

Nocardiosis in ectopic ACTH syndrome: A case report and review of 11 cases from the literature

LICHEN XU^{1,2*}, QIAOMAI XU^{1,2*}, MEIFANG YANG^{1,2}, HAINV GAO^{1,2}, MINGZHI XU³ and WEIHANG MA^{1,2}

¹State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine; ²The Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases; ³Department of Endocrinology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003, P.R. China

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Abstract. Ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) associated with nocardiosis is rare, and little information is available regarding its clinical characteristics. In this study, the case of a 35-year-old male patient who showed significant cushingoid features and had a cough with yellow phlegm for 1 month is described. Pulmonary computed tomography (CT) scanning and ¹⁸F-fluorodeoxyglucose positron emission tomography combined with CT identified two different lesions in the mediastinum and pulmonary region, respectively. The lesion in the mediastinum was finally diagnosed as an ACTH-secreting mediastinal paraganglioma via biopsy. The sputum culture confirmed pulmonary nocardiosis. The patient was effectively treated with complete tumor resection following the treatment of nocardiosis using trimethoprim-sulfamethoxazole. Following the present case, 11 additional cases of nocardiosis in EAS were identified in the literature and their clinical characteristics were compared and evaluated. It may be concluded that, although *Nocardia* remains a rare opportunistic infection pathogen in EAS, it is necessary to consider nocardiosis as a diagnosis for patients with pulmonary imaging findings of cavity, consolidation or nodule, particularly when there are brain and extra-pulmonary lesions as well as a poor response to regular treatment.

Introduction

Endogenous Cushing syndrome (ECS) results from lengthy and inappropriate exposure to excessive levels of glucocorticoid secretion, and is generally divided into adrenocorticotrophic hormone (ACTH)-dependent and ACTH-independent. Ectopic ACTH syndrome (EAS) is characterized by hypercortisolemia as a result of extra-pituitary ACTH secretion and accounts for 20% of ACTH-dependent Cushing syndrome cases (1).

Nocardia spp., a gram-positive bacterium, causes local or disseminated infection in humans and animals. Patients with depressed cell-mediated immunity are at high risk for infection, including those with solid-organ or hematopoietic stem cell transplantation, human immunodeficiency virus infection, long-term steroid use or malignancy (2). Although *Nocardia* has been considered to be rare, a previous report has shown that its incidence is increasing (3). Extremely high glucocorticoid doses in patients with ECS affect virtually every cell type involved in immunity and the inflammatory response, particularly cell-mediated immunity, which causes such patients to be a target of nocardiosis (4). However, the clinical features of few cases of nocardiosis in EAS have been documented.

In the present study, a case of rare ectopic ACTH-secreting paraganglioma in the mediastinum associated with nocardiosis is presented. In addition, the clinical features of 11 published cases of EAS associated with *Nocardia* infection were analyzed (5-11). The aim of this study was to provide guidance for the clinical diagnosis and treatment of *Nocardia* infection associated with EAS.

Case report

The patient and their family were informed that data from the case would be submitted for publication and provided consent accordingly. A 35-year-old male patient first presented to the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) in February 2012, with weakness, polyuria and polydipsia for 7 years and had been diagnosed as having hypertension with unsatisfactory drug control for 6 months. Frequently, the patient suffered from blurred vision, headache and limb numbness. One month prior to presentation, he had developed a cough with dark yellow phlegm

Correspondence to: Dr Weihang Ma, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, Zhejiang 310003, P.R. China
E-mail: weihangma2014@126.com

*Contributed equally

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without fever and dyspnea. The patient was transferred to this hospital to obtain a definite diagnosis. Physical examination on admission found the patient to have a blood pressure of 172/102 mmHg, heart rate of 80 beats/min with occasional arrhythmia, body mass index of 25 kg/m², and normal body temperature. The patient exhibited a moon face, buffalo hump, polycythemia, edema of the feet and central obesity. Other positive findings included purple striae in the abdomen, acne, and a dark skin color. There were no clinically palpable nodules. Other systemic examination findings were normal.

