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A SILENT INVADER: ASYMPTOMATIC RHODOCOCCUS INFECTION UNMASKED IN A PATIENT WITH ECTOPIC ACTH-DEPENDENT CUSHING'S SYNDROME

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ABSTRACT

Introduction: *Rhodococcus* species, particularly *Rhodococcus equi*, are rare opportunistic pathogens that typically affect immunocompromised individuals. These infections usually present with respiratory or systemic symptoms and are often linked to environmental exposure. Asymptomatic *Rhodococcus* infections are exceedingly rare and pose unique diagnostic and therapeutic challenges.

Case description: We report the case of a 29-year-old male who presented with new-onset diabetes mellitus, resistant hypertension and significant weight gain. Physical examination revealed features consistent with Cushing's syndrome. Biochemical evaluation confirmed ACTH-dependent hypercortisolism with an elevated plasma ACTH level, and a lack of suppression on high-dose dexamethasone testing; imaging identified a suspicious pulmonary nodule. Bronchoscopic biopsy revealed no malignancy, however cultures grew *Rhodococcus* species. The patient denied any respiratory symptoms or environmental exposure. Initial antibiotic therapy with ciprofloxacin and rifampin was started. Follow-up imaging showed rapid enlargement of the pulmonary mass, prompting surgical resection. Histopathology revealed malakoplakia, and repeat cultures again yielded *Rhodococcus spp.* Antibiotics were adjusted to azithromycin and rifampin, and the patient was started on ketoconazole to manage hypercortisolism.

Conclusion: This case highlights the importance of considering opportunistic infections such as *Rhodococcus spp.* in immunocompromised patients, even in the absence of symptoms. It underscores the diagnostic value of investigating incidental findings in such populations and illustrates the need for prompt, multidisciplinary management to prevent disease progression.

KEYWORDS

Rhodococcus equi, Cushing's syndrome, ectopic ACTH secretion, opportunistic infection and immunosuppression

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LEARNING POINTS

- This case highlights the diagnostic complexity of incidental pulmonary nodules in immunocompromised patients, reinforcing the need for thorough microbiological investigation even in the absence of infection symptoms.
- It illustrates a rare, asymptomatic presentation of *Rhodococcus* infection in the context of ectopic ACTH-dependent Cushing's syndrome, a scenario not widely reported in the literature.
- Practical is given guidance on managing opportunistic infections and evaluating ectopic ACTH sources, aiding internists in navigating similar diagnostic and therapeutic challenges in complex endocrine-infectious overlaps.

INTRODUCTION/BACKGROUND

Rhodococcus species, particularly *Rhodococcus equi*, are rare opportunistic pathogens primarily affecting immunocompromised individuals[1,2]. These infections are most commonly associated with exposure to environmental sources such as soil, water or livestock, and typically present with respiratory or systemic manifestations[3]. Common clinical features include persistent cough, dyspnoea, fever and constitutional symptoms, which reflect pulmonary involvement or disseminated disease[4]. However, asymptomatic *Rhodococcus* infections are exceedingly uncommon, posing unique diagnostic and management challenges[5].

We present the case of a 29-year-old male with Cushing's syndrome secondary to suspected ectopic adrenocorticotropic hormone (ACTH) secretion, who was incidentally found to have *Rhodococcus spp.* cultured from a pulmonary nodule biopsy. Despite the presence of a positive culture, the patient exhibited no clinical symptoms consistent with infection such as fever, respiratory distress or systemic involvement. Additionally, the patient reported no history of exposure to environmental sources commonly associated with *Rhodococcus* infection. This unusual, asymptomatic presentation highlights the potential for opportunistic pathogens to arise in the context of immunosuppression due to chronic hypercortisolism. The incidental nature of this finding raises important considerations about the clinical significance, diagnostic evaluation and management of such cases, particularly in the absence of typical risk factors or symptomatology.

CASE DESCRIPTION

A 29-year-old male presented with new-onset diabetes mellitus that remained uncontrolled despite oral hypoglycaemic therapy, and resistant hypertension unresponsive to multiple antihypertensive regimens. Over the past year, the patient reported a rapid and significant weight gain of approximately 70 pounds. He denied any previous history of endocrine or metabolic disorders.

Recent cardiology evaluations, including an echocardiogram, an aldosterone-to-renin ratio test and plasma metanephrine levels were within normal limits. However, his clinical presentation raised concern for hypercortisolism. Physical examination revealed moon facies, marked central obesity with a tense, distended abdomen, prominent violaceous striae over the abdomen and bilateral +3 pitting oedema in the lower extremities.

The patient was evaluated for suspected Cushing's syndrome, with the results shown in *Table 1*.

