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Case Report

Metastatic Virilizing Adrenocortical Carcinoma: A Rare Case of Cure with Surgery and Mitotane Therapy

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A 57-year-old white woman with metastases to lungs and liver from virilizing adrenocortical carcinoma (ACC) was treated with radical nephroadrenalectomy followed by oral mitotane 3 to 6 g/day for 5 months. She developed complete response and remained free of disease for more than 25 years. Here we present the case and review the literature. ACC is a rare tumor and may occur at any age. About 60% are functional tumors with hormonal secretions and clinical manifestations due to specific hormone secretions: Cushing's syndrome due to cortisone, virilizing tumor due to androgens, feminizing tumor due to estrogens, or hypertension due to aldosterone. Stage I and II disease is curable with surgery. Stage III and IV disease may benefit from mitotane orally with gradual adjustment of the dosage to a tolerable level. Plasma mitotane level at 14 to 20 g/L results in optimal response both in hormonal secretion and symptom control, as well as tumor regression. Addition of chemotherapy (streptozotocin or a combination of etoposide, cisplatin and doxorubicin) to mitotane also produced responses along with increased survival among responders. An international study has been started by randomizing between two of the above combinations by the Collaborative Group for Adrenocortical Carcinoma Treatment.

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Adrenal cortical carcinoma (ACC) is a relatively rare malignancy (0.2% of all cancers and incidence of 2 per 1 million population)[1] that presents a significant clinical challenge for optimal treatment. Successful treatment depends on appropriate identification of the lesion, accurate staging, surgical resectability and response to subsequent mitotane, as well as cancer chemotherapy for residual or microscopic disease. We report a case of a 57-year-old woman diagnosed with right ACC with metastasis to the lungs and liver. She underwent right radical nephroadrenalectomy and liver nodule biopsy and received mitotane monotherapy for approximately 5 months, developing a complete response. She was followed regularly with physical assessment, laboratory testing, X-rays, and computed tomography (CT) scans and remained disease-free during the following 25 years.

Case Report

A 57-year-old white woman was found to have abnormal liver function test results on routine medical evaluation in December 1983. She reported a 22-pound weight loss over the previous 2 years and abnormal hair growth on her abdomen.

Physical examination revealed normal vital signs. Hair growth was present in the face without temporal balding and on the abdomen with male-type distribution. The liver was palpable 5 cm below the right costal margin, soft and non-tender. Lymph nodes and systemic examinations were negative. Pelvic examination revealed no enlargement of the clitoris or adnexal abnormalities.

Laboratory testing revealed no anemia, normal white blood cell count and normal differential counts. Fasting blood sugar was 88 mg/dL and serum creatinine 0.9 mg/dL, and normal serum electrolytes. Liver function tests were normal except for elevation of serum alkaline phosphatase 150 units/L (normal 32 to 100 units/L) and lactic dehydrogenase 343 units/L (normal 110 to 240 units/L). Urinalysis was normal.

Hormone studies revealed a serum dehydroepiandrosterone level of 9.9 ng/mL (normal 2 to 8 ng/mL), serum testosterone 1.8 ng/mL (normal 0.2 to 1.3 ng/mL), 24-hour urine-free cortisol of 141 mg (normal 56 to 159 µg), 17-hydroxycorticoids 18.2 mg (normal 2 to 10 mg), and plasma cortisol of 31 mg/dL (normal 2 to 10 mg/dL) in the morning and 18 mg/dL (normal 8 to 33 mg/dL) in the afternoon.

Ultrasound of the upper abdomen revealed a 12 cm solid, right suprarenal mass. A CT scan of the chest and abdomen confirmed the mass without evidence of local tissue invasion or lymphadenopathy and showed multiple non-calcified pulmonary nodules in both lower lobes and a small nodule in the right lobe of the liver.

Initially an open lung biopsy was performed by a small incision to establish histology. Biopsy showed metastatic ACC. She received cortisol supplementation and underwent right radical nephroadrenalectomy and biopsy from one of the many liver nodules discovered intra-operatively. Postoperative recovery was uneventful. Pathology confirmed moderately differentiated ACC from the adrenal mass and metastatic lesion in the liver nodule.

