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Rhodococcus equi Related Bacteremia and Cavitary Lung Lesion in a Patient Receiving Renal Transplant: A Rare Case Report

Böbrek Nakil Alıcısı Olan Bir Hastada Rhodococcus equi İlişkili Bakteriyemi ve Kaviter Akciğer Lezyonu: Nadir Bir Olgu Sunumu

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Abstract

Rhodococcus equi is a rare cause of cavitary lung infection that is often mistaken for tuberculosis in immunosuppressed patients who are HIV positive and in organ transplant recipients. A 69-year-old male kidney transplant patient was admitted to an external healthcare center with complaints of weight loss, cough and hemoptysis that had started 6 months earlier. A computed tomography revealed a cavity in the upper segment of the left lung lower lobe, and a PET-CT revealed a high SUV-max uptake. Upon application to our hospital, the same symptoms were identified, along with R. *equi* growth observed in Bronchoalveolar Lavage and blood cultures. The patient was followed up with mechanical ventilator as intubated. *Acinetobacter baumannii* grew in the control ETA (endotracheal aspirate) culture on the 6th day of hospitalization, and he died subsequently on the 23rd day of hospitalization from colistin-induced nephrotoxicity. To the best of our knowledge this is the first case in which *R. equi* cavitary pneumonia has been seen together with *R. equi* bacteremia in our country.

Key words: *Rhodococcus equi, Immunocompromised host, Cavitary lung lesion.*

Öz

Rhodococcus equi is HIV pozitif ve organ nakil alıcısı olan immunsüpresif hastalarda özellikle tüberküloz ile sıklıkla karışan kaviter akciğer infeksiyonuna neden olan nadir bir etkendir. Altmış dokuz yaşında böbrek transplant alıcısı ve immünsüpresif tedavi alan erkek hasta 6 aydır devam eden kilo kaybı, öksürük ve hemoptizi semptomları olması üzerine dış merkeze başvurmuş. Çekilen bilgisayarlı tomografide sol akciğer alt lob üst segmentte kavite saptanmış. Malignite düşünülmesi üzerine PET-CT çekilmiş ve yüksek SUV-max tutulumu tespit edilmiş. Hasta hastanemize başvurduğunda mevcut şikayetleri devam etmekteydi. Alınan Bronkoalveolar Lavaj kültüründe ve kan kültürlerinde *R. equi* üremesi oldu. Hasta entübe edilerek mekanik ventilatör ile takip edildi. Kontrol ETA (endotrakeal aspirat) kültüründe *A. baumannii* üremesi oldu. Bunun üzerine tedaviye kolistin de eklendi. Hasta tedavisinin 23. gününde kolistine bağlı nefrotoksisite nedeniyle exitus oldu. Bildiğimiz kadarıyla bu olgu ülkemizde *R. equi* kaviter pnömonisinin *R. equi* bakteriyemisi ile birlikte görüldüğü ilk olgudur.

Anahtar Sözcükler: *Rhodococcus equi, Bağışıklığı baskılanmış konak, Kaviter akciğer lezyonu.*

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Rhodococcus equi is a facultative aerobic, non-motile, non-spore-forming, intracellular gram-positive, weak acid-resistant *coccobacillus* belonging to the nocardioform actinomycetes group (1), and is a rare zoonotic organism that affects predominantly the immunocompromised (2). *R. equi* can cause various infections in humans, primarily cavitary pneumonia, bacteremia, infective endocarditis and meningitis (1,3-5).

Here, we present a case of bacteremia and cavitary pneumonia due to *R. equi* in a 69-year-old male renal transplant recipient. *R. equi* is often difficult to identify, being similar to other bacterial pathogens such as diphtheroids, mycobacterium and nocardia species (6). The identification of *R. equi* is made with MALDI-TOF MS (Bruker Daltonics), being more reliable and accurate than Vitek MS (7). The aim with the present study is to increase awareness of *R. equi* among physicians as one of the rare causes of cavitary pneumonia in immunosuppressed patients, especially in transplant recipients.

CASE

A 69-year-old male patient who had undergone a kidney transplant 7 years earlier due to diabetic nephropathy, and who had been in contact with such animals as cattle, was admitted to an another hospital with complaints of weight loss, cough and hemoptysis that had started 6 months earlier. A computed tomography of the thorax revealed a cavitary lesion in the lower lobe superior segment of the left lung (Figure 1). BAL EZN (Ehrlich-Ziehl-Neelsen) staining was negative for AFB (acid fast basil). To investigate whether the cavitation was due to malignancy, a PET-CT (positron emission tomography-computed tomography) was performed, and in the cavity was intensely FDG avid (SUVmax 5.6), while no FDG uptake was present elsewhere. A transthoracic biopsy was then performed but was non-diagnostic, and the patient refused a repeat biopsy.