The findings strongly suggest ectopic ACTH secretion, likely originating from the 1.2 cm pulmonary nodule in the right lower lobe *(Fig. 1)*.

For the pulmonary nodule evaluation, the patient underwent a bronchoscopy with biopsy of two nodules in the right lower lobe. The histopathological analysis resulted in no malignant

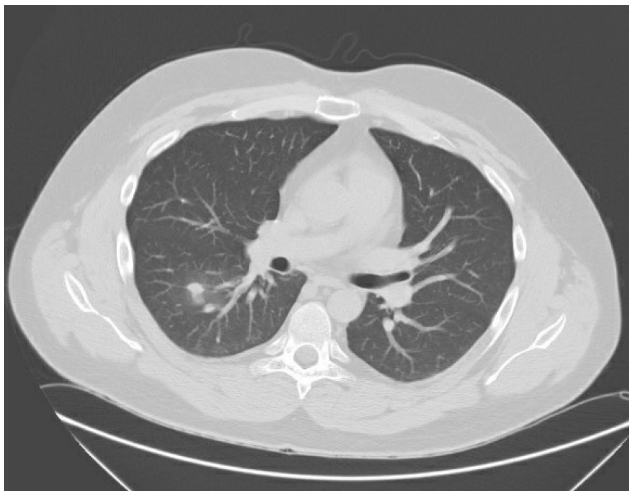


Figure 1. A 1.2 cm nodule in the right lower lobe and adjacent 8 mm satellite nodule.

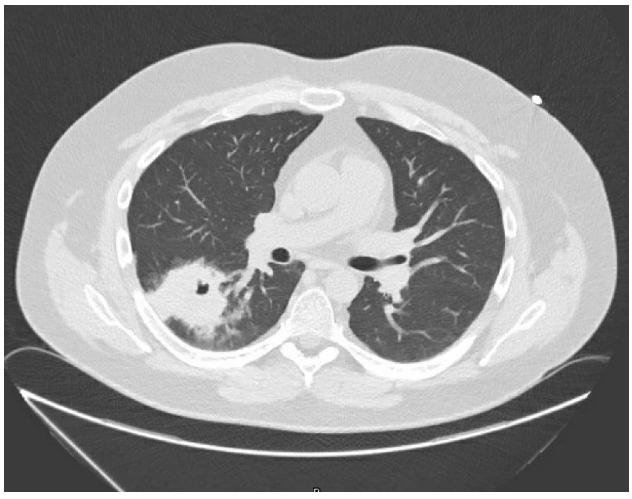


Figure 2. Superior segment of the right lower lobe with abnormal substantially enlarged density, now measuring 5.2 × 4.8 × 4.7 cm versus 1.6 cm the previous month.

Test/Procedure	Result	Interpretation
AM cortisol (µg/dl)	42.8	Significantly elevated; suggests hypercortisolism
24-hour urinary free cortisol (UFC) (µg/24 hours)	9.9	Normal to low; atypical finding for Cushing syndrome
High-dose dexamethasone suppression test (µg/dl)	37.6	No significant suppression; suggests an ectopic ACTH source.
Plasma ACTH level (pg/ml)	230	Markedly elevated; confirms ACTH-dependent hypercortisolism, likely ectopic
CT Abdomen	Normal	No evidence of adrenal tumor
MRI Brain	Normal	No evidence of pituitary adenoma.
CT Chest	1.2 cm nodule in R lower lobe & adjacent 8mm satellite nodule	Suspicious for ectopic ACTH-producing tumor (e.g., pulmonary nodule).

Table 1. Summary of diagnostic evaluation for suspected Cushing's syndrome.

cells identified. Cultures were performed on sheep blood agar and chocolate agar, and *Rhodococcus* species grew as a pure isolate on both media within 48 hours. Colonies appeared smooth, salmon-pink and mucoid.

The patient had no symptoms commonly associated with *Rhodococcus* infection (e.g. persistent cough, dyspnoea, fever, chest pain or fatigue). Furthermore, there were no signs of systemic or extrapulmonary involvement, and no known history of exposure to potential sources of *Rhodococcus* (e.g. contaminated soil, water or livestock). This asymptomatic presentation with *Rhodococcus* culture positivity is atypical and likely reflects an opportunistic infection due to the patient's immunocompromised state from chronic hypercortisolism.

During the one-month follow-up, a high-resolution computed tomography (CT) scan revealed a significant increase in the size of the pulmonary mass from 1.6 cm on previous imaging to 5.2 cm *(Fig. 2)*. Given the rapid progression patient was readmitted and CT surgery was consulted; the patient underwent a robotic right lower lobe segmentectomy.

