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Pulmonary *Rhodococcus equi* infection in a renal transplant patient: case report with review of literature

Pneumonija uzrokovana Rhodococcus equi *bakterijom u bolesnika s bubrežnim presatkom: Prikaz slučaja uz pregled literature*

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Summary

Aim: *Rhodococcus equi* (*R. equi*) is an opportunistic, Gram-positive coccobacillus, largely unknown and whose infections are often misdiagnosed in transplant patients. The aim of this article is to acquaint the medical public with *R. equi* infections in order to include them in the differential diagnosis of pneumonia in transplanted and immunocompromised patients.

Case report: We report a case of a renal transplant patient with a productive cough. Chest X-ray showed pulmonary infiltrate. Three months into the disease *R. equi* was identified in the sputum. Treatment with vancomycin, azithromycin and levofloxacin rendered the improvement in a few months. To the authors' knowledge, this is the first case of *R. equi* infection in a renal transplant patient in Croatia.

Conclusion: Since the clinical presentation and diagnostic results can be unspecific and misleading, *R. equi* infections are often misdiagnosed and might be more frequent than usually thought. There is a need for establishing treatment guidelines, as inconsistent antimicrobial combinations of various duration were reported in literature

Key words: *Rhodococcus equi,* pneumonia, kidney transplantation, immunosuppression, opportunistic infections

Sažetak

Cilj: *Rhodococcus equi (R. equi)* je oportunistički, gram-pozitivni kokobacil, uglavnom nepoznat u medicinskoj javnosti i infekcije uzrokovane ovim uzročnikom često su pogrešno dijagnosticirane u transplantiranih bolesnika. Cilj ovoga članka je upoznati medicinsku javnost s *R. equi* infekcijama, kako bi se one uvrstile u diferencijalnu dijagnozu pneumonija u transplantiranih i imunokompromitiranih bolesnika.

Prikaz slučaja: Izvješćujemo o slučaju bolesnice s presađenim bubregom kojoj se bolest u početku očitovala produktivnim kašljem. Na radiološkoj snimci pluća nađen je plućni infiltrat. Tri mjeseca nakon početka bolesti, *R. equi* identificiran je u iskašljaju. Liječenje vankomicinom, azitromicinom i levofloksacinom dovelo je do poboljšanja u nekoliko mjeseci. Prema znanju autora, ovo je prvi slučaj infekcije *R. equi* u bolesnika s transplantiranim bubregom u Hrvatskoj.

Zaključak: Budući da klinička slika i rezultati dijagnostičkih pretraga mogu biti nespecifični i navoditi na pogrešan trag, infekcije *R. equi* često su pogrešno dijagnosticirane i mogle bi biti češće nego što se do sada mislilo. Potrebno je uspostaviti smjernice za liječenje ove bolesti, jer su u literaturi zabilježene različite antimikrobne kombinacije raznolikog trajanja.

Ključne riječi: *Rhodococcus equi,* pneumonija, bubrežna presadba, imunosupresija, oportunističke infekcije

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Introduction

Rhodococcus equi (*R. equi*) is an opportunistic, Gram-positive, weakly acid-fast coccobacillus that primarily causes infection in HIV (Human Immunodeficiency Virus)-positive individuals.[1]

R. equi is commonly present in soil across all continents except Antarctica and it predominantly causes infections in domestic animals. *R. equi* is present in herbivore feces, in particular in horse feces, as well as in contaminated soil. Furthermore, it can also be found in equine farms, around horse breeding areas.[2-4] The most common routes of transmission of *R. equi* to humans are contact with contaminated manure of foals through inhalation or wound inoculation.[5-7] As previously described, cats and dogs infected with R. equi might also represent a source of infection for immunocompromised humans.[8]

The first human *R. equi* infection was reported in 1967, with an increasing incidence in the past few decades, coincident with more prevalent HIV related acquired immunodeficiency, immunosuppressive (IS) medications after organ transplantation (TX) and chemotherapy for malignancies. Still, 10 – 15% of the infections occur in immunocompetent hosts. Currently, more than a hundred cases have been documented, the majority in the HIV-infected. Around 10% of *R. equi* infections occur in transplant recipients, although unique data are difficult to obtain since no meta-analyses have been performed on this matter.[2-4] Due to the rarity of the infection in transplant patients, it often leads to confusion and misdiagnosis.[6,13,14]

Although several cases of *R. equi* infections have been reported in renal transplant patients, it is still largely unknown and often misdiagnosed in that population. We report a case of a renal transplant patient that presented with productive cough and an overall poor feeling. To the authors' knowledge, this is the first case of *R. equi* infection in a transplant patient in Croatia.

Case Report

A 55-year-old Caucasian woman was admitted to the Department of Nephrology with productive cough (white, yellow and brown sputum), malaise and anorexia. She was previously empirically treated with amoxicillin with clavulonic acid and moxifloxacin by her family physician. The patient underwent cadaveric kidney TX for end stage renal disease caused by chronic interstitial nephritis 18 months prior to the hospitalization. Her IS regimen consisted of tacrolimus 5 mg, mycophenolate mofetil 2 × 1 g and prednison 5 mg. She lived in a rural area and reported contacts with horses.

Upon admission she was eupnoic, normotensive, afebrile, pale and cushingoid with no peripheral lymphadenopathy. Bronchial breathing with left basal crackles was present. Leucocytosis 10.4×10^9/L, anemia - RBC 3.23×10^{12}/L, C- reactive protein 92.2 mg/L and creatininemia 130 μmol/L were found.

The chest X- ray showed an inhomogeneous opacity in the posterior middle zone of the right lung with an obscured right costophrenic angle. During the hospitalization, three additional chest radiographs were performed. The X-ray taken two weeks after admission showed a round opaque area with an inhomogeneous center in the middle zone of the right lung. Three weeks upon admission, a ring like opacity was found in the same location, suggesting a singular cavitation with a thickened wall and homogenous parenchymal inflammatory infiltrate. Considering possible malignancies, tumor markers (CA19-9, CA 15-3, CEA, CYFRA and NSE) were measured and were within normal ranges. By bronchoscopy, an area with anthracotic pigmentation in the posterior basal segment of the left lung was found and the analysis of the aspirate found no malignant cells, *Mycobacterium Tuberculosis (M. tuberculosis)*, or fungi. The aspirate was negative for common bacteria, as well. Quanti-FERON test for *M. tuberculosis* was also negative.

The sputum was tested for acid-fast bacilli (AFB) five times, but no AFB were found. On one occasion, a microbiological analysis of the sputum showed *Klebsiella pneumoniae* ESBL (extended spectrum beta-lactamases) and *Candida albicans*. The patient received fluconazole and a five-day ertapenem. Itraconasole was added to the regimen afterwards. Quantitative PCR (proteinase chain reaction) was performed on a blood sample, 2720 copies/mL of CMV DNA (cytomegalovirus deoxyribonucleic acid) were detected and valgancyclovir was administered for a duration of three months. The treatment did not yield radiographic or symptomatic regression. The patient was febrile with a non-productive cough. A control chest X-ray showed a change in the right middle zone, which now appeared as a solid soft tissue opacity 3.5 cm in diameter, unshapely limited from the surrounding parenchyma, which could suggest a solid tumor or an inflammatory infiltrate. Empirical antibiotic regimen including meropenem, fluconazole, and after the third day, cefepime was then applied. By that time, her IS therapy was reduced in dose to tacrolimus 4 mg, myco-phenolate mofetil 2 × 500 mg and prednison 5 mg.

One month and two weeks upon admission, the patient underwent thoracic computorized tomography (CT) (Figure 1).