The patient was registered on the Eastern Cooperative Oncology Group protocol E1879 clinical trial study for management of metastatic ACC with some features of virilization.[2] She was started on mitotane 2 g three times daily, cortisone acetate and fludrocortisone. Mitotane was continued for a period of 5 months in varying dosages due to side effects, such as ataxia, vertigo, nausea, vomiting and diarrhea. Follow-up CT scans and chest X-rays revealed resolution of the metastases in the lungs and no recurrence in the liver. She continues to see her oncologist annually for follow-up and endocrinologist for diabetes (developed later). There has been no evidence of recurrence of malignancy for 25 years since her initial management. Incidentally, she suffered from interstitial lung disease which responded to oral steroids. Currently, she is on thyroid replacement for hypothyroidism, clonazepam for anxiety disorder, metoprolol for hypertension, atorvastatin for hyperlipidemia, and oral hypoglycemic agent for diabetes.

Discussion

ACC is a rare cancer associated with poor prognosis. The incidence is about 1 case per 1.7 million population per year, and the prevalence has been variably reported at 2 cases per 1 million population per year worldwide, accounting for 0.05% to 0.2% of all cancers.[1] In an autopsy series, 2.1% of persons were found to have clinically inapparent adrenal mass (ranging from less than 1% in patients less than 30 years and 7% in those above 70 years).[3] ACC can present at all ages, from infancy to the seventh or eighth decades of life with bimodal age distribution and peaks in the first and fourth decades.[1] One review study reported 60% of the tumors as functional.[4] The functioning tumors may secrete excessive glucocorticoids (Cushing's syndrome), mineralocorticoids and their precursors, including androgens (virilization) and/or estrogens (feminization), as well as aldosterone causing hypertension. Cushing's syndrome presents with weight gain, centripetal obesity, muscle wasting, hypertension and acne. Virilizing ACC (caused by excess androgen) presents with oligomenorrhea, hirsutism, temporal baldness, and clitoromegaly in females and gonadal enlargement in males. ACC with excess aldosterone causes hypertension. The non-functioning tumors may present with pain or fullness in the abdomen due to mass effect, weight loss, weakness, fever, and myalgias,[4] or it may be discovered incidentally during radiographic imaging (CT or magnetic resonance imaging scan of abdomen) performed for other reasons.[3] Incidentalomas are benign in two-thirds of individuals with no history of cancer but malignant in three-fourths of those who have some history of cancer. Adrenal masses <4 cm, 4 to 6 cm, and more than 6 cm are ACC in 2%, 6%, and 25% of cases.[3]

Clinical staging of the tumor at the time of diagnosis is essential for developing the treatment plan, as well as for prognosis determination. For staging tumor, node, and metastasis (TNM) system of the American Joint Committee on Cancer should be used. Tumor size of 5 cm or less with no spread to surrounding tissues or to lymph nodes without distant metastasis is classified as stage I. A tumor larger than 5 cm with other stage I characteristics is classified as stage II. Tumor invasion to nearby tissues and/or spread to nearby lymph nodes is classified as stage III. Distant metastasis is classified as stage IV.[4] Clinical stage of the tumor at the time of diagnosis is a significant prognostic factor. For stages I through IV, the approximate 5-year survival has been reported at 15% to 45%, 12% to 57%, 5% to 18%, and 0%, respectively.[5] Children have a better prognosis than adults due to earlier diagnosis (as a result of hormonal manifestations such as virilization or Cushing's syndrome) and increased surgical resectability.[1] Our patient had stage IV disease with a tumor size of 12 cm and distant metastases to lungs and liver. She went into complete sustained remission after initial radical nephroadrenalectomy followed by 5 months of mitotane therapy.

Surgical resection is the mainstay of treatment for ACC whenever possible.[6] Radical resection of adrenal gland, sometimes with removal of the adjacent kidney with lymphadenectomy has been shown to effect curability.[7] Mitotane[o,p'-DDD;2,2bis(2-chlorophenyl-4-chlorophenyl)-1, 1-dichloroethane] causes selective cytotoxic atrophy of the adrenal cortical cells which is associated with unresponsiveness to ACTH administration (the exact mechanism of this action is actually unknown). It is taken orally (35% to 45% absorption)

and has a long half-life (18 to 159 days). It has been used in the adjuvant setting, as well as in metastatic disease with variable results.[4] During therapy, measurement of the plasma o,p'-DDD levels is important. Primary mitotane treatment (10 to 20 g/day) in ACC often reduces symptoms due to a decrease in hormone production.[4] When the plasma o,p'-DDD level was maintained at >14 mg/L, 38% objective response in metastatic disease was noted with no response at <14 mg/L.[8,9] However, serum levels >20 mg/L produced neurotoxicity.[8,9] Terzolo et al[10] found that therapeutic drug levels (14 to 20 g/L) can be achieved with prolonged tolerable use of low dose (3 g/day) of mitotane in 3 to 5 months. Nausea, vomiting, anorexia, weight loss, rash, diarrhea, lethargy, sedation, dizziness, ataxia, gynecomastia, leucopenia and reversible growth arrest in children are the common side effects of mitotane therapy.[4] Hypercholesterolemia, hypoadrenalcorticism, hypouricemia or abnormal liver enzymes can occur. Glucocorticoid and mineralocorticoid deficiency[4] occurs frequently, hence hydrocortisone and fludrocortisone supplementation is necessary during prolonged mitotane treatment. In functional tumors, follow-up measurements of appropriate hormones (positive at initial diagnosis) will help to identify tumor recurrence.

