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Rhodococcus Equi Pneumonia and Paradoxical Immune Reconstitution Inflammatory Syndrome in a Patient with Acquired Immune Deficiency Syndrome (AIDS)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 47
Final Diagnosis: *Rhodococcus equi* pneumonia • paradoxical immune reconstitution inflammatory syndrome
Symptoms: Cough • fever • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases





Objective: Rare co-existence of disease or pathology
Background: Pulmonary infections are a major cause of mortality and morbidity in patients infected with human immunodeficiency virus (HIV) and can progress rapidly to respiratory failure and death without appropriate therapy. Herein, we present a rare case of an advanced HIV infection and *Rhodococcus equi* (*R. equi*) pneumonia in a young male who had severe paradoxical immune reconstitution inflammatory syndrome (IRIS).

Case Report: A 47-year-old nonsmoking Hispanic man with advanced HIV infection presented with severe acute necrotizing pneumonia secondary to *R. equi*. Although his initial response to antimicrobial therapy was optimal, he became symptomatic again in spite of continuation of antibiotics as he developed severe paradoxical IRIS 3 weeks after starting a new highly active anti-retroviral therapy (HAART).

Conclusions: The diagnosis of IRIS remains challenging because of the wide variations in the clinical presentation and etiologies. In spite of its rarity as an opportunistic pathogen, we recommend that *R. equi*, an intracellular pathogen, be included in the differential list of pathogens associated with IRIS.

MeSH Keywords: Acquired Immunodeficiency Syndrome • Immune Reconstitution Inflammatory Syndrome • *Rhodococcus equi*

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Background

Pulmonary infections are a major cause of mortality and morbidity in patients infected with human immunodeficiency virus (HIV) and can progress rapidly to respiratory failure and death without appropriate therapy, especially in those with a CD4 count less than 100 [1]. Bacterial pathogens are a frequent cause of pneumonia in the United States and Western Europe, while tuberculosis (TB) is the dominant pathogen in sub-Saharan Africa. Depending upon the availability of highly active anti-retroviral therapy (HAART) and opportunistic infection (OI) prophylaxis, the spectrum of pulmonary pathogens causing pneumonia in the West may be limited [2].

Rhodococcus equi (*R. equi*) pneumonia is known to mimic TB and can pose a diagnostic challenge. Early and accurate identification of infection in HIV-infected individuals is critical as mortality rates were higher in these patients when compared to patients without HIV.

We report a rare case of an advanced HIV infection with *R. equi* pneumonia in a patient who had severe paradoxical immune reconstitution inflammatory syndrome (IRIS) following initiation of HAART. Physicians should be aware of this complication, which includes paradoxical worsening of treated opportunistic infections or the unmasking of previously sub-clinical, untreated infection. Therefore, vigilance for clinical signs and symptoms for IRIS is an important part of HIV care in the initial months of HAART [3,4].

In a review of the literature, we were able to identify another case of paradoxical worsening of radiological findings with HAART reported in AIDS patients with *R. equi* infection [5]. We speculate that the worsening of the radiological findings was not worsening pneumonia but IRIS. In contrast, another published case described worsening *R. equi* infection despite HAART and antimicrobial therapy. The patient unfortunately had ineffective immune recovery; this emphasizes the importance of immune recovery in patients with OI [6].

Case Report

A 47-year-old nonsmoking Hispanic man with a history of HIV infection was admitted with a 3-month history of cough productive of yellowish sputum associated with dyspnea, fever, and weight loss of 13 lbs. The patient also complained of right-sided chest pain, aggravated by coughing and breathing. He denied night sweats, hemoptysis, or sick contacts. He denied alcohol and illicit drug abuse and recently moved from Puerto Rico, where he was treated for pneumonia 6 months ago. The patient had worked on a farm and had exposure to horses owned by his neighbor in Puerto Rico. He had been diagnosed

with HIV 10 years earlier and was on fixed-dose single-tablet rilpivirine 25 mg, tenofovir disoproxil fumarate (TDF) 300 mg, and emtricitabine 200 mg for years. Prior HIV care and hospitalization records were not available. The patient has been compliant with his HIV regimen but did not know his most recent CD4 count or viral load on admission.