The initial laboratory evaluation revealed hypokalemia (K level, 2.48 mmol/l; reference, 3.50-5.20 mmol/l), hyperglycemia (fasting plasma glucose, 10.97 mmol/l; reference, 3.9-7.8 mmol/l) and hyperlipidemia (triglycerides, 4.41 mmol/l; reference, 0.3-1.7 mmol/l). Blood routine tests showed a normal leukocyte count leukocyte count (8.1x10⁹/L; reference, 4-10x10⁹/L) but mildly increased neutrophil percentage (83.6%; reference, 50-70%). A hormonal assessment panel was performed, which revealed markedly increased urinary (3,118.08 µg/24 h; reference, 55.5-286.0 µg/24 h) and serum (>50 µg/dl; reference, 5.0-25.0 µg/dl) cortisol and serum ACTH (372 pg/ml; reference, 0.0-46.0 pg/ml) levels.

High-dose dexamethasone suppression test: The measurement of serum cortisol between 8:00 and 9:00 AM before and after a high-dose (8 mg) oral night intake of dexamethasone and is considered suggestive of suppression when a reduction of >50% is observed compared to the baseline value.

Low-dose dexamethasone suppression test was performed after an overnight oral intake (between 11:00 PM and 12:00 AM) dexamethasone (1 mg), and blood collection for measurement of serum cortisol should occur in the subsequent morning between 8:00 and 9:00 AM. Cortisol values above 1.8 µg/dL are considered abnormal. Cortisol levels were not suppressed by high- or low-dose dexamethasone.

To investigate the symptoms of cough and expectoration, chest computed tomography (CT; Fig. 1) scanning was performed. The resulting image showed a soft tissue shadow in the anterior mediastinum and multiple nodules with a partial cavity lesion in bilateral lung fields. Brain magnetic resonance imaging (MRI) revealed a slightly swollen pituitary gland, but this MRI result was not able to explain the patient's clinical manifestations. Laboratory tests, and the MRI and CT scans supported a preliminary diagnosis of ectopic ACTH-secreting tumor. However, it was not possible to determine whether the multiple lesions in the lung constituted an infection focus or metastasis focus. For further clarification, the patient underwent ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) combined with CT (Fig. 2). The resulting imaging showed a tumor focus with mildly increased ¹⁸F-FDG metabolism in the anterior mediastinum. Multiple clear-boundary nodular changes in the bilateral pulmonary region suggested possible infection. Histopathological analysis revealed tumor cells arranged in nests. Immunohistochemistry showed that the periphery of the cell nests was positive for chromogranin A and S-100. Immunohistochemistry analysis was performed using a Dako Autostainer with Envision™ Detection Kit, chromogranin A (DAK-A3; 1:200) and polyclonal S-100 (1:300; Dako Denmark A/S, Glostrup, Denmark). Those microscopy findings confirmed paraganglioma.

Treatment was initiated while the imaging and laboratory examinations were ongoing. According to his manifestations, the patient was initially treated with potassium replacement (oral potassium chloride solution, 60 ml/day), insulin (mixed protamine zinc recombinant human insulin injection adjusted according to plasma glucose), intravenous fluids (Ringer's solution; adjusted according to intake and output record) and anti-hypertension medication (amlodipine, 5 mg/day; perindopril, 4 mg/day). As the patient had symptoms of cough and expectoration, antibiotics (cefoperazone/sulbactam; dosage, 2 g; q8h) were administered after admission, but there was no improvement in the symptoms after 5 days. Following discussion with a doctor of infectious diseases and consideration of the pulmonary CT scan results, a possible diagnosis of pulmonary aspergillosis could not be eliminated. Caspofungin (March 6, 2012; 20 days after admission) at a dosage of 50 mg/day, combined with a formal antibiotics regimen was recommended. Gram staining and sputum culture were performed concurrently. Gram staining of the sputum on March 9, 2012 (23 days after admission) revealed thin-beaded, gram-positive branching rods and modified acid-fast staining was then performed, according to previously described methods (12). The finding that these branching rods were partially acid-fast positive was suggestive of infection with *Nocardia*. The subsequent culture confirmed this result. According to the clinical, radiological and etiological findings, pulmonary nocardiosis was identified. In consideration of the possibility of co-infection with *Aspergillus*, a new antibiotic treatment was initiated with oral trimethoprim-sulfamethoxazole (TMP-SMZ) at a dosage of 15 mg/kg/day (960 mg/day) and intravenous infusion of caspofungin at a dosage of 50 mg/day. Approximately 1 week after starting the new regimen, the patient's condition had improved. At 17 days after antibiotic adjustment, a pulmonary CT scan showed a clear reduction of the bilateral pulmonary foci, which strengthened the diagnosis of infectious lesions in the lungs. Caspofungin was discontinued because the rapid lung lesion shrinkage in the CT images did not support aspergillosis. Furthermore, the *Aspergillus* antigen levels were within the normal ranges and no evidence in the microscopic examination indicated *Aspergillus*. Following stabilization of hypokalemia, hyperglycemia, hypertension and infection at 43 days after admission, the patient was transferred to the Department of Thoracic Surgery. The mass in the anterior mediastinum and a nodule in the left upper pulmonary lobe were resected. Pathological evaluation suggested a chronic inflammatory focus in left upper pulmonary lobe with no evidence of malignancy. The pathological features and immunohistochemical observations for the mass in the anterior mediastinum indicated paraganglioma and corresponded with the result of formal biopsy.