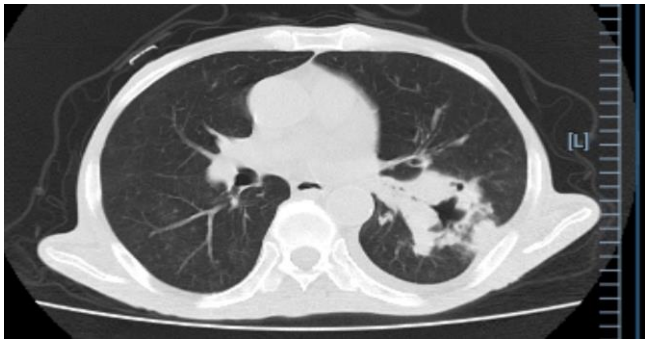

Figure 1: *Cavitary lesion in the lower lobe superior segment of the left lung*

The patient applied to our hospital in January 2021 with complaints of cough, shortness of breath, weight loss and anorexia. A physical examination revealed no abnormality in lung auscultation except tachypnea (22/min). Oxygen saturation at room air was 89%. The patient was using mycophenolate mofetil (500mg/day) and tacrolimus (0.5 mg/day). His past medical history included diabetes mellitus, while there was no previous history of tuberculosis. He had been smoking for 30 pack years. Laboratory parameters at the time of admission were: Glucose 343.9 mg/dL (74-106), Urea 84.1 mg/dl (17-43), Creatinine 1.41 mg/dl (0.67-1.17), CRP 20.52 mg/dl (0 -0.5), WBC count 5740 /mm^3 (3700-10100), Hb 8.8 g/dl (12.9-14.2), HCT 25.9% (37.7-53.7) and PLT 164.106/ml. (155.106-366.106).

The patient was admitted to the chest diseases intensive care unit to investigate the cause of the cavitary lung lesions. Tuberculosis infection was primarily investigated. A FOB (Fiberoptic bronchoscopy) was planned, during which purulent secretions were seen in the main bronchus of the left lung. BAL (Bronchoalveolar Lavage) was taken from the patient and sent to the tuberculosis and bacteriology laboratory for BAL culture, tuberculosis culture, gram and EZN staining. Partial acid-resistant *coccobacillus* was revealed by the EZN staining (Figure 2). The specimen was inoculated on 5% sheep blood agar, chocolate agar and MacConkey's agar plates incubated for 48 h at 37°C. Soft mucoid pink bacterial colonies were identified on the 5% sheep blood agar and the chocolate agar, but not on MacConkey's agar, and these were identified as *R. equi* based on a matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) Bruker Daltonics ® mass spectrometry (MS) with >2 score (Figure 3). In addition to the MALDI-TOF MS identification, traditional tests were also performed for verification purposes. Catalase, CAMP (Figure 4), and urease tests applied to the microorganism were positive, the oxidase test was negative and was found to be non-motile. The high success of the Matrix-Assisted Laser Desorption to Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) method in literature, together with the clinical and radiological appearance of the patient being compatible with the agent, and the biochemical properties of the agent was being compatible with *R. equi*. There was no need for identification via a molecular method. The mycobacterial culture was negative, and gram-positive coccobacillus was seen on the Gram stain (Figure 5). The antibiotic MIC values of the isolate were determined by E-test method (Table 1).

