Severe Cavitary Pneumonia Caused by a Non-*equi Rhodococcus* Species in an Immunocompetent Patient

Stephanie Ng DO, Christopher S King MD, Jun Hang PhD, Robert Clifford PhD, Emil P Lesho DO, Robert A Kuschner MD, E Darrin Cox MD, Roscea Stelsel, ASCP(MT), and Rupal Mody MD

Introduction

Rhodococcus equi is a Gram-positive coccobacillus that can cause a variety of infections in humans, most commonly severe pneumonia.[1-4] These infections typically occur in immunocompromised hosts, although, rarely, immunocompetent hosts may be affected as well.[1-4] Non-*equi Rhodococcus* species have been implicated in human disease, albeit less commonly than *R equi*. We report a case of severe cavitary pneumonia in an immunocompetent host caused by a non-*equi Rhodococcus* species.

Case Summary

A 73-year-old man who resides on a ranch in Texas presented to our hospital with a complaint of one month of increasing cough, dyspnea, hemoptysis, and 9-kg weight loss after inhalational exposures during wild fires that occurred approximately 1 month prior to admission. Shortly after these inhalational exposures, he presented to his primary care physician with acute onset of hemoptysis. He was treated for community-acquired pneumonia with an unknown antibiotic, with slight improvement in his symptoms, but began to experience worsening shortness of breath and blood streaked sputum 3 days prior to admission. The patient denied fevers, chills, or night sweats. His medical history was notable for mild COPD and neuropathy following surgical repair of an abdominal aortic aneurysm. Admission medications included ergocalciferol, gabapentin, acidophilus, and loperamide as needed. The patient noted prior exposures to cattle, sheep, horses, and dogs, but denied direct exposures within the past few years. He smoked 1 pack of cigarettes per day for the past 59 years, and denied alcohol use.

On presentation, the patient's vital signs were within normal limits; no tachypnea or hypoxemia was noted. His physical examination was unremarkable except for rhonchi in the left upper lobe. Laboratory testing revealed an initial white-blood-cell count of 15.1×10^3 cells/μL, with 87% neutrophils and 5% lymphocytes. His blood chemistry was only notable for a serum sodium of 128 mEq/L. Quantiferon tuberculosis testing, human immunodeficiency virus (HIV) testing, and blood cultures were negative.

Contrast enhanced computed tomography (CT) of the chest revealed a segmental pulmonary embolus and a $9.0 \times 7.2 \times 7.8$ cm left upper lobe area of consolidation (Fig. 1). Initial bronchoscopy performed revealed only growth of coagulase negative *Staphylococcu*s and viridans *Streptococci.* Direct fluorescent antibody stain test for *Pneumocystis* was negative, and fungal and mycobacterial stains and cultures were negative after 8 weeks of growth. Urine *Legionella* antigen, cryptococcal antigen, Q-fever, tularemia, brucella, and serology for endemic fungi were also negative. Given concern for a malignancy, a CT-guided needle biopsy was performed, which showed necrotic material, with no malignant cells. The patient was started on moxifloxacin for presumed lung abscess. A chest

Dr Ng is affiliated with the Department of Internal Medicine; Dr Cox is affiliated with the Department of Thoracic Surgery; Ms Stelsel is affiliated with the Department of Microbiology/Immunology; and Dr Mody is affiliated with the Department of Infectious Diseases, William Beaumont Army Medical Center, El Paso, Texas. Dr King is affiliated with the Department of Pulmonary/Critical Care Medicine, Fort Belvoir Community Hospital, Fort Belvoir, Virginia. Drs Hang and Kuschner are affiliated with the Viral Diseases Branch; and Drs Clifford and Lesho are affiliated with the Multidrug Resistant Organism Repository and Surveillance Network, Walter Reed Army Institute of Research, Silver Spring, Maryland.

The authors have disclosed no conflicts of interest.

The views expressed in this paper are those of the authors and do not reflect the policy or position of the Department of the Army, Department of Defense, or the United States Government.

Correspondence: Christopher S King MD, Department of Pulmonary/Critical Care, Walter Reed Army Medical Center, 3831 Georgia Avenue NW, Washington DC 20307. E-mail: Christopher.s.king@health.mil.