Repeat lung biopsy and pleural fluid analysis showed no evidence of malignancy. However, histopathological evaluation revealed foamy histiocytes with Michaelis–Gutmann bodies, consistent with pulmonary malakoplakia, and cultures once again grew *Rhodococcus* species despite the patient having been on rifampin and ciprofloxacin for one month.

Fungal (Sabouraud agar), acid-fast bacilli (Lowenstein-Jensen) and Legionella cultures were also performed and returned negative. Serum galactomannan, beta-D-glucan and Histoplasma urine antigen tests were negative. Immunostaining for ACTH was negative.

In subsequent antibiotic sensitivity testing using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute guidelines, the isolate demonstrated intermediate sensitivity to ciprofloxacin. As a result, the patient's antibiotic regimen was adjusted to azithromycin in combination with rifampin, with a plan for prolonged treatment lasting approximately 6 to 12 months.

The management plan had two parts. For infectious management the patient was initially treated with oral ciprofloxacin and rifampin for one month. Due to persistent *Rhodococcus* positivity and reduced ciprofloxacin sensitivity, therapy was replaced with azithromycin plus rifampin, with planned long-term treatment (6–12 months). For ectopic ACTH management the patient was started on ketoconazole, a steroidogenesis inhibitor, to manage hypercortisolism and mitigate its immunosuppressive effects during the diagnostic workup. Concurrently, localisation efforts were initiated with positron emission tomography (PET) imaging; however, given that the pulmonary nodule biopsy did not demonstrate ACTH immunoreactivity, the diagnosis of ectopic ACTH secretion remains presumptive. If the source remains occult despite current imaging, future diagnostic steps will include serial functional imaging such as repeat Ga-68 DOTATATE PET/CT, whole-body MRI and potentially bilateral inferior petrosal sinus sampling to definitively exclude a pituitary origin. Continued clinical monitoring and biochemical surveillance will be essential to assess disease progression or eventual localisation of the ectopic source.

DISCUSSION

Rhodococcus infections, though rare, are most frequently encountered in immunocompromised hosts, such as those with HIV/AIDS, post-transplant immunosuppression or malignancies undergoing chemotherapy[6]. In these patients, the organism's ability to survive intracellularly within macrophages contributes to its pathogenicity and often results in respiratory infections, systemic dissemination or abscess formation[7]. Chronic hypercortisolism leads to impaired cell-mediated immunity, diminished natural killer cell activity and functional defects in neutrophils and macrophages. These changes increase susceptibility to opportunistic infections including fungal, mycobacterial and less common pathogens such as *Rhodococcus spp.*[8]

The distinction between colonisation and true infection

remains challenging in immunocompromised individuals. In this case, although the patient lacked symptoms, the radiographic progression and repeat positive cultures despite antibiotic therapy suggest a low-grade infection rather than benign colonisation. Opportunistic organisms such as *Rhodococcus spp.* can persist intracellularly, and asymptomatic presentations may precede dissemination in vulnerable hosts.

The case presented here is unique due to the incidental detection of *Rhodococcus spp.* in an asymptomatic patient with hypercortisolism secondary to ectopic ACTH secretion. Chronic hypercortisolism is known to impair the immune response through various mechanisms, including reduced T-cell proliferation and function, inhibition of macrophage activation and suppression of pro-inflammatory cytokine production[9]. These immunosuppressive effects likely predisposed the patient to opportunistic colonisation by *Rhodococcus*, even in the absence of environmental exposure or typical clinical symptoms.

Another distinguishing feature of this case is the atypical presentation with no respiratory symptoms, systemic involvement or evidence of dissemination. This underscores the importance of a high index of suspicion in immunocompromised patients and highlights the need for microbiological evaluation in seemingly benign or incidental findings, such as pulmonary nodules. The detection of *Rhodococcus* in this context necessitated treatment, as immunosuppressed patients are at higher risk of progression to symptomatic or disseminated infection if left untreated[10]. Management of *Rhodococcus* infections typically involves prolonged combination antibiotic therapy due to the organism's intrinsic resistance to many antimicrobials[11]. This case illustrates the complexity of managing incidental opportunistic infections in immunocompromised hosts, highlighting the need for thorough microbiological evaluation and a cautious approach to antimicrobial selection in the absence of classic clinical symptoms.

Ectopic ACTH secretion can present a significant diagnostic challenge. In around 12–20% of cases, the source remains occult despite extensive imaging and biochemical evaluation[12]. This case also illustrates the importance of further evaluation of incidental findings, such as the pulmonary nodules, which were ultimately suspected as the source of ectopic ACTH secretion. A PET scan was scheduled to provide additional insight and guide definitive management.

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