At 3 days after the surgery, the plasma ACTH level dropped sharply to 12.7 pg/ml, which was within the normal range. The patient was discharged without any postoperative complications and continued oral treatment with TMP-SMX for 6 months. A CT scan 4 months after surgery indicated the lung lesion had been replaced by fibrous striped shadows without signs of recurrence. There was no recurrence of either nocardiosis or paraganglioma during a 3-year follow-up.

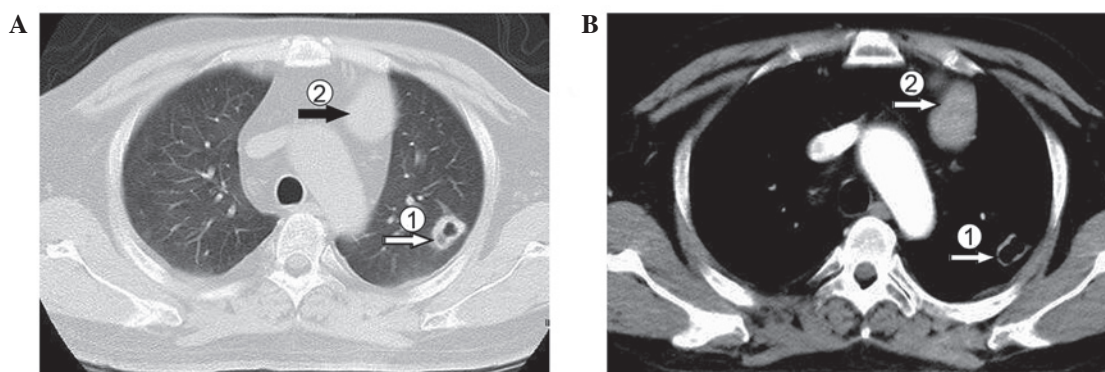


Figure 1. Multiple nodules in bilateral lung fields and a cavity lesion are visible with (A) partial nodular enhancement (arrow 1) and (B) obvious enhancement (arrow 1). A soft tissue density mass can be identified in the anterior mediastinum, adjacent to the aortic arch, with (A) a clear boundary (arrow 2) and heterogeneous enhancement (arrow 2).