DOI: 10.4187/respcare.02017

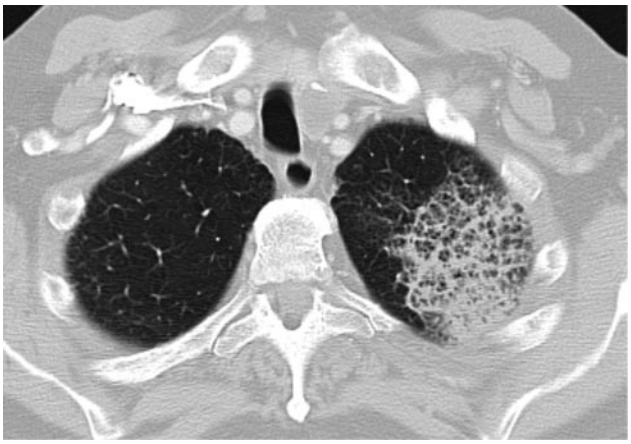

Fig. 1. Initial computed tomogram shows a 9.0 × 7.2 × 7.8 cm consolidation in the left upper lobe, with honeycombed appearance.

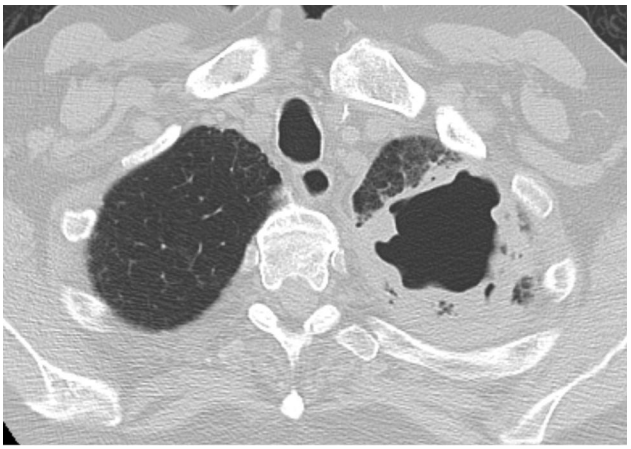

Fig. 2. Computed tomogram 1 month later shows new cavitation and increase in size of the left upper lobe lesion.

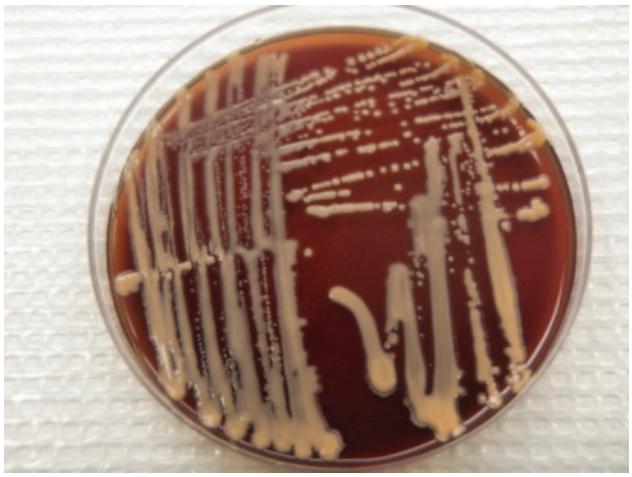

Fig. 3. Salmon pink colored colonies on chocolate agar.

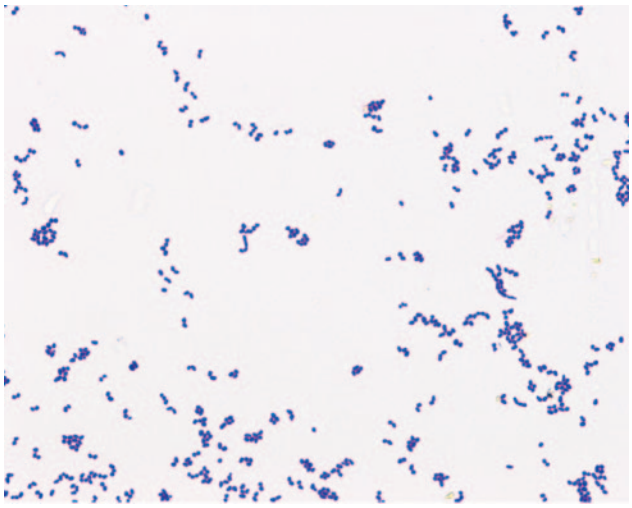

Fig. 4. Gram-positive coccobacilli (magnification 100×).

