

# Opportunistic infections in patients with ectopic ACTH-secreting tumors

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The ability of glucocorticoids to alter normal immunity and resistance to infection is well recognized, but has been infrequently reported as a complication of ectopic ACTH-secreting tumors.<sup>1,2</sup> We recently treated two such patients in whom opportunistic infections developed; one with *Nocardia asteroides* and one with *Aspergillus fumigatus*. In the same 3 years, 19 other patients have had presenting features of Cushing's syndrome of other causes. In none of these patients did serious opportunistic infections develop. In the 38 patients from 1951 to 1973 with Cushing's disease previously reported,<sup>3</sup> there were no cases of opportunistic infection. Also, we have unpublished data on an additional 20 cases of Cushing's syndrome from 1973 to 1977. Again, no serious infections occurred. Thus, we agree with Anthony and Greco<sup>4</sup> that the natural history of Cushing's syndrome appears to have changed since the classic series of Plotz et al.<sup>5</sup> Since we have encountered no opportunistic infections in the other 77 patients with endogenous Cushing's syndrome from 1951 to 1980, we postulate that the difference is due to a dose-dependent immunosuppression by circulating corticosteroids.

Our experience with the 21 patients with presenting symptoms of Cushing's syndrome between July 1977 and July 1980 is summarized (*Table*). The

**Table.** Laboratory values in 21 patients with Cushing's syndrome

Case	Age	Sex	Etiology of Cushing's syndrome	Plasma ACTH	Serum cortisol		Urinary cortisol	17-OH steroids
					8:00 am	4:00 pm		
Normal values				6-52 pg/dl	8.3-29 µg/dl	3.3-15 µg/dl	16-100 µg/14 hr	M 3-12 F 2-6 µg/24 hr
1	27	F	Ectopic ACTH	230	104	100	2295	113
2	47	M	Ectopic ACTH	1128	44	37	882	35
3	61	F	Adenoma	13	25	31	126	10
4	35	M	Adenoma	10	32	26	75	19
5	64	F	Adenomatous hyperplasia	38	22	27	78	11
6	60	F	Pituitary	39	25	35	224	5
7	30	F	Pituitary	74	23	ND	171	13
8	51	F	Pituitary	107	33	30	241	8
9	22	F	Pituitary	108	29	20	116	12
10	27	F	Pituitary	119	44	25	621	22
11	24	F	Pituitary	118	31	26	1445	16
12	53	F	Pituitary	20	17	18	724	12
13	39	F	Pituitary	23	20	18	82	18
14	17	M	Pituitary	77	22	30	ND	24
15	30	F	Pituitary	133	13	13	260	19
16	60	F	Pituitary	31	23	10	36	30
17	32	F	Pituitary	14	24	27	184	6
18	64	F	Pituitary	29	44	27	283	29
19	48	F	Pituitary	65	31	10	170	10
20	29	M	Pituitary	142	26	23	135	16
21	38	F	Pituitary	30	17	18	83	14
Average for 2 patients with ectopic ACTH				679 ±635	74 ±42	68 ±45	1588 ±999	74 ±55
Average for 19 patients with Cushing's of other etiology				63 ±45	37 ±46	34 ±48	281 ±343	15 ±7
Statistical significance between means by Student's t-test				p < .0001	p < .0001	p < .0002	p < .0005	p < .0001

methods used for determining ACTH and cortisol have been reported.<sup>3</sup> Several of the urinary free cortisol values were determined by a fluorometric method, which has since been supplanted by radioimmunoassay. The values of the fluorometric determinations have been adjusted to correspond with the newer methods for purposes of comparison.