His physical examination showed an ill-looking man with mild respiratory distress. His vital signs were heart rate 104/min, blood pressure 145/91 mm Hg, respiratory rate 18 breaths/min, oxygen saturation 91% on room air, and temperature 102°F. He had a non-productive cough, and auscultation of the chest revealed reduced breath sounds in the right lung base with right basal crackles. There was no clubbing. His cardiac examination revealed tachycardia but no murmurs, rubs, or gallop. There was no hepatosplenomegaly, and the neurological exam was normal. Laboratory studies showed no leukocytosis, mild anemia of chronic diseases, and low albumin levels. Urinalysis was unremarkable. Chest radiography showed a 4.5 cm rounded mass-like opacity in the right hilar area. Therefore, a computed tomography (CT) scan of the chest was obtained, which revealed a right lower lobe cavitory mass/consolidation measuring 7.8×6.5 cm, with minimal right pleural effusion (Figure 1).

The patient was placed on respiratory isolation to rule out TB. He started broad-spectrum antibiotics, including intravenous vancomycin 1 g every 12 hours, ceftriaxone 1 g daily, azithromycin 500 mg daily, and clindamycin 600 mg every 8 hours. Pan-cultures including sputum culture and Gram stain, sputum acid-fast bacilli, interferon gamma release assay, HIV RNA, and CD4 count were obtained. Blood, sputum, and urine cultures were negative. TB workup also was negative. His viral RNA showed 30,628 copies with pending viral genotype; CD4 count was 14. A CT-guided lung biopsy was then performed with samples sent for Gram stain, bacterial and fungal cultures, and histology. The pathologic analysis revealed severe acute necrotizing pneumonia with some pulmonary fibrosis and numerous gram-positive rods. Lung biopsy culture reported *R. equi*.

His initial intravenous antibiotic regimen was changed to linezolid 600 mg every 12 hours, levofloxacin 750 mg daily, and azithromycin 500 mg daily. His condition improved significantly, he became afebrile, cough and chest pains resolved, and he was discharged in stable condition on oral azithromycin 500 mg daily and levofloxacin 750 mg daily for 8 weeks. The patient was also referred to the outpatient HIV program at the hospital for follow-up, where his HAART regimen was changed to ritonavir 100 mg daily, darunavir 800 mg daily, and emtricitabine-tenofovir 200–300 mg, as genotypic resistance indicated failure of rilpivirine. Three weeks after the switch to the new HAART and while on week 4 of levofloxacin and azithromycin, the patient started having right-sided chest pain and cough with low-grade temperature. The repeat CD4