CT 1 month later showed substantial expansion and cavitation of the lesion (Fig. 2).

Due both to concerns for undiagnosed malignancy and inadequately controlled infection, the patient underwent partial left upper lobe lobectomy. Intraoperative histopathology showed necro-inflammatory debris with mixed Gram-positive and Gram-negative cocci and rods on Brown-Hopps staining, with special stains negative for fungi and mycobacteria. Within 2 weeks the intraoperative cultures were noted to be growing salmon-pink colonies in multiple mycology media bottles and on chocolate agar, which were phenotypically consistent with *Rhodococcus* species (Fig. 3). Gram stain revealed Gram-positive coccobacilli, which were identified as a *Rhodococcus* species (Fig. 4). The initial *Rhodococcus* isolate could not be speciated in our lab; therefore, the sample was sent for susceptibility testing, optical genome mapping, and definitive identification with genome sequencing. Comparative analysis of the 16S ribosomal RNA (rRNA) gene with those available in GenBank clearly demonstrated the isolate belongs to the *R rhodochrous* clade (*R rhodochrous*, *R gordoniae*, and *R pyridinivoran*), and was phylogenetically distant from *R equi*. In particular, the 16S rRNA gene sequencing was > 99% compatible with *R rhodochrous*. Susceptibility tests showed the species to be sensitive to erythromycin, minocycline, and rifampin.

Prior to initial presentation to the hospital, the patient was treated with an initial antibiotic (possibly azithromycin) that may have partially treated him. Once the *Rhodococcus* species was isolated, the patient was treated with intravenous meropenem, vancomycin, and rifampin once susceptibility results were available, and then switched to oral minocycline and rifampin after 6 weeks of intravenous therapy to complete a total of approximately 4 months of therapy for cavitary pneumonia due to *Rhodococcus* species. Upon completion of his treatment course he re-

ported improved strength and energy, with resolution of his cough and shortness of breath. A repeat chest CT was performed 3 months postoperatively and showed appropriate healing and no new cavitary lesions.

Discussion

Rhodococcus is a Gram-positive coccobacillus that can grow as branching filaments. The organism grows easily on nonselective media and typically develops a salmon hue after 4–7 days of growth.[1] The bacteria often appear diphtheroid-like on Gram-stain, and may be misread as normal flora. If the diagnosis is suspected, laboratory staff should be alerted to help avoid misclassification. *Rhodococcus* species are commonly isolated from soil and animal dung, but rarely cause disease in humans. Although classically associated with exposure to livestock or a farming environment, 10 of 19 cases of *R equi* in immunocompetent patients reported in a review had no such discernible exposure.[2]

R equi is the most common pathogenic *Rhodococcus* species in humans. Typically, *Rhodococcus* acts as an opportunistic pathogen in immunocompromised patients, including transplant recipients and patients with HIV. The most common site of infection is the lung, which is involved in the majority of patients, but *R equi* can also cause bacteremia, central nervous system infection, soft tissue infection, and organ abscess.[3] Lung involvement is often characterized by upper lobe necrotizing pneumonia, which can be complicated by cavitation, abscess, empyema, chest wall invasion, and pneumothorax.[1,4] The differential diagnosis for necrotizing pneumonia includes typical bacteria such as *Staphylococcus aureus*, *Klebsiella pneumonia*, *Streptococcus* species, and anaerobes; atypical bacterial infections, including mycobacteria and fungi; and non-infectious etiologies, including vasculitis and malignancy. Most patients initially present with nonspecific, subacute complaints, including malaise, cachexia, weight loss, and fever.[5] Infrequently, *R equi* cause disease in immunocompetent patients, most commonly as localized infections. Pneumonia occurs much less frequently in immunocompetent hosts, accounting for 42% of *Rhodococcus* infections, as compared to 84% in immunocompromised hosts.[2]

The diagnostic approach to suspected *R equi* infection is similar to that for other pathogens. The organism can be isolated from affected body tissues, sputum, or pleural fluid. Bronchoscopy may be useful if an adequate sputum sample cannot be obtained. Blood cultures should also be obtained, as concurrent bacteremia may occur.[1,5]