Although overall survival is poor, occasionally long-term survival had been noted in metastatic disease. A 3.5 year-old boy with a virilizing metastatic ACC (stage IV) who was treated with radical nephroadrenalectomy also received low-dose mitotane for 2 years, 7 months and remained disease-free 17 months later off treatment.[11] A 69-year-old man was treated with adrenalectomy followed by low-dose mitotane 5 to 10 g/day to maintenance dose 1 g/day for 6 years 4 months. He remained disease free 17 months later off treatment.[11] A 39-year-old woman with virilizing Cushing's syndrome received mitotane 3 to 6 g/day for disease recurrence 2 years following radical surgery and later 1 g/day for 13 years. A second 24-year-old woman received mitotane 2.5 g/day after radical nephroadrenalectomy for metastatic ACC. Mitotane dosage was gradually reduced to 1 g/day over 8 years. Both patients were stage IV at time of diagnosis and remained disease free for 14 years and 16 years, respectively, on low-dose mitotane maintenance.[12] A 24-year-old woman with virilizing ACC (stage II) received mitotane 4 to 6 g/day for 3 months after radical adrenalectomy. After treatment she conceived twice and remained disease-free 8 years after treatment.[13] Another 2-month-old male infant with Cushing's syndrome received mitotane 2 g/day for 6 months after removal of a large adrenal mass for metastatic ACC (stage IV). Metastatectomy was done from the lungs at 6 months and dose of mitotane was increased to 2.5 g/day and mitotane dose level was maintained at 10 to 15 µg/mL for 18 months. He lived 15 years. Although growth and development was stunted during treatment, after discontinuation of mitotane he recovered almost completely except for slight intellectual impairment.[14]

Patients do better after surgical resection of the primary tumor whenever possible, as in our case. Since mitotane has a long half-life with considerable gastrointestinal and neurologic side effects, the drug should be started at a low dose (0.5 to 1 g daily) and later gradually increase to tolerable dosage with usage of modern anti-emetics. At that point a plasma mitotane level should be obtained to establish a level of 14 to 20 mg/L and periodically tumor status should be evaluated. In case of stable disease or partial response the drug may be continued with further observation. When complete response is noted, patients may receive two more months of the drug, which may then be discontinued with further observation. In case of progression, combination of mitotane with streptozotocin[15] or with etoposide, doxorubicin and cisplatin should be considered.[16]

Following radical nephroadrenalectomy, our patient received approximately 3 to 6 g of mitotane per day for a period of 5 months and mitotane was later discontinued because of the side effects. Follow-up CT scans and chest X-rays showed complete resolution of the metastases in the lungs and liver and >25 years of tumor-free survival or cure. This case illustrates the importance of debulking surgery and adequate trial with mitotane therapy to achieve tumor regression and prolonged survival.

A Collaborative Group for Adrenocortical Carcinoma Treatment had been organized in Europe and at the University of Michigan in the United States to study the efficacy of etoposide, doxorubicin, and cisplatin plus mitotane versus streptozotocin plus mitotane as first time treatments in locally advanced or metastatic ACC not amenable to radical surgery (stage III and IV). Quality-of-life measures and mitotane blood levels (14 to 20 mg/L) are included. Oncologists should consider participating in this study if a similar rare patient enters into his/her practice by reviewing the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment.[17]

Conclusion

Although ACC is a rare tumor associated with a grim prognosis, complete response is possible with resection followed by mitotane, either alone or in combination with chemotherapy. Mitotane therapy should be monitored by measurements of o,p'-DDD levels, maintaining levels of 10 to 20 mg/L. Side effects may be combated with modern anti-emetics and anti-diarrheal agents. Prolonged mitotane therapy may not be necessary if complete response can be achieved. Oral steroid maintenance is necessary during and after mitotane therapy. Even in the absence of complete response, mitotane therapy can reduce tumor size and hormone levels in functioning tumors with reduction of systemic symptoms.

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