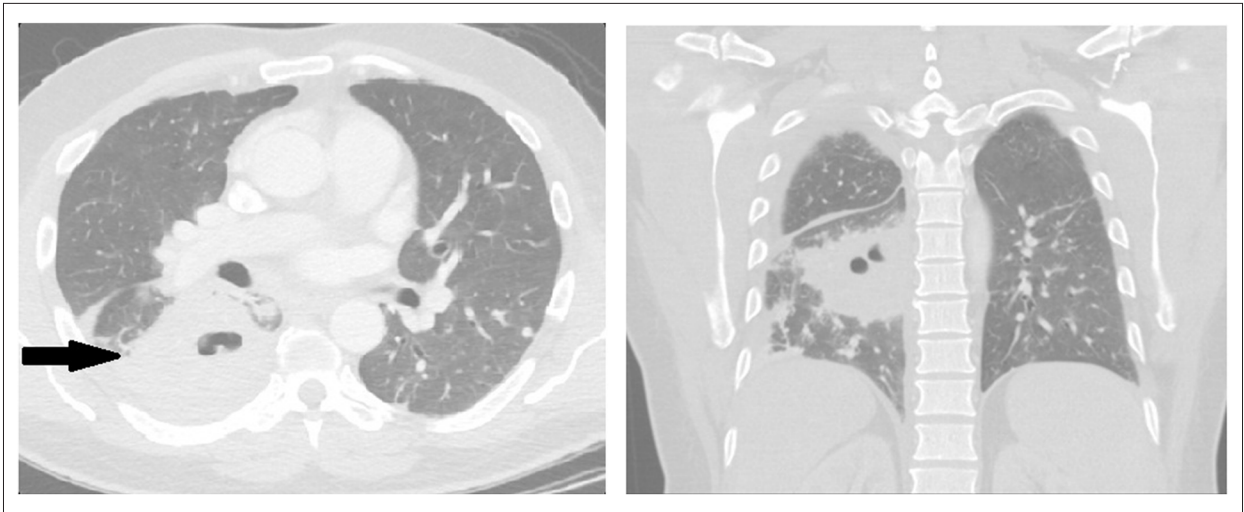


Figure 1. Chest CT scan showing a right lower lobe cavitary mass/consolidation with minimal right pleural effusion (black arrow).

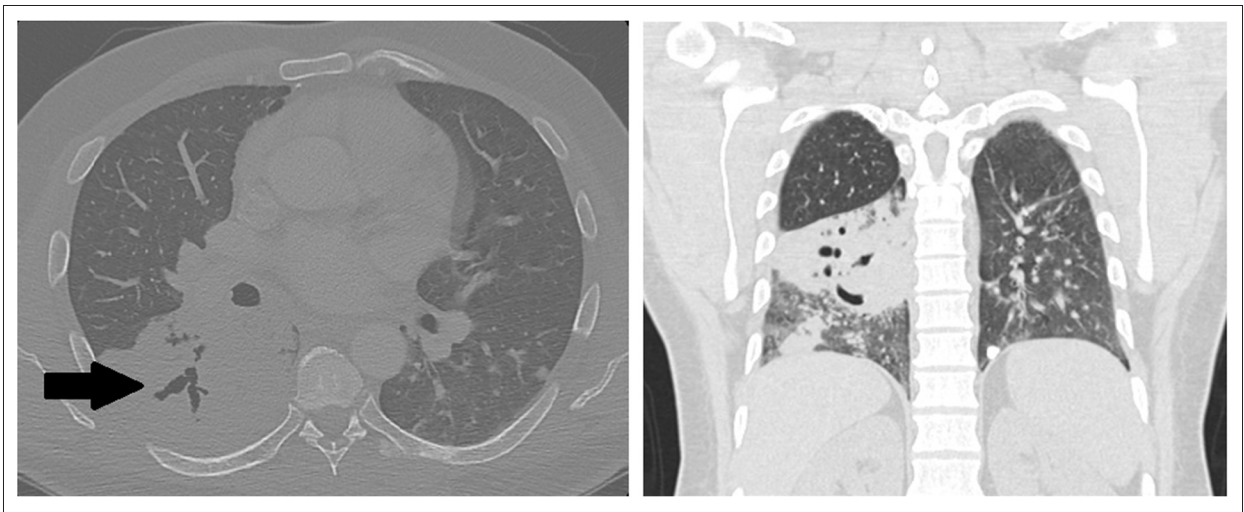


Figure 2. Chest CT scan demonstrating increased mass-like consolidative opacity (black arrow).

count was 62 cells/ μ m and a viral load of 86 copies/mL. A repeat (2nd) CT scan of the chest demonstrated increased mass-like consolidative opacity measuring 9.7×7.9 cm. The cavitation itself was roughly stable at 2 cm (Figure 2).

