The Use of Ketoconazole in Ectopic Adrenocorticotropic Hormone Syndrome

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The authors report a patient with ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) resulting from small cell lung cancer. Treatment with ketoconazole (KCZ) resulted in significant suppression of serum cortisol levels. The authors confirmed KCZ to be a useful adjunct in the treatment of Cushing's syndrome. *Cancer* 67:1447–1449, 1991.

ECTOPIC adrenocorticotropic hormone (ACTH) syndrome (EAS) has been reported with tumors of the lung, thymus, and pancreas. Although 60% of cases of EAS result from small cell carcinoma of the lung,[1] only 3% of small cell tumors elaborate sufficient biologically active ACTH to produce Cushing's syndrome.[2] In this event, the metabolic and clinical consequences of the hypercortisolemia (hypokalemic alkalosis, polyuria, and myopathy) can be profoundly debilitating. Conventionally, aminoglutethimide has been used in an attempt to reduce the cortisol levels. However the doses required to achieve adequate suppression are often associated with unacceptable side effects, particularly drowsiness, and even then suppression often is not complete.

Recently, attention has been drawn to the use of the antifungal imidazole derivative, ketoconazole (KCZ), in palliation of the hypercortisolemia of Cushing's syndrome. KCZ is now established as a potent inhibitor of adrenal and testicular steroid synthesis by virtue of its inhibitory effect on the cytochrome P450 enzyme system, where it appears to interact with the heme iron site.[3] However, reports of the use of KCZ in EAS are scanty. There is one report of the use of KCZ in a patient with small cell lung cancer (Shepherd *et al.*[4]) and one reference to its use in a patient with a pancreatic tumor (Engelhardt *et al.*[5]). Here we add our experience of the effect of KCZ in a patient with EAS resulting from an anaplastic small cell lung cancer.

Case Report

A 60-year-old woman was seen in March 1989 with a 2-month history of polyuria and polydipsia and 3 weeks of general malaise, ankle edema, and painful weakness of the thighs. There was a 30-year history of smoking 40 cigarettes per day but no change in the pattern of a chronic mild morning cough.

Examination revealed a woman of normal appearance without excess pigmentation or obesity. Blood pressure was 180/80 mmHg. The remainder of the cardiorespiratory and abdominal examination was normal. There was a mild proximal myopathy.

Twenty-four-hour urine volumes were of the order of 4 l and had negative results for sugar. Chest roentgenograms revealed right upper lobe collapse, and bronchoscopic examination showed a tumor obliterating the right upper lobe bronchus. Histologic findings confirmed anaplastic small cell carcinoma.

Initial electrolyte levels were as follows: sodium 153 mmol/l, potassium 2.9 mmol/l, chloride 105 mmol/l, bicarbonate 31 mmol/l, creatinine 0.07 mmol/l, fasting blood sugar 7 mmol/l. Full blood count was normal except for a slightly elevated leukocyte count (12×10^9/l with normal differential). Results of the liver scan were normal. Bone scan demonstrated multiple metastases, and this was confirmed with bone marrow aspirate. EAS was confirmed with a serum ACTH level of 660 pg/ml, 24-hour urine free cortisol level of 6650 nmol, and evening cortisol level of 1080 nmol/l.

In the initial investigative week before therapy there was a rapid worsening of the myopathy such that the patient was unable to sit up in bed and there was exacerbation of hyperglycemia with random sugars up to 18 mmol/l.

Hypokalemia was treated with oral supplementation and spironolactone. The hypercortisolemia was treated with KCZ 800 mg daily in divided doses, and anticancer therapy was initiated 6 days later with etoposide. By that time, serum cortisol levels had decreased to 660 nmol/l and 5 days later were down to 575

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nmol/l. This was accompanied by improvement in the polyuria, hypokalemia, hypernatremia, hyperglycemia, and myopathy. A biochemical/clinical remission was maintained for 5 weeks, after which time the KCZ was reduced to 400 mg daily. Over the ensuing 3 weeks the patient's condition deteriorated in association with rapidly increasing ACTH and cortisol levels and she died 3 months after presentation.

Discussion

Our patient with small cell carcinoma of the lung presented with typical ectopic ACTH syndrome, notable for the lack of classical cushingoid appearance and dominance of features related to mineralocorticoid excess (*i.e.*, hypokalemic alkalosis, renal concentrating deficit, and myopathy). KCZ used at a daily dose of 800 mg resulted in an approximately 40% reduction in serum cortisol levels before chemotherapy was started—a similar response to the patient of Shepherd *et al.* with small cell carcinoma.[4] The patient of Engelhardt *et al.* with a pancreatic tumor had a normalization of serum cortisol levels.[5] Of interest, ACTH levels decreased as shown in Figure 1, with the value at point V being immediately after chemotherapy consistent with reduced tumor secretion. Shephard *et al.* reported persistent elevation of ACTH levels during treatment with KCZ, but the patient of Engelhardt *et al.* demonstrated a significant reduction in ACTH levels. Because we did not measure ACTH levels immediately before chemotherapy, we don't know the impact of KCZ on ACTH levels, although we are aware of the suggestion that KCZ may inhibit tumor elaboration of ACTH, as has been reported with pituitary-dependent Cushing's disease.[6]