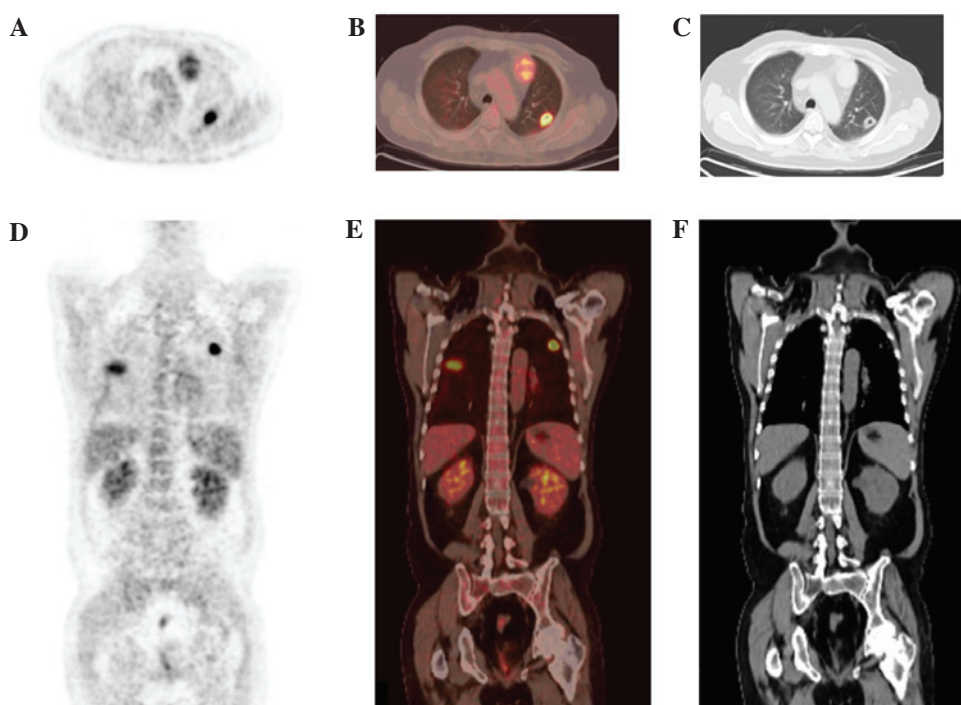


Figure 2. (A-C) Coronal and (D-F) transverse planes of (A and D) ^{18}F -FDG PET and (B and E) ^{18}F -FDG PET/CT showed focuses increase ^{18}F -FDG metabolism in the anterior mediastinum (SUV=4.42) and in bilateral pulmonary (left upper pulmonary nodule, SUV=10). (C and F) Computed tomography scan showed a homogeneous tumor-like focus in the anterior mediastinum and multiple clear-boundary nodule changes in bilateral pulmonary images. ^{18}F -FDG PET/CT, ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value.

Discussion

The English-language literature published from January 1980 to January 2014 (34 years) in the PubMed database, Google Scholar and Web of Science database was searched using the key words 'Nocardia', 'Nocardia infection', 'Nocardiosis' and 'ACTH Syndrome, Ectopic', 'Ectopic ACTH Syndrome', 'Ectopic ACTH Syndromes'. In addition, the references in the articles that referred to nocardiosis and ectopic ACTH syndrome were also examined. A total of 9 articles with full-text describing 11 cases were available (5-14). Including the present case, the clinical characteristics of EAS with *Nocardia* infection in 12 cases were analyzed. Information concerning the demography and clinical characteristics of the cases are summarized in xs I and II.

The literature review found that EAS complicated with nocardiosis was more common in men (9 cases, 75%) than in women. This result is consistent with previous studies of *Nocardia* spp. infection, which have reported that males are more susceptible to infection than females (15,16). However, a survey of cases of EAS indicated that men constitute 40-50% of patients (17). The mean age at diagnosis was 48 years, which falls within the range of mean ages reported previously (17,18).

Typical cushingoid features were readily observed in these cases. The majority of patients exhibited skin changes and muscle weakness, which are often observed in cases of exposure to long-term and extra high-dose glucocorticoids. Those manifestations may indicate that patients with EAS associated with nocardiosis tend to have chronic disease. The 24-h free urine cortisol concentration in the 12 cases examined in the

Table I. Clinical symptoms and signs of patients with ectopic ACTH syndrome (n=12).

Variable	Value
Mean age (range), years	48 (24-72)
Gender, n (%)	
Female	3 (25.00)
Male	9 (75.00)
Hypertension, n (%)	
Yes	6 (50.00)
No	5 (41.67)
Not reported	1 (8.33)
Weakness, n (%)	
Yes	9 (75.00)
No	2 (16.67)
Not reported	1 (8.33)
Hirsutism, n (%)	
Yes	3 (25.00)
No	8 (66.67)
Not reported	1 (8.33)
Skin change ^a , n (%)	
Yes	9 (75.00)
No	2 (16.67)
Not reported	1 (8.33)
Central obesity, n (%)	
Yes	5 (41.67)
No	6 (50.00)
Not reported	1 (8.33)
Edema, n (%)	
Yes	2 (16.67)
No	9 (75.00)
Not reported	1 (8.33)
Body weight, n (%)	
Increase	3 (25.00)
Decrease	5 (41.67)
Not reported	4 (33.33)
Psychiatric disorders, n (%)	
Yes	1 (8.33)
No	10 (83.33)
Not reported	1 (8.33)
Infections, n (%)	
<i>Nocardia</i>	12 (100.00)
Lung involved	12 (100.00)
Brain involved	1 (8.33)
Skin involved	2 (16.67)
Opportunistic pathogen co-infection ^b	4 (33.33)
<i>Pneumocystis carinii</i>	3 (25.00)
<i>Aspergillosis</i>	2 (16.67)

