

Ectopic ACTH Syndrome Resulting in Nocardiosis and Acute Respiratory Failure

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Nocardial infection often occurs in the setting of immunocompromise because cell-mediated and T-cell immune responses play an important role in the host defense to *Nocardia* species.¹ Prolonged steroid use is an independent risk factor for developing nocardiosis.² Similarly, severe hypercortisolism caused by ectopic adrenocorticotrophic hormone (ACTH) production leads to an increased risk of opportunistic infection. Pulmonary nocardiosis presents with a diverse array of clinical and radiographic findings, often resulting in misdiagnosis. This article presents a case of nocardiosis and acute respiratory failure in a patient who was immunocompromised secondary to hypercortisolism from ectopic ACTH production. The published case literature of opportunistic infections in the setting of endogenous hypercortisolism is reviewed.

CASE PRESENTATION

A 68-year-old man was transferred from another hospital for diagnostic and therapeutic evaluation of new-onset respiratory failure. His past medical history was significant for mild hypertension for 40 years, chronic obstructive pulmonary disease, and a 40 pack-year tobacco smoking history.

History of Present Illness

He was in his usual state of health until 1 month prior to transfer, when he underwent uncomplicated rotator cuff surgery, was discharged home on postoperative day 3, and was placed on diuretics for suspected fluid retention. Follow-up within a few days revealed a serum potassium level of 1.7 mEq/L; the patient was hospitalized for potassium replacement and subsequently was discharged on potassium supplementation.

Approximately 1 week later, the patient complained of dyspnea and was readmitted for acute respiratory failure, with a PaO₂ of 36 mm Hg on 4 L supplemental oxygen flow. Chest radiograph and computed tomographic (CT) scan of the chest showed a right lobe infiltrate

with pretracheal lymphadenopathy. A radionuclide ventilation-perfusion scan was interpreted as low probability for pulmonary embolus. Bronchoscopy with biopsy was negative for malignancy and infection. A transthoracic echocardiogram showed left ventricular hypertrophy with a left ventricular ejection fraction of 60%. The patient was placed on noninvasive positive-pressure ventilation, and antibacterial therapy with levofloxacin and piperacillin/tazobactam was initiated; despite these measures, his Pao₂ did not exceed 64 mm Hg.

The patient was noted at this time to have intractable hypertension, with systolic blood pressures of 180 to 190 mm Hg despite maximal therapy with 5 antihypertensive medications. He continued to have persistent hypokalemia despite repletion with 90 mEq of potassium daily and administration of a potassium-sparing diuretic. Other problems included a persistent metabolic alkalosis, new glucose intolerance, anemia, and thrombocytopenia. A low-dose dexamethasone test was positive for hypercortisolism. An abdominal CT scan was negative for an adrenal mass.

Physical Examination and Diagnostic Evaluation

The patient was transferred to our institution on hospital day 7 with persistent hypoxemia despite maximal noninvasive oxygen delivery by face mask. On physical examination, the patient was in marked respiratory distress. He was afebrile, with a blood pressure of 180/100 mm Hg, a pulse of 85 bpm, and a respiratory rate of 30 breaths/min. He had bilateral rhonchi and rales with coarse breath sounds. Results of cardiac and neurologic examinations were unremarkable. Besides scattered ecchymoses on his upper body, skin examination was unremarkable.

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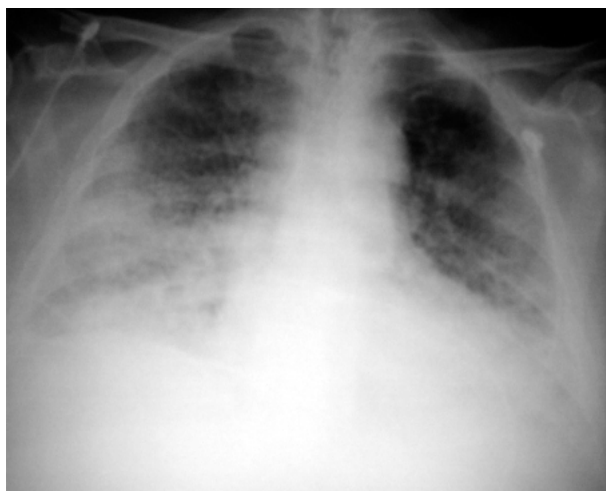


Figure 1. Chest radiograph of the case patient.