Because *Rhodococcus* is such an unusual pathogen, few data exist to guide treatment. While antimicrobial therapy alone has been reported to be successful in case series, surgical debulking may be entertained in refractory disease.[1] Limited data are available on non-*equi Rhodococcus* species, but *R equi* is generally susceptible to macrolides, rifampin, aminoglycosides, vancomycin, imipenem, and quinolones.[2,6] Excellent moxifloxacin susceptibility has been reported to in vitro isolates of *R equi*.[7] The reference laboratory was unable to perform moxifloxacin susceptibility testing of the non-*equi Rhodococcus* species isolated in our patient, and there is uncertainty as to whether susceptibility to ciprofloxacin (minimum inhibitory concentration ≤ 0.5 μg/mL) reported on this patient's isolate can be extrapolated to moxifloxacin.

Reasons for the failure of initial therapy with moxifloxacin in our patient might have been due to resistance to moxifloxacin, initial susceptibility to moxifloxacin and subsequent development of in vivo resistance with the use of monotherapy, or inadequate penetration of antibiotics into the abscess cavity. Finally, it is possible that an abscess cavity had developed with secondary infection due to *Rhodococcus* species, since initial non-operative cultures did not grow *Rhodococcus*. However, this lack of initial growth was more likely due to inadequate specimen sampling or reduced bacterial inoculum in the setting of prior antibiotic therapy. Use of certain β-lactam antibiotics is not recommended, due to either resistance to penicillins and cephalosporins, or to the possibility of development of resistance despite in vitro susceptibility.[2,3]

Combination therapy with 2 or 3 antimicrobials is generally recommended, with duration dictated by the patient's immune status, response to therapy, and the site and degree of tissue involvement.[1] An intravenous regimen of vancomycin, imipenem, and rifampin has been most effective in animal models.[8] Hence, a regimen of a carbapenem, vancomycin, and rifampin was administered to our patient, based on surrogate data from studies with *R equi*. Combinations of rifampin/erythromycin, rifampin/minocycline, minocycline/erythromycin, and imipenem/amikacin have been effective in vitro against *R equi*.[9] In our patient, oral minocycline and rifampin were chosen over a macrolide based regimen due to this patient's intolerance of macrolides. Aminoglycosides were avoided due to concern over renal dysfunction. Typically, oral therapy is given until signs and symptoms of disease have improved, such as in our patient.

The prognosis of *R equi* infection varies with immune status. Mortality is estimated at 11% in immunocompetent patients, as compared to 20–25% in non-HIV immunocompromised patients, and 50–55% in HIV-infected individuals.[2] A high index of suspicion, prompt identification, and aggressive treatment of the organism are essential to optimize outcomes.

Non-*equi Rhodococcus*, as in our patient, have previously been implicated as pathogens in humans, although less commonly than *R equi*.[10,11] Reported types of infection include meningoencephalitis, pneumonia, skin and soft

tissue infections, osteomyelitis, and corneal ulceration.[10,11] Our patient had severe cavitary pneumonia caused by a non-*equi Rhodococcus* species. We hypothesize that the wildfires may have led to aerosolization of soil-dwelling *Rhodococcus* with resultant inhalation by our patient. The incidence of *Rhodococcus* disease has been associated with increased airborne concentrations of *R equi* and with environmental conditions that promote aerosolization, such as low soil moisture, poor grass coverage, high ambient temperature, and dry windy weather.[12-14] Aerosolization of organisms from soil and windborne spread has also been implicated in the transmission of other pathogens to humans, including coccidioides, foot-and-mouth disease, and Q fever.[15-17]

Teaching Points

- *Rhodococcus* species have distinctive morphology and Gram-stain appearance that can be misinterpreted as normal flora. Clinicians should maintain a high index of suspicion for *Rhodococcus* and should alert laboratory personnel to the possibility of *Rhodococcus* infection if the typical phenotypic characteristics (eg, salmon-pink colonies) are seen in the laboratory.
- In our patient the *Rhodococcus* was likely missed, since it typically takes 4–7 days for the characteristic pigmentation to occur, and no further workup would have been done, but the organism was eventually identified on medium that was cultured for > 3 days.
- Although mostly commonly an opportunistic infection, *Rhodococcus* infection can occur in immunocompetent hosts.
- Lung involvement is often characterized by upper lobe cavitation or necrotizing pneumonia, and may be complicated by abscess, chest wall invasion, or empyema.
- Antimicrobial susceptibility testing can help guide antibiotic selection, and patients should generally be treated with 2 to 3 antibiotics.
- Although *R equi* is the most common human pathogen, non-*equi Rhodococcus* species are a potential cause of pulmonary disease in humans.