Oral linezolid 600 mg twice a day was added to azithromycin and levofloxacin. All three antibiotics were continued for 2 weeks, and then azithromycin and levofloxacin were discontinued. Linezolid was continued for a total of 4 weeks to complete a total course of 8 weeks of therapy. The CT scan findings were concerning; however, given the patient's improved virological and immunological status and negative workup for other potential differential diagnoses, he was treated symptomatically with low-dose non-steroidal anti-inflammatory agents and close biweekly clinic follow-ups. His symptoms continued to improve, and he gained close to 30 lbs in the following 4 months, with HIV RNA becoming fewer than 20 copies

and CD4 count of 236 cells/mL. He had an episode of herpes zoster involving right 10–11th thoracic dermatomal distribution, which was treated with oral valacyclovir 1 g three times a day for 10 days. No steroids were used during this episode. The patient has been free of any other OI or *R. equi* relapses since discharge from hospital in the past 8 months, and a repeat (3rd) CT of chest (Figure 3) showed almost complete resolution of infiltrates.

Discussion

R. equi is a facultative, intracellular, nonmotile, non-spore-forming, gram-positive, weakly acid-fast pleomorphic bacterium that has the ability to exist as a coccus or bacillus or intermediate form. *R. equi* primarily infects foals, but the organism has also been identified in a variety of land and water

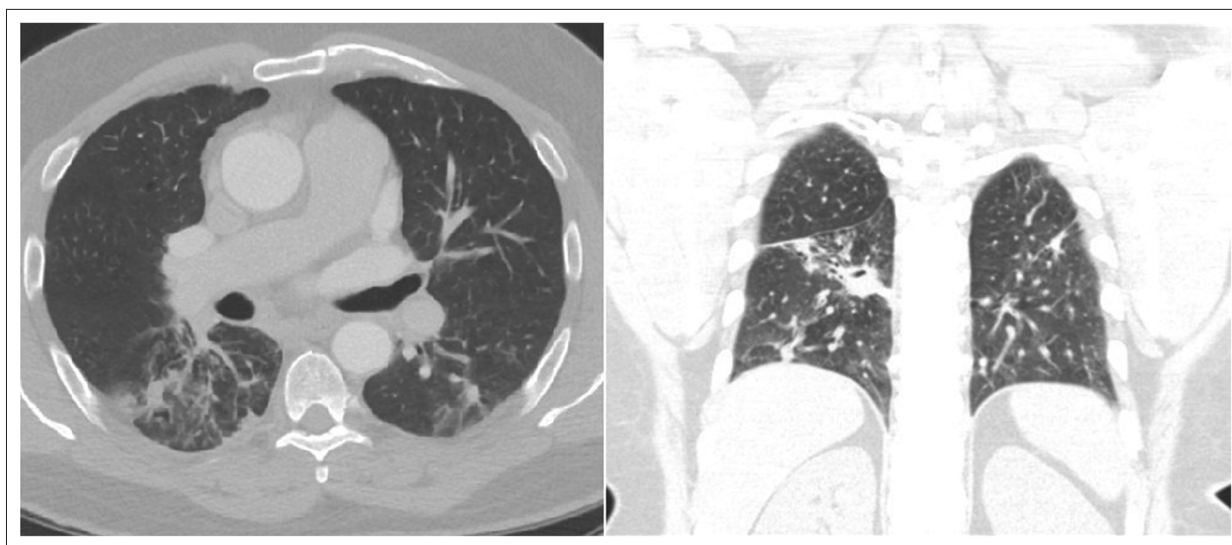


Figure 3. A repeat CT scan of chest showing complete resolution of infiltrates.

animals. In humans, infections are rare and primarily seen in immunocompromised, especially HIV-infected, individuals, transplant recipients, and patients on chemotherapy or treated with monoclonal anti CD52 [7].

Initiation of HAART and appropriate antimicrobials is an essential part of management and prevention of relapses as well as dissemination to other organs including CNS [8,9]. HAART has impressively reduced morbidity and mortality in HIV-related OIs and other comorbidities [10].