Initial laboratory results revealed a platelet count of $52 \times 10^9/\text{mm}^3$ and a hematocrit of 30.6%. An arterial blood gas analysis showed a pH of 7.50, a PaCO_2 of 44 mm Hg, a PaO_2 of 64 mm Hg, and a bicarbonate level of 34 mEq/L. A chest radiograph showed diffuse bilateral interstitial infiltrates and a right base consolidation (**Figure 1**). A chest CT showed extensive bilateral lower lobe consolidation and a moderately sized cavitating lesion within the right lower lobe (**Figure 2**). A sputum Gram stain on the day of transfer revealed filamentous gram-positive rods, and acid-fast staining was partially positive. Sputum culture grew *Nocardia farcinica* susceptible to trimethoprim-sulfamethoxazole and resistant to quinolones and β -lactams. Twenty-four-hour urine cortisol was 4322 μg (normal 2.0–42.4 $\mu\text{g}/24\text{ h}$). Serum cortisol level was 82 $\mu\text{g}/\text{dL}$ (normal, 8–25 $\mu\text{g}/\text{dL}$) and ACTH level was 519 ng/L (normal 3–52 ng/L). Because of unexplained anemia and thrombocytopenia, a bone marrow biopsy was performed and showed a neuroendocrine tumor consistent with metastatic small-cell lung carcinoma.

Clinical Course

Despite the substitution of high dose trimethoprim-sulfamethoxazole for the previous antibiotics and the administration of carboplatin and etoposide, the patient's hypoxemia progressed, and he required intubation and mechanical ventilation. High-dose ketoconazole was instituted to block adrenal steroidogenesis, and cortisol levels decreased to 32 $\mu\text{g}/\text{dL}$. Nevertheless, the patient had a continued downhill course complicated by a pneumothorax, neutropenia, enterococcal bacteremia, *Clostridium difficile* colitis, and multi-organ sys-



Figure 2. Chest computed tomographic scan of the case patient.

tem failure. An endotracheal aspirate from hospital day 14 grew *N. farcinica* and *Aspergillus* species. The patient died on hospital day 30.

DISCUSSION

This patient had the classic manifestations of ectopic ACTH syndrome. The elevated mineralocorticoid effects of excess cortisol were expressed as intractable hypertension, hypokalemia, and metabolic alkalosis. The simultaneous extreme elevations of ACTH and cortisol levels in the setting of metastatic small-cell lung cancer confirmed the diagnosis. The patient was placed on chemotherapy to treat the small-cell lung cancer and ketoconazole to inhibit steroidogenesis. Ketoconazole, in addition to its antifungal properties, inhibits steroid synthesis in humans by blocking C17-20 lyase, 11 β -hydroxylase, and cholesterol side-chain cleavage of the steroid synthesis pathway.³ Despite showing evidence of improvement with decreased serum cortisol levels, the aggressive nature of the underlying disease led to the patient's death.

Rapid progression of respiratory failure and presence of bilateral infiltrates in this patient were most consistent with acute respiratory distress syndrome. CT scanning showed bilateral consolidations and a cavitary lesion. Pulmonary nocardiosis has a diverse clinical and radiographic presentation, including nodules, masses, cavitations, interstitial or lobar infiltrates, subpleural plaques, and pleural effusions.^{1,4} The patient's bilateral infiltrates and cavitary lesion, thus, were consistent with nocardial infection. Later in the hospital course, the patient's endotracheal aspirate grew *Aspergillus* species. Although *Aspergillus* also presents in the immunocompromised setting and with a variety of radiographic findings,⁵ this patient had numerous previous cultures that failed to grow *Aspergillus*. Therefore,

the *Aspergillus* finding was thought to reflect a late colonization or infection that did not explain the patient's initial presentation.

Opportunistic Infection in the Setting of Ectopic ACTH Syndrome

Endogenous hypercortisolemia in this patient led to an immunocompromised state, making him susceptible to *Nocardia* infection. Case reports have linked nocardiosis and Cushing's syndrome, some specifically associated with ectopic ACTH.^{6,7} In one review,⁸ opportunistic infections were most prevalent with the hypercortisolism associated with ectopic ACTH syndrome. This was thought to be explained by the very high plasma cortisol concentrations seen in this condition.⁸ In a review of 23 cases, opportunistic infections in the setting of Cushing's syndrome were mostly seen with either ectopic ACTH or adrenal tumors rather than exogenous or pituitary causes of Cushing's syndrome.⁷ Infections with *Aspergillus* species, *Cryptococcus neoformans*, *Pneumocystis carinii*, and *Nocardia asteroides* predominated.⁷ In the setting of endogenous hypercortisolism without other risk factors for immunocompromise, the presence of these infections should raise suspicion for ectopic ACTH syndrome.

In a review of patients with small-cell lung cancer and ectopic ACTH syndrome, 4 of 10 patients died from infectious complications.⁹ In a similar review of cases, 3 of 14 patients with small-cell lung cancer and ectopic ACTH syndrome died as a result of infection; these 3 patients also had the highest cortisol levels.¹⁰ Given the susceptibility for opportunistic and aggressive infections in the presence of excess cortisol production, an empiric broad-spectrum antimicrobial regimen should be considered in ectopic ACTH patients exhibiting signs of infection.