### Case reports

**Case 1.** A 27-year-old white woman had mild hypertension in the fifth month of pregnancy. In the 37th week of gestation, proteinuria and marked hypertension prompted

admission to another hospital. She complained of muscle weakness, palpitations, increased sweating, severe headaches, drowsiness, and blurred vision. Physical findings included blood pressure of 230/140 mm Hg, an acneiform rash on her face and upper back, papilledema, moon facies, abdominal striae, and proximal muscle weakness. Emergency cesarean section was performed due to fetal distress, and a normal baby girl weighing 3.0 kg was delivered. Postoperatively, the patient remained hypertensive and disoriented. Clinical evidence of disseminated intravascular coagulation developed, and a grand mal seizure occurred. Intravenous pyelography revealed a right suprarenal mass. A pheochromocytoma was sus-

pected, and urinary metanephrines measured 15.8 mg/24 hr (normal, 0.3–0.9 mg/24 hr). The patient was transferred to the Cleveland Clinic Hospital. On admission, blood pressure was 150/115 mm Hg supine and 130/90 mm Hg sitting, with a persistent tachycardia of 110 beats/min. The previously noted Cushingoid features were observed, along with a petechial rash and evidence of hypertensive retinopathy. Baseline laboratory values are listed in the *Table*.

Plasma cortisol and urinary steroid levels were not suppressed on a daily regimen of dexamethasone (Decadron), 0.5 mg/6 hr, or 2 mg/6 hr. Plasma catecholamines were 15,168  $\mu$ g/ml and urinary catecholamines 60  $\mu$ g/24 hr. These values were considered diagnostic of pheochromocytoma.<sup>6</sup> Surgery was planned, but on the 12th hospital day, the patient became lethargic, incontinent of urine and stool, and febrile to 39.4 C. Cerebrospinal fluid examination was normal. Chest roentgenogram disclosed a left upper lobe infiltrate. Empiric nafcillin, tobramycin, erythromycin, and trimethoprim-sulfamethoxazole therapy was begun until positive blood cultures were subsequently identified as *Escherichia coli* sensitive to tobramycin. On the 14th hospital day, the patient became deeply comatose with fixed, non-reactive pupils, lack of spontaneous respirations, and profound hypotension. Computed tomography (CT) of the head revealed multiple brain abscesses, and the electroencephalogram was isoelectric. After discussion with her family, supportive measures were withdrawn and the patient died on the 17th hospital day. Postmortem examination revealed almost total replacement of the lungs by *Aspergillus fumigatus*, as well as multiple aspergillus abscesses in the brain, kidney, spleen, gastrointestinal tract, liver, and heart. Immunohistochemical stains confirmed the presence of ACTH in the pheochromocytoma cells. Extraction of the pheochromocytoma showed a 50-fold increase in ACTH compared to that of the other adrenal gland. No evidence of metastasis was noted.

**Case 2.** A 47-year-old white man was admitted for evaluation of fever, pulmonary

infiltrates, superior mediastinal mass, and diffuse myalgias. Insulin-secreting islet cell adenomas of the pancreas had been excised, leaving the patient at age 20 an insulin-dependent diabetic. When he was 21, a parathyroid adenoma was excised. He was well until age 45 when the left lower parathyroid was excised for recurrent hyperparathyroidism. A duodenal ulcer was noted when he reached 46. Fasting serum gastrin was 515 pg/ml (normal, 30–155). The patient's 24-year-old daughter had also undergone parathyroid excision for hyperparathyroidism.

One month before admission the patient had become acutely ill with abdominal pain, nausea, vomiting, fever, night sweats, and pedal edema. He was admitted to another hospital where the chest roentgenogram showed right-sided infiltrates and a mediastinal mass. Sputum cultures grew *E. coli* and *Pseudomonas* species; appropriate therapy was begun. His clinical status and roentgenographic picture failed to improve and he was transferred to the Cleveland Clinic Hospital. On examination, the patient appeared chronically ill, weighing 62 kg; his usual weight was 70 kg. His temperature was 38.3 C. Basilar rales were noted on chest examination. There was marked proximal muscle weakness and increased skin pigmentation but no striae or Cushingoid habitus. The remainder of the examination was normal. Admission potassium was 2.0 mEq/dl with otherwise normal routine laboratory data. Endocrine studies are summarized in the *Table*. Aspiration biopsy of the multiple round densities on chest roentgenogram grew *Nocardia asteroides*, which responded to treatment with intravenous sulfadiazine and oral cycloserine. Abdominal CT scan revealed bilateral adrenal enlargement, and the patient was thought to have Cushing's syndrome due to ectopic ACTH secretion. Dexamethasone suppression was not attempted because of the *Nocardia* infection, and treatment was begun with the blocking agents metyrapone and aminoglutethimide. Extensive examination for a primary tumor disclosed only an undifferentiated small-cell tumor in the bone marrow, thought to be consistent with apudoma. Five-fluorouracil,