^aSkin changes including violaceous striae, easy bruising and cutaneous pigmentation. ^bOne case with *Nocardia*, aspergillosis and *Pneumocystis carinii* triple infection. ACTH, adrenocorticotropic hormone.

present case was apparently higher than in certain previous reports (19,20). However, restricted by the limited number of cases, it is not possible to determine the exact association of elevated 24-h free urine cortisol concentration with nocardiosis. The level of cortisol determines the degree of immunosuppression. The greater the extent by which cortisol levels exceed the normal value, the greater the possibility of opportunistic infections and the higher the mortality rate (21). The present review demonstrated that, of the 12 cases involving *Nocardia* spp., the patients who had a fatal outcome as a result of serious infection had comparatively higher urinary levels of corticoids. In addition, patients with higher urine cortisol concentrations tended to be co-infected with other opportunistic pathogens, especially *Aspergillus* and *Pneumocystis carinii*. Thus, the possibility of co-infection should be considered for patients with high level of corticoids and a combination antibiotic regimen applied as early as possible.

Radiography is a helpful diagnostic tool in localizing primary tumors and identifying infection lesions. For EAS patients, chest imaging is necessary to identify infection, particularly for individuals without pulmonary symptoms. Imaging results of the 12 cases showed the lung was the most common site of nocardiosis and was involved in all cases included in this literature review. Chest imaging is crucial in providing evidence of *Nocardia* spp. infection. Although a variety of radiological findings, such as cavities, consolidations/infiltration, nodules/masses and pleural effusion were present in the current case and previous patients in chest CT or X-ray images, the main findings comprised cavity (6 cases, 50%) and consolidation/infiltration (5 cases, 42%). Of note, the 4 cases (33%) of mass/nodule tended to be multiple. In a previous study of nocardiosis involving 51 cases performed by Blackmon *et al*, it was shown that airspace consolidation and discrete nodules were the most common manifestations while cavities were found in 21 cases (39.6%) (22). The high rate of cavities in the present review may result from delayed diagnosis, due to the low incidence and variable manifestations of nocardiosis in EAS. Previous data indicated that cavity formation mostly occurred within 2 weeks of infection (23). The mean time to establish a diagnosis of nocardiosis may be as long as 42 days (24). Formation of a cavity may be facilitated by a prolonged disease course. In conclusion, cavity lesions and consolidation/infiltration were the major findings of pulmonary nocardiosis for patients with EAS in the present study. Accordingly, nocardiosis should be considered as a differential diagnosis for EAS patients who have cavity formation or consolidation nodules in the lung, particularly when these manifestations are associated with brain and extra-pulmonary lesions. It is noteworthy that the imaging features of pulmonary nocardiosis in EAS patients are nonspecific and often mimic malignancy or other infection such as fungal infection and tuberculosis (19). In the present case and another previous study (25), PET/CT imaging showed that nocardiosis is often indicated by a high uptake of ¹⁸F-FDG, which is similar to that in malignant lesions. In this situation, a combination of PET/CT and image-guided biopsy can be a useful supplementary method for making a differential diagnosis.

In general, patients from the literature with only pulmonary infection exhibited sensitivity to TMP-SMZ monotherapy.

Table II. Summary of clinical information.

