repaired in January 1998. In 2001, she was diagnosed with hypothyroidism and was placed on Synthroid therapy. In April 2003, the patient was found to have primary hyperparathyroidism and a right parathyroid adenoma. She subsequently underwent a thyroidectomy and parathyroidectomy. Pathology showed multifocal papillary thyroid carcinoma and parathyroid adenoma, and she received postoperative radioactive iodine therapy without further sequelae.

In September 2004, the patient underwent resection of a right abdominal wall mass demonstrated to be recurrent adrenal cortical carcinoma. The specimen was felt to be identical when compared with her original 1996 pathology slides. A November 2004 PET scan demonstrated uptake in the abdominal wall and right adrenal fossa, as well as a 4-cm anterior right abdominal mass. The patient underwent resection of the 4-cm mass and the 1.5-cm nodule in the right adrenal fossa; both masses were consistent with recurrent adrenocortical carcinoma. In July 2005 she had a new herniation in the right abdominal wall and had repeat hernia repair surgery in August 2006. In September and October of 2007, she was found to have a mass at the right adrenal bed, a right adrenal mass with bed uptake in the right oblique abdominal musculature with a 17 mm nodule and uptake in the right lower mediastinum as well as a small hypodense lesion adjacent to the right aspect of the esophagus at the level of the azygoesophageal recess. In December 2007 her chest lesions spontaneously decreased in size. In January 2008, she underwent resection of the right abdominal wall mass and subsequent radiofrequency ablation. Her pathology report demonstrated a poorly differentiated carcinoma consistent with adrenocortical carcinoma. Surgical margins were clear and her postoperative course has been uneventful. Adjuvant mitotane has been discussed, but the patient has declined. She remains clinically well at present, 12 years after her original diagnosis.

Discussion

Adrenocortical carcinoma is a rare disease. As demonstrated above, the natural history of the disease is quite variable, and because of its rarity, most clinicians do not encounter many cases of ACC. Unfortunately this disease is poorly studied, and there

are no known reliable biomarkers for this disease. Patient one's disease affected her entire skeleton (she lived nearly eight years with this diagnosis), whereas patient two's disease caused death within 10 months by respiratory failure and refractory Cushing's disease. Patient three's death was caused by progressive liver disease after 2 years, while patient four remains alive 12 years after diagnosis, with noted indolent disease and periodic local recurrences managed surgically. This disease clearly requires further study in an effort to find biomarkers to help predict biologic behavior of this disease. The value of this type of study would be to help define prognostic as well as predictive factors to determine early those who will have aggressive disease behavior, requiring a more aggressive approach in therapy, versus those with less aggressive disease, requiring less aggressive therapy.

The correlation between nonfunctioning or functioning tumors and survival rate remains controversial. As illustrated in this report, the heterogeneity of this disease demonstrates the challenge to correlate functioning or nonfunctioning tumors to a patient's overall clinical outcome. In evidence of this, the cases above show one patient with Cushing's syndrome, one with virilization, and two patients with nonsecreting tumors. In this report, despite the small number of cases, there is no correlation to functioning or nonfunctioning tumors and their relation to prognosis or disease behavior.

Surgery remains the most efficacious modality in treating these tumors[2-3]. Postoperative mitotane may be administered to prolong recurrence-free survival[4]. Chemotherapy including mitotane can be used for metastatic disease[4-5]. In addition, radiation, chemoembolization, radiofrequency ablation, and hormone replacement are other active and supportive treatments to be utilized[5].

Unfortunately, the cause of ACC is unknown, so its prevention is not yet attainable. The 5-year survival rate[2] for stage I and stage II is 50% to 60%, stage III 20%, and stage IV less than 10%. The 10-year survival rate remains low[2] at 10%. As mentioned, the rarity of this disease presents researchers with a dearth of clinical studies. Patients with adrenocortical carcinoma should be referred to centers of excellence, such as the UCLA Medical Center's Endocrine Surgery Team, which offers multidisciplinary management from a team of experts specializing in management of these rare diseases.

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