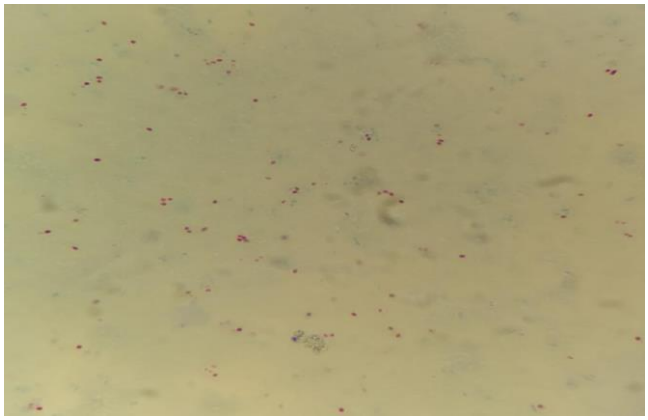

Figure 2: Partial acid-resistant coccobacillus in the EZN staining

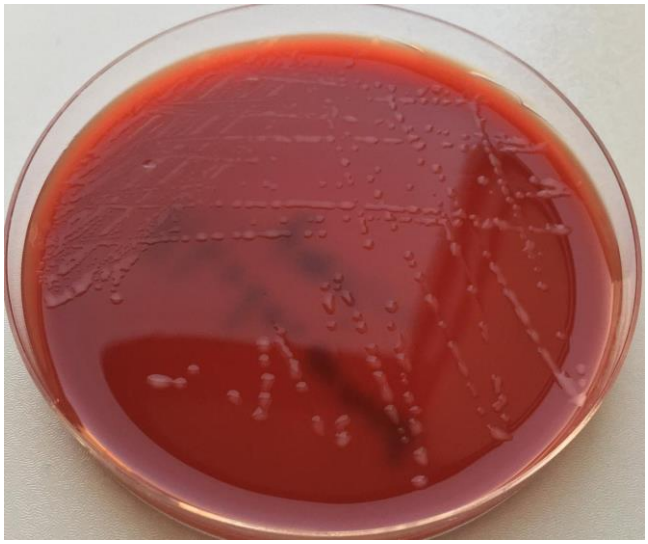

Figure 3: Soft mucoid pink bacterial colonies on 5_ sheep blood agar

The patient was treated with meropenem 500 mg IV (intravenous) (3 x 1) + vancomycin 1 g IV (2 x 1) and levofloxacin 500 mg IV (2 x 1) for cavitary pneumonia caused by *Rhodococcus equi*. For deep vein thrombosis prophylaxis, 40 mg enoxaparin was started. A computed tomography of the brain was made given that there may have been an association of *Rhodococus equi* with brain abscess, but the CT revealed no evidence of abscess in the brain. Subsequently, with the development of thrombocytopenia, heparin-induced thrombocytopenia (HIT) was considered, and enoxaparin prophylaxis was discontinued. HIT was excluded due to the persistence of thrombocytopenia, which was attributed to meropenem, and treatment with ampicillin-sulbactam was continued in place of meropenem. The Tacrolimus was stopped and treatment continued with mycophenolate mofetil due to the high tacrolimus blood level. Respiratory failure and confusion developed on the third day of antibiotic treatment. The patient was followed up with a mechanical ventilator as intubated. *Acinetobacter baumannii* grew in the control ETA (endotracheal aspirate) culture on the 6th day of the patient's hospitalization. Imipenem IV 4 x 500 mg + colistin IV 300 mg maximal tolerable dose and a 2 x 150 mg maintenance dose were added to the antibiotic treatment. The ampicillin-sulbactam treatment was discontinued. The patient had high inflammatory biomarkers and was followed up intubated. Acute renal damage developed due to colistin nephrotoxicity, and *Rhodococcus equi* also grew in the blood cultures of the patient in their septic condition. The patient died from septic shock on the 23rd day of hospitalization.

DISCUSSION

R. equi is a gram-positive, nonmotile, facultative intracellular, weak acid resistant, catalase, and urease positive, obligate aerobic microorganism. Its microscopic appearance can change from cocci to bacillus, depending on the stage of the growth cycle and growth conditions, and so can be considered a component of normal flora or as bacteria from *Diphtheroid Bacillus*, *Micrococcus* or *Bacillus* species and delay diagnosis. *Rhodococcus equi* can be confused with mycobacterium clinically (insidious beginning and chronic course) in terms of the lung region in which it is located (usually upper lobes), as well as CT findings, granuloma formation and acid-resistant properties (1,3,4,6). In the present case, the cavitary consolidation observed in the lower lobe superior segment of the lungs initially suggested tuberculosis granuloma, and so a BAL sample was collected from the patient and investigated for tuberculosis. Bacteria with the morphology of *coccoccobacilli* that were partially resistant to acid were detected in EZN staining, but upon further examination the agent growing in BAL was identified as *R. equi*. Nocardia, which can cause pulmonary infection in immunosuppressed humans opportunistically, can be clinically mistaken for *R. equi* pulmonary infection, and it is also a Gram-positive aerobic bacterium that stains acid-fast, and that can be mistaken microbiologically for *R. equi* (6,8). Failure to identify the pathogen and the insidious course of the clinic in human *R. equi* infections may delay diagnosis and treatment. *R. equi* easily grows on non-selective media and under aerobic conditions, and often forms mucoid, large and irregular colonies on the medium. The red-pigmented colonies that form become characteristic salmon-colored colonies after 48 hours of incubation (6). When we defined the pathogen isolated from this case based on traditional methods, it was identified as catalase and urease positive, nonmotile, CAMP-test positive and oxidase negative gram-positive *coccoccobacillus*. In previous studies, Matrix-Assisted Laser De-

sorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) has been found to be successful in defining *R. equi* at a species level, in which the 16S rRNA gene sequencing method was used as a reference method (7). The agent defined as *R. equi* in both BAL and blood culture with a > 2 scoring on the automated system was found to be compatible with *R. equi* when using conventional methods.

The patient's clinical and radiological findings were consistent with *R. equi* infection. The colony appearance on the medium was specific for *R. equi*, as were its biochemical properties, and MALDI-TOF MS was also successful in identifying *R. equi*. As such, there was no need to carry out a molecular identification of the pathogen. *Rhodococcus equi* is a bacterium found in water and soil that can infect animals and humans through respiration and nutrition. Bacteria can also enter the body through wounds or the mucosa and cause an infection, while no human-to-human transmission has been detected to date (9). In our case, the source of infection could not be determined precisely, although it was learned that the patient had been in contact with cattle for feeding. While it rarely infects humans, *R. equi* is the most common *Rhodococcus* species behind human infections (10). Only 10--15% of the patients in whom *R. equi* is detected as a pathogen is immunocompetent, while immunosuppressive patients are frequently infected. The majority of patients identified with an *R. equi* infection were found to be HIV-positive. *R. equi* has been identified in more than 100 cases of infection to date, and most (approximately 50%) were localized infections. Respiratory infections account for 80% of all cases. Lung infections (mostly necrotizing pneumonia) have been detected in 84% of immunosuppressed patients and 42% of immunocompetent patients. Chronic cavitary pneumonia infection caused by *R. equi* often results in relapse, despite long-term antibiotic treatment, and the mortality rate is high. *R. equi* infections result in death in 50% of HIV-infected patients, 20–25% of patients with immunosuppressive diseases due to non-HIV causes, and approximately 11% of immunocompromised patients (8,9,11-14). *R. equi* is a facultative intracellular pathogen that has the ability to survive and destroy human macrophages, which is the basis of the pathogenesis of the infection and its resistance to antibiotics. It is also thought to be effective in the development of severe and/or recurrent infections (15,16). Extrapulmonary spread is generally thought to occur as a late manifestation of pulmonary infection, occurring through the bloodstream, and extrapulmonary relapse is usually seen in the central nervous system in the form of brain abscess or meningitis. It can also cause extrapulmonary infections such as wound infections, subcutaneous abscesses, pericarditis, osteomyelitis, cervical adenopathy, endophthalmitis, lymphangitis and mastoiditis (17). The medical history of the presented case included a diagnosis of diabetes mellitus, being a disease that suppresses the immune system, and the use of immunosuppressive drugs following a kidney transplantation. The patient had both cavitary pneumonia and extrapulmonary bacteremia. The microorganism is phagocytosed by alveolar macrophages, and macrophages continue to grow in it, leading to a granulomatous inflammatory reaction and the subsequent development of necrosis. Pneumonia can start without symptoms and may be overlooked, especially in immunosuppressed patients. Often, symptoms such as weight loss, cachexia, pleuritic chest and pain accompanied by fatigue, fever and cough are observed (9). *R. equi* can also be isolated in blood cultures due to the bacteremia in pulmonary infections. Bacteremia has been observed at a rate of 10% in immunocompetent patients and 25% in HIV-infected solid organ transplant recipients (15,17).