Evaluation and Management of Nocardiosis

The incidence of nocardial infection in the United States is estimated to be 500 to 1000 new cases per year, with this possibly being an underestimate owing to the difficulty of diagnosis and an increasing number of at-risk patients.¹ In a review of 1050 patients with nocardiosis, 63% had underlying immunocompromise. Patients at risk include those with hypercortisolism, AIDS, organ transplantation, alcoholism, or diabetes.¹

The diagnosis of nocardiosis usually is made based upon respiratory secretions, skin biopsies, or aspirates from deep collections. *Nocardia* may take from 48 hours to several weeks to culture, but colonies are usually seen after 3 to 5 days.¹¹ This delay can result in delays in diagnosis and susceptibility testing. Nocardial infec-

tion was diagnosed in the present case by the prompt results of the sputum sample, including both the Gram stain and acid-fast stain.

Differentiation of *N. farcinica* from other members of the *N. asteroides* complex is important because of the propensity of *N. farcinica* for causing disseminated infection and antimicrobial resistance.¹² In a study of 63 patients with nocardial infection, 57.1% of patients with *N. farcinica* infection died compared with 17.6% of those infected with *N. asteroides*.¹³ In this study, *N. asteroides* exhibited variable resistance whereas *N. farcinica* isolates were systematically resistant to most antibiotics.

In addition to being susceptible to the standard nocardial antimicrobial trimethoprim-sulfamethoxazole, *N. farcinica* also has demonstrated susceptibility to amikacin, ciprofloxacin, and imipenim.¹⁴ Interestingly, this patient had been treated empirically with levofloxacin and piperacillin/tazobactam prior to transfer to our institution, but the *N. farcinica* isolate was resistant to these antibiotics.

CONCLUSION

This case illustrates the importance of recognizing that patients with extreme hypercortisolism from ectopic ACTH syndrome are susceptible to opportunistic infections such as nocardiosis. In this patient without other identifiable causes of respiratory failure, a thorough diagnostic evaluation resulted in the diagnosis of *N. farcinica* infection. In addition to a reduction in cortisol levels, early antimicrobial therapy aimed at opportunistic infections must be considered in patients with extreme hypercortisolism.

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REFERENCES

1. Beaman BL, Beaman L. *Nocardia* species: host-parasite relationship. Clin Microbiol Rev 1994;7:213–64.
2. Kontoyiannis DP, Ruoff K, Hooper DC. *Nocardia* bacteremia. Report of 4 cases and review of the literature. Medicine (Baltimore) 1998;77:255–67.
3. Sonino N, Boscaro M. Medical therapy for Cushing's disease. Endocrinol Metab Clin North Am 1999;28:211–22.
4. Feigin DS. Nocardiosis of the lung: chest radiographic findings in 21 cases. Radiology 1986;159:9–14.
5. Rau WS. *Aspergillus* infection of the lung: radiological signs. Mycoses 1997;40 Suppl 2:25–32.
6. Natale RB, Yagoda A, Brown A, et al. Combined *Pneumocystis carinii* and *Nocardia asteroides* pneumonitis in a patient with an ACTH-producing carcinoid. Cancer 1981; 47:2933–5.
7. Graham BS, Tucker WS Jr. Opportunistic infections in endogenous Cushing's syndrome. Ann Intern Med 1984; 101:334–8.
8. Bakker RC, Gallas PR, Romijn JA, Wiersinga WM.

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- Cushing's syndrome complicated by multiple opportunistic infections. *J Endocrinol Invest* 1998;21:329–33.
9. Collichio FA, Woolf PD, Brower M. Management of patients with small-cell carcinoma and the syndrome of ectopic corticotropin secretion. *Cancer* 1994;73:1361–7.
 10. Delisle L, Boyer MJ, Warr D, et al Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. *Arch Intern Med* 1993;153:746–52.
 11. Sorrell TC, Iredell JR, Mitchell DH. *Nocardia* species. In: Mandell GL, Douglas RG, Bennett JD, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 5th ed. Churchill-Livingstone; 2000: 2637–43.
 12. Shetty AK, Arvin AM, Gutierrez KM. *Nocardia farcinica* pneumonia in chronic granulomatous disease. *Pediatrics* 1999;104(4 Pt 1):961–4.
 13. Boiron P, Provost F, Chevrier G, Dupont B. Review of nocardial infections in France from 1987 to 1990. *Eur J Clin Microbiol Infect Dis* 1992;11:709–14.
 14. Wallace RJ Jr, Tsukamura M, Brown BA, et al. Cefotaxime-resistant *Nocardia asteroides* strains are isolates of the controversial species *Nocardia farcinica*. *J Clin Microbiol* 1990;28:2726–32.

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