The subsequent elevation in ACTH levels (Fig. 1, segment V-W) after etoposide treatment was started is difficult to explain but could result from tumor lysis. Segment W-Y, showing decreasing ACTH levels, would then represent the combined effect of KCZ and anticancer therapy. In segment X-Y, cortisol levels increased coincident with

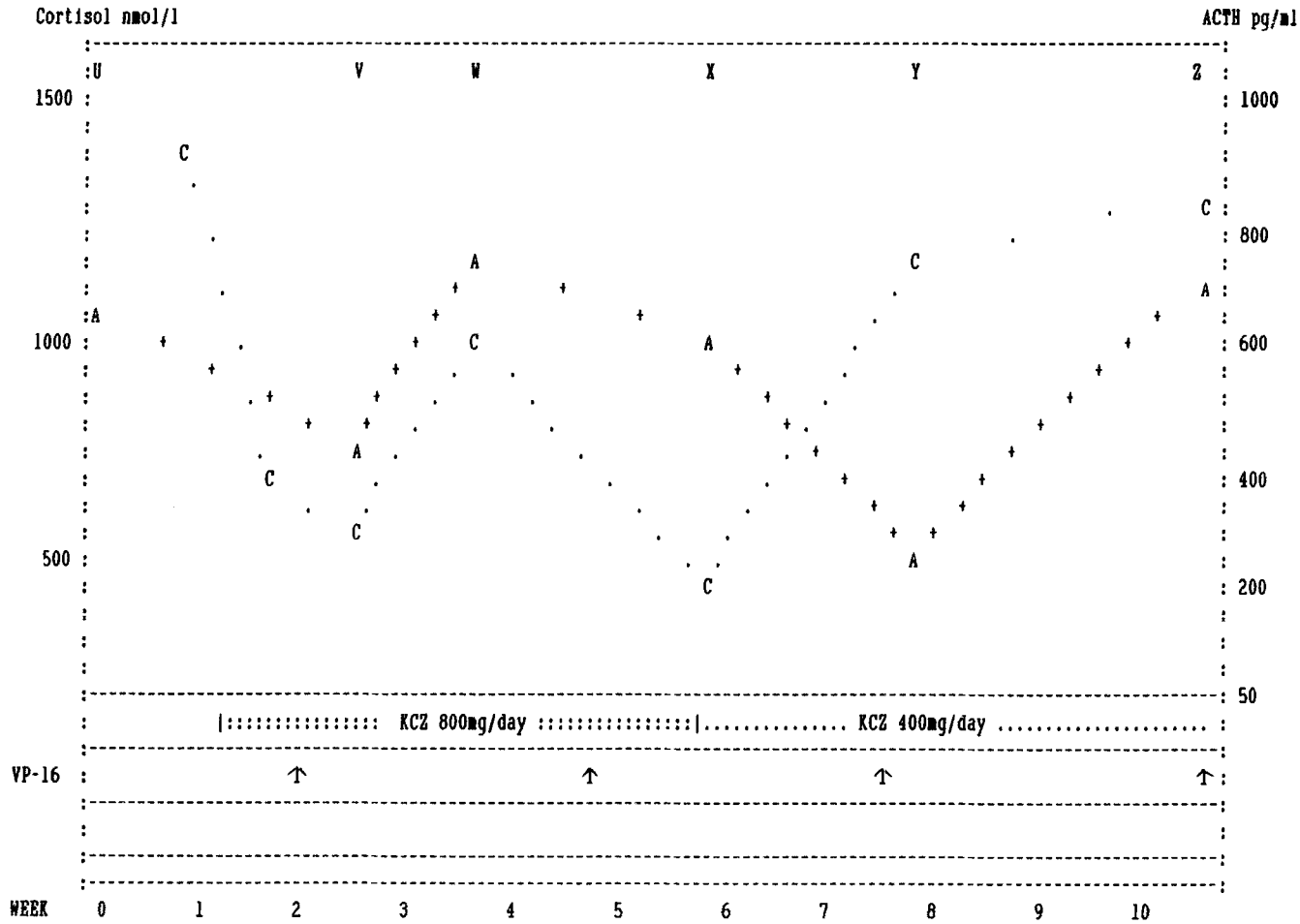

FIG. 1. ACTH and cortisol levels during 10-week course of patient's illness. A: ACTH; C: cortisol; KCZ: ketoconazole; VP-16: etoposide; ↑: start of 3-day course of etoposide. Segments U to Z are referred to in text.

reduction of KCZ dose to 400 mg. Decreasing ACTH levels reflect continuing tumor reduction and later increasing levels (segment Y-Z) probably represent tumor progression despite chemotherapy, soon before the patient died. We are unable to draw conclusions on whether or not the KCZ influenced responsiveness to etoposide, but this may be a possibility because cytochrome P450 may be important in glutathione transferase enzyme activity and one small study reported a correlation between drug resistance and glutathione S-transferase levels in lung cancer lines.[7]

In conclusion, although the longevity of the patient was unlikely to have been influenced, KCZ was an effective adjunct to anticancer therapy in amelioration of the disabling metabolic consequences of the hypercortisolemia of EAS.

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