Although a wide variety of antimicrobial agents are active *in vitro* against *R. equi*, many of these drugs are reported to be ineffective *in vivo*, presumably because of poor cellular uptake and the resulting low intracellular concentrations [11]. Therefore, selection of appropriate antibiotics may be a difficult task. Linezolid use resulted in successful outcomes in transplant recipients and published *in vitro* efficacy data against *R. equi* [12,13]. The mortality can be as high as 50% in *R. equi* infections when diagnosis is delayed or treatment is not started in a timely way in immunosuppressed patients. The current recommended regimens are to be used for a minimum of 2 months with various regimens discussed elsewhere. However, in cases in which underlying immunosuppression cannot be restored, as in the case of transplant patients, duration of therapy may be prolonged up to 6 months [14].

The ultimate clearance of *R. equi* infection requires a robust response from the cellular immune system. *R. equi* survives in macrophages by inhibiting the formation of the phagosome-lysosome complex and thereby its degradation [15]. In addition, defective production of interferon gamma and tumor necrosis factor alpha by AIDS mononuclear cells after *in vitro* exposure to *R. equi* has been reported [16].

IRIS is a clinical diagnosis that comprises two distinct syndromes: paradoxical IRIS and unmasking IRIS. Paradoxical IRIS refers to the worsening of underlying infection that is already being treated with appropriate antimicrobial therapy upon start of HAART. Unmasking IRIS refers to a new presentation of underlying infectious pathology upon start of HAART, usually within 3 months. IRIS may usually last 2–3 months but has been reported to last up to 12 months on occasion. In general about 10–40% of patients receiving HAART will show signs and symptoms of either form of IRIS. Clinical criteria have been defined for IRIS diagnosis, but it is clear that rapid decline in HIV RNA and rebound in CD4 counts are two important factors in development of IRIS. The lower the CD4 count is, the higher the risk of IRIS. In general, IRIS can be managed with NSAIDs and antimicrobial therapy for OI; corticosteroids may be considered with life-threatening tuberculosis infections or cryptococcal meningitis. However, interruption of HAART is not recommended [17–19].

IRIS or simply immune restoration disease is triggered by initiation or reinitiation of HAART, or sometimes a change to more effective HAART (as in our case) in deeply immunosuppressed HIV patients. In addition, there are very limited data on how to treat IRIS due to lack of prospective, randomized clinical trial data. There is no uniform explanation of pathogenesis, which is largely speculative, with the syndrome being linked to increasing CD4 counts after treatment of HIV is started. The pre-existing perturbations in T cell regulatory functions in proinflammatory and cytokine regulations may also determine the severity and degree of IRIS cases. It was also suggested that IRIS can be more severe in patients with heavy organism burden. Incidence and features of IRIS also depend on the type of OI encountered. It has been noted that IRIS occurred in more than 10% of patients with Kaposi sarcoma, tuberculosis, and cryptococcal infection [16,18]. There is no consensus

regarding the optimal time to initiate HAART in patients with recently diagnosed OIs. The ACTG 5164 study indicates a benefit of immediate HAART that outweighs the risk of IRIS. It also re-demonstrated that a high CD4 count and percentage and a low HIV viral load on HAART were associated with development of IRIS [18]. In our view, TB, *Mycobacterium avium* complex (MAC), and cryptococcal infections require a different approach and require HIV expert opinion. Patients with profound immune deficiency and AIDS have varying degrees of IRIS incidence and IRIS severity that can be mild to moderate to severe, making recognition and incidence estimates vary in different reports [20]. Finally, we were diligent in diagnosing the paradoxical IRIS in our patient, in whom HAART was recently reinitiated, who did not have inadequate antimicrobial therapy, and who did not have sepsis or bacteremia or a drug reaction at the time of reemergence of fever, cough, and

radiological worsening upon his steeply declining viral load and increasing CD4 count.

Conclusions

The diagnosis of IRIS remains challenging because of the wide variations in the clinical presentation and etiologies. In spite of its rarity as an opportunistic pathogen, we recommend, if our finding is confirmed by other similar reports, that *R. equi* be considered for inclusion in the differential list of pathogens associated with IRIS.

Conflicts of interest

None.

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