Figure 4: *CAMP test of the microorganism*

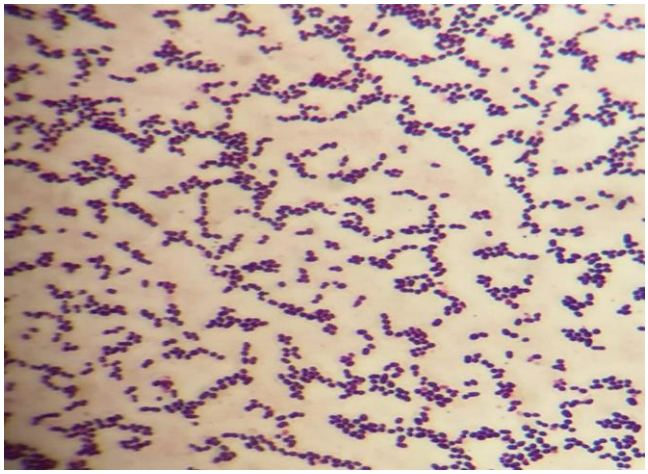

Figure 5: Gram-positive coccobacillus on the Gram stain

Table 1: Antibiotic mic values of the isolate

ANTIBIOTIC	MIC(mg/L)
Cefotaxim	0,094
Ceftriaxon	0,25
Cefoxitin	8
Imipenem	0,047
Meropenem	0,125
Doripenem	0,064
Daptomycin	>256
Tigecyclin	0,25
Vancomycin	0,19
Linezolid	2

In the presented case, the patient had experienced shortness of breath, cough and severe weight loss within the last year, consistent with previous studies. He had developed cavitation in the lung, and the radiological appearance was compatible with pneumonia. The agent that was first isolated from the respiratory tract showed systemic spread a few days later, and was isolated from both right and left peripheral blood cultures.

Menon et al. (18) identified 40 cases of *R. equi* in organ transplant patients prior to 2012, the majority of which were male (82.5%) and kidney transplant recipients (58.5%). It has been determined that infections can develops over a period ranging from 3 months to 19 years after transplantation. In the presented case, *R. equi* cavitary pneumonia and bacteremia developed in a kidney transplant recipient 7 years after transplantation, consistent with literature.

The most appropriate protocol and duration of treatment for *R. equi* infections have yet to be determined, and it is currently recommended that each patient be evaluated individually. The duration of treatment should be determined according to the infection site, immunity and clinical response (14).

Azap et al. (19) published a similar article in our country, but bacteremia was also present in our case. As such, this is the first case of *R. equi* cavitary pneumonia together with *R. equi* bacteremia to be reported on in our country.

Based on both in vitro studies and clinical experience, it has been suggested that two or three drugs, including imipenem, vancomycin, ciprofloxacin, aminoglycoside, rifampin and/or erythromycin, can be administered intravenously in combination, with vancomycin in particular, can be recommended in combination (20,14).

In the presented case, since the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set no limit value as a reference for the *R. equi* antibiotic susceptibility test, the MIC values of the antibiotics were determined using the E-test method. The treatment was subsequently planned as meropenem 500 mg IV (3x1) + vancomycin 1 g IV (2x1) + levofloxacin 500 mg IV (2x1), in accordance with the findings of previous studies. The response of *R. equi* to treatment could not be fully evaluated. While the patient's treatment was continuing, colistin was added to the protocol with the development of pneumonia due to *A. baumannii*, and the patient died of renal toxicity, being a side effect of colistin. In conclusion, the *R. equi* pathogen should be considered in cases of cavitary pneumonia, especially in immunosuppressed patients with a history of solid organ transplantation. Rare bacteria can be identified using automated systems in routine laboratory services, allowing infectious diseases to be diagnosed early, and facilitating the immediate start of treatment.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - F.K., H.K., H.S.Ş., S.Y., N.U.; Planning and Design - F.K., H.K., H.S.Ş., S.Y., N.U.; Supervision - F.K., H.K., H.S.Ş., S.Y., N.U.; Funding - F.K.; Materials - F.K., H.K., N.U.; Data Collection and/or Processing - F.K., H.K., N.U.; Analysis and/or Interpretation - F.K., H.K., S.Y.; Literature Review - F.K., H.K.; Writing - F.K., H.K.; Critical Review - H.S.Ş., S.Y.

YAZAR KATKILARI

Fikir - F.K., H.K., H.S.Ş., S.Y., N.U.; Tasarım ve Dizayn - F.K., H.K., H.S.Ş., S.Y., N.U.; Denetleme - F.K., H.K.,

H.S.Ş., S.Y., N.U.; Kaynaklar - F.K.; Malzemeler - F.K., H.K., N.U.; Veri Toplama ve/veya İşleme - F.K., H.K., N.U.; Analiz ve/veya Yorum - F.K., H.K., S.Y.; Literatür Taraması - F.K., H.K.; Yazıyı Yazan - F.K., H.K.; Eleştirel İnceleme - H.S.Ş., S.Y.

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