REFERENCES

1. Yamschchikov AV, Schuetz A, Lyon GM. *Rhodococcus equi* infection. Lancet Infect Dis 2010;10(5):350-359.
2. Kedlaya I, Ing M, Wong S. *Rhodococcus equi* infections in immunocompetent hosts: case report and review. Clin Infect Dis 2001; 32(3):e39-e47.
3. Verville TD, Huycke MM, Greenfield RA, Fine DP, Kuhls TL, Slater LN. *Rhodococcus equi* infections of humans. 12 cases and a review of the literature. Medicine (Baltimore) 1994;73(3): 119-132.
4. Lasky JA, Pulkingham N, Powers MA, Durack DT. *Rhodococcus equi* causing human pulmonary infection: review of 29 cases. South Med J 1991;84(10):1217-1220.
5. Guyssens V, Vandekerckhove L, Colle I, De Rudder P, Blots S, Vogelaers D. Invasive infection with *Rhodococcus equi*—two case reports and review of the literature. Acta Clin Belg 2010;65(4):271-275.
6. Jacks SS, Steeve G, Nguyen A. In vitro susceptibilities of *Rhodococcus equi* and other common equine pathogens to azithromycin, clarithromycin, and 20 other antimicrobials. Antimicrob Agents Chemother 2003;47(5):1742-1745.
7. Rolston KV, Frisbee-Hume S, LeBlanc B, Streeter H, Hsi Ho D. In vitro antimicrobial activity of moxifloxacin compared to the other quinolones against recent clinical bacterial isolates from hospitalized and community-based cancer patients. Diagn Microbiol Infect Dis 2003;47(2):441-449.
8. Nordmann P, Kerestedjian J, Ronco E. Therapy of *Rhodococcus equi* disseminated infections in nude mice. Antimicrob Agents Chemother 1992;36(6):1244-1248.
9. Nordmann P, Ronco E. In-vitro antimicrobial susceptibility of *Rhodococcus equi*. J Antimicrob Chemother 1992;29:383-393.
10. Gopaul D, Ellis C, Maki A Jr, Joseph MG. Isolation *of Rhodococcus rhodochrous* from a chronic corneal ulcer. Diagn Microbiol Infect Dis 1988;10(3):185-190.
11. Spark RP, McNeil MM, Brown JM, Lasker BA, Montano MA, Garfield MD. Rhodococcus species fatal infection in an immunocompetent host. Arch Pathol Lab Med 1993;117(5):515-20.
12. Muscatello G. *Rhodococcus equi* pneumonia in the foal—part 1: pathogenesis and epidemiology. Vet J 2012;192(1):20-26.
13. Muscatello G, Anderson GA, Gilkerson AJ, Browning GF. Associations between the ecology of virulent *Rhodococcus equi* and the epidemiology of *R. equi* pneumonia on Australian thoroughbred farms. Appl Environ Microbiol 2006;72(9):6152-6160.
14. Fujimori SK, Katsuzaki K, Tsubaki S. Ecology of *Rhodococcus equi* in horses and their environment on horse-breeding farms. Vet Microbiol 1987;14(3):233-239.
15. Kazar J. *Coxiella burnetii* infection. Ann NY Acad Sci 2005;1063: 105-114.
16. Williams PL, Sable DL, Mendez P, Smyth LT. Symptomatic coccicioidomycosis following a severe natural dust storm. An outbreak at the Naval Air Station, Lenmoore, Calif. Chest 1979; 76(5):566-570.
17. Gloster J, Champion HJ, Sørensen JH, Mikkelsen T, Ryall DB, Astrup P, et al. Airborne transmission of foot-and-mouth disease virus from Burnside Farm, Heddon-on-the-wall, Northumberland, during the 2001 epidemic in the United Kingdom. Vet Rec 2003; 152(17):525-533. Erratum in: Vet Rec 2003;152(20):628.