Case	Urine cortisol ($\mu\text{g}/24\text{ h}$)	Plasma ACTH (pg/ml)	Pulmonary imaging	Primary tumor	Antibiotic therapy	Outcome	Ref.
1	2,000	68.5	Cavity lesion ^a	Occult	TMP-SMZ	Unreported	(5)
2	27,216	159	Cavity lesions ^a	Adenocarcinoma	TMP-SMZ	Mortality	(5)
3	9,088	255	Consolidation; pleural effusion ^a	Occult	TMP-SMZ	Survival	(5)
4	Unreported	152	Nodules ^a	Carcinoid tumor	TMP-SMZ	Survival	(6)
5	21,469	1,013	Mediastinal lesion; cavity lesion ^a	Occult	TMP-SMZ; voriconazole	Mortality	(7)
6	>5,000	79	Infiltration lesion ^a	Occult	Gentamicin; meropenem; minocycline	Mortality	(8)
7	16,340	296	Nodules; bilateral effusion ^a	Neuroendocrine carcinoma	TMP-SMZ; vancomycin, Meropenem; amikacin; metronidazole	Mortality	(9)
8	10,338	122	Consolidation; cavity lesion ^b	Small-cell lung carcinoma	TMP-SMZ	Mortality	(10)
9	4,322	519	Infiltration; mediastinal mass ^b	Islet-cell carcinoma	Sulfadiazine; cycloserine	Mortality	(11)
10	11,820	112	Infiltration and cavity ^b	Bronchial carcinoid	TMP-SMZ	Mortality	(12)
11	Unreported	Unreported	Cavity lesions ^a	Medullary carcinoma	Sulfinamide	Mortality	(13)
12 ^c	3,118	372	Nodules; cavity lesion; density mass in anterior mediastinum ^a	Paraganglioma	TMP-SMZ	Survival	-
Normal range	24-108	9-52					

^aCT scan; ^bchest radiography; ^cpresent case. ACTH, adrenocorticotropic hormone; TMP-SMZ, trimethoprim-sulfamethoxazole.

Considering the high incidence and poor prognosis of *Aspergillus* co-infection, an antibiotic regimen containing an antifungal drug is recommended for early application since it is not possible to eliminate a diagnosis of fungal infection. However, TMP-SMX monotherapy appears to be inadequate in severe or disseminated cases (8-10,14). Although optimal antimicrobial treatment regimens were not firmly established, combined antibiotic therapy with a sulfa-containing agent has been recommended for severe or systematic disease (26). A combination of amikacin and imipenem or broad-spectrum cephalosporin was more effective than TMP-SMZ monotherapy in an experimental mouse model (27). However, a combination of imipenem and amikacin was poorly tested in patients, which is inadequate for drawing a conclusion. A three-drug regimen comprised of TMP-SMZ, amikacin, and either ceftriaxone or imipenem has been recommended when there is no evidence of resistance (28). Also, linezolid as an effective alternative has been reported in several cases of nocardiosis (29). Moreover, differing antimicrobial susceptibility patterns for different *Nocardia* species will induce varying therapeutic effects. Therefore, susceptibility tests provide significant information for adjustment of the antibiotic, particularly in cases insensitive to initial empirical treatment. Generally, a treatment duration of 6 months is recommended for EAS patients with pulmonary or cutaneous infection and 12 months for those with central nervous system infection or dissemination.

Controlling the plasma level of cortisol not only can improve clinical manifestation but also help in the prevention of *Nocardia* spp. infection. A study of opportunistic infection indicated that 11 of 12 (92%) patients succumbed when hypercortisolemia was not controlled, whereas 11 of 19 (58%) survived with effective control of hypercortisolemia (30). Complete tumor resection is a direct and effective curative method whenever possible, yet the success rate is only 30-47% (19). Medical therapy to control cortisol overproduction has been offered to those who are not indicated for complete resection. Metyrapone, ketoconazole and mitotane can all be used to lower plasma cortisol by acting directly to inhibit synthesis and secretion in the adrenal gland (31). These drugs are not effective as solo long-term treatments and are mainly used as preoperative preparations or as an adjunctive therapy after surgery (31). When the cortisol level cannot be controlled properly, when drug treatment is ineffective or not well tolerated or the resource remains unclear after long-term follow-up, total bilateral adrenalectomy will reduce cortisol levels and rapidly resolve clinical features. Following surgery, long-term treatment with glucocorticoids is necessary.

In conclusion, male patients are more vulnerable to infection. Patients with EAS who have extra-high urine cortisol levels and with a long disease course are at higher risk for *Nocardia* spp. infection. CT presentations of pulmonary nocardiosis in EAS at the time of diagnosis were heterogeneous. Cavity (50%), consolidation/infiltration (42%) and nodule/mass (33%) lesion were three common imaging findings in the present review. Optimal antimicrobial treatment regimens have not been firmly established. TMP-SMZ remains the first choice in EAS associated with pulmonary nocardiosis empirically, while combined antibiotic therapy with a sulfa-containing agent is recommended for severe or disseminated cases.

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