streptozocin, and Cytosan therapy was begun. Complete clearing of the chest roentgenograms, improved appetite and weight gain were noted, and the patient was discharged from the hospital. On return for weekly chemotherapy, he appeared to be doing well, but died suddenly at home 9 days after discharge. Autopsy revealed recurrent islet-cell tumor of the pancreas with metastasis to the superior mediastinal and hilar lymph nodes, pulmonary pleura and parenchyma, and pericardium. Bilateral adrenal hyperplasia was present. Immunoperoxidase staining confirmed the presence of ACTH in the tumor cells. He was presumed to have died of a cardiac arrhythmia related to tumor involvement of the pericardium.

#### Comment

Infections that develop in compromised hosts can often be traced to specific abnormalities of host defense mechanisms associated with the underlying disease. Host defenses against infections with extracellular pathogens such as pneumococci, streptococci, staphylococci, and coliforms depend primarily on an intact humoral system including opsonization, neutralization of toxins, and complement activation. Defense against fungal and certain intracellular bacterial infections, such as *Listeria*, *Nocardia*, and others, requires a competent cellular immune response.

The altered host defenses observed in patients with ACTH-secreting tumors would appear to result from the effects of increased cortisol levels. The precise mechanism by which corticosteroids induce such an acquired state of immunodeficiency is not clear, for corticosteroids are capable of affecting virtually every limb of the immune system to varying degrees. Humoral immunity as assayed by antibody production appears to be most resistant to the effects of corticosteroids, being suppressed only in the presence of high concentrations.<sup>7</sup>

The phagocytic system, namely neutrophil function of chemotaxis, phagocytosis, and phagocytic killing, has not been shown to be inhibited by corticosteroids, whereas corticoids have been demonstrated to suppress the sticking of leukocytes at sites of tissue injury, and to inhibit diapedesis and migration of white blood cells through tissue.<sup>8</sup> Monocyte and macrophage function, particularly their bactericidal and fungicidal properties, appears to be susceptible to inhibition by corticoids.<sup>7</sup> Cellular or T cell-mediated immunity also appears to be sensitive to the effects of corticosteroids as demonstrated experimentally both in vitro and in vivo.<sup>9</sup> The precise mechanism of this inhibition appears to be complex, and may reflect the differential sensitivity of T-cell subpopulations to corticosteroids, redistribution of T-cell subpopulations, or even inhibition of T cell-effector cell interactions.<sup>10</sup> Whatever the mechanism, patients with corticosteroid excess would be expected to be most deficient in handling chronic intracellular pathogens as opposed to handling the more common extracellular pyogenic infections. Our clinical observation supports this theory.

There also seems to be a dose-dependent effect of corticosteroids on immunosuppression. In our total experience with 77 patients with pituitary or adrenal Cushing's syndrome, no opportunistic infections were seen prior to treatment. Yet, serious infections developed in two of three patients with ectopic ACTH secretion. *Escherichia coli* sepsis and anergy to previously positive delayed hypersensitivity skin testing developed in the third patient, but it was difficult to determine whether this immunosuppression resulted from ectopic ACTH secretion or chemotherapy given for medullary carcinoma of the thyroid, so the case was excluded from analysis,

despite clinical and laboratory findings similar to Cases 1 and 2. Urinary free cortisol levels are believed to be an accurate measure of cortisol production.<sup>11</sup> In our recent experience with 19 patients with pituitary or adrenal Cushing's syndrome, the average urinary free cortisol was 281  $\mu\text{g}/24$  hr with all but two cases less than 624  $\mu\text{g}/24$  hr, or two standard deviations from the mean. In contrast, the two patients with ectopic ACTH secretion had urinary free cortisol levels of 2295 and 882  $\mu\text{g}/24$  hr, respectively. We postulate that the profound immunosuppression in the ectopic ACTH patients is due to the much higher production of corticosteroids. Additional support of the dose-response hypothesis can be found in a study by Fauci and Dale.<sup>12</sup> Intravenous administration of 100 mg of hydrocortisone produced no effect, but administration of 400 mg greatly diminished the lymphocyte response to pokeweed mitogen. Further definition of this phenomenon would be desirable.

In our cases, altered immunity was manifested by opportunistic infection. The mechanisms by which the host responds to intracellular bacterial or chronic fungal infections are not well understood. The increased incidence of infections of this nature in patients with T-cell deficiency states is suggestive of a key role for cell-mediated immunity.<sup>10</sup> In the past, this observation plus the fact that patients with disseminated chronic infections frequently have depressed cell-mediated immunity suggested a generalized depression of T-cell function. Results of recent work have suggested that many acquired states of depressed cellular immunity result from overactivity of T-cell suppressor populations and may be a result rather than a cause of the underlying disorder.<sup>13</sup>

*Aspergillus fumigatus* diagnosed post-

mortem was thought to be the cause of the fever, chest infiltrates, and ultimate death of patient 1. Disseminated aspergillosis is a disease of immunosuppressed hosts that is difficult to diagnose and treat, and is usually lethal.<sup>14</sup> *Aspergillus fumigatus* is a ubiquitous agent with a broad spectrum of clinical disease. A hypersensitivity reaction or bronchopulmonary aspergillosis may develop in persons with atopic conditions.<sup>15</sup> An association between disseminated aspergillosis and Cushing's syndrome due to ectopic ACTH secretion has been reported.<sup>1,2</sup> Pulmonary aspergillosis often occurs after severe gram-negative bacterial infection<sup>14</sup> and appears to have followed *E. coli* infection in our patient. One explanation for this phenomenon, borne out by animal studies, is that dormant spores germinate in the presence of severe infection and corticosteroid therapy.<sup>16</sup> Open lung biopsy and aggressive therapy with amphotericin-B would seem to be indicated in immunosuppressed patients with pulmonary infiltrates unresponsive to antibiotic therapy.<sup>17</sup>

In patient 2, *Nocardia* was successfully diagnosed and treated. Although often considered a fungus, *Nocardia* is actually a gram-positive bacillus of the family Actinomycetaceae, which is closely related to the mycobacteria and shares staining and growth characteristics.<sup>18</sup> Drawing from the analogy to tuberculosis, the primary infection is probably the result of inhalation of the organism followed by multiplication and insemination via lymphatics and eventually the bloodstream. It is postulated that healthy persons can harbor the infection without clinical consequence, in a manner similar to other commensal organisms, but conclusive evidence of a large reservoir of subclinical disease is lacking.<sup>19</sup> A history of steroid use or immu-

nosuppression can be elicited from most patients with nocardial infection.<sup>18</sup> Experimental evidence in guinea pigs suggests that macrophage function is essential for specific host defense against *Nocardia*.<sup>20</sup> Since corticosteroids suppress macrophage function,<sup>7</sup> it is presumably this suppression that allows development of serious infection in patients with excessive corticosteroid levels. Of interest is the predominance of this infection in male subjects with systemic lupus erythematosus who have been treated with steroids or cytotoxic agents.<sup>21</sup> This suggests that further host factors, perhaps hormonal, are also important in the pathogenesis of the infection.

In summary, we believe that ectopic ACTH secretion impairs host defense mechanisms, possibly in a dose-dependent manner to account for the observed differences between patients with ectopic ACTH-secreting tumors and Cushing's disease of other causes. The precise mechanism is not well understood, and we are prospectively studying detailed immunologic function in patients with this disease. This impaired immunity is manifested by infection with agents such as fungi and intracellular bacteria that are normally handled by the T-cell arm of the immune system. Recognition of this deficit and prompt diagnosis and therapy of pulmonary infiltrates with appropriate antimicrobial agents may lead to improved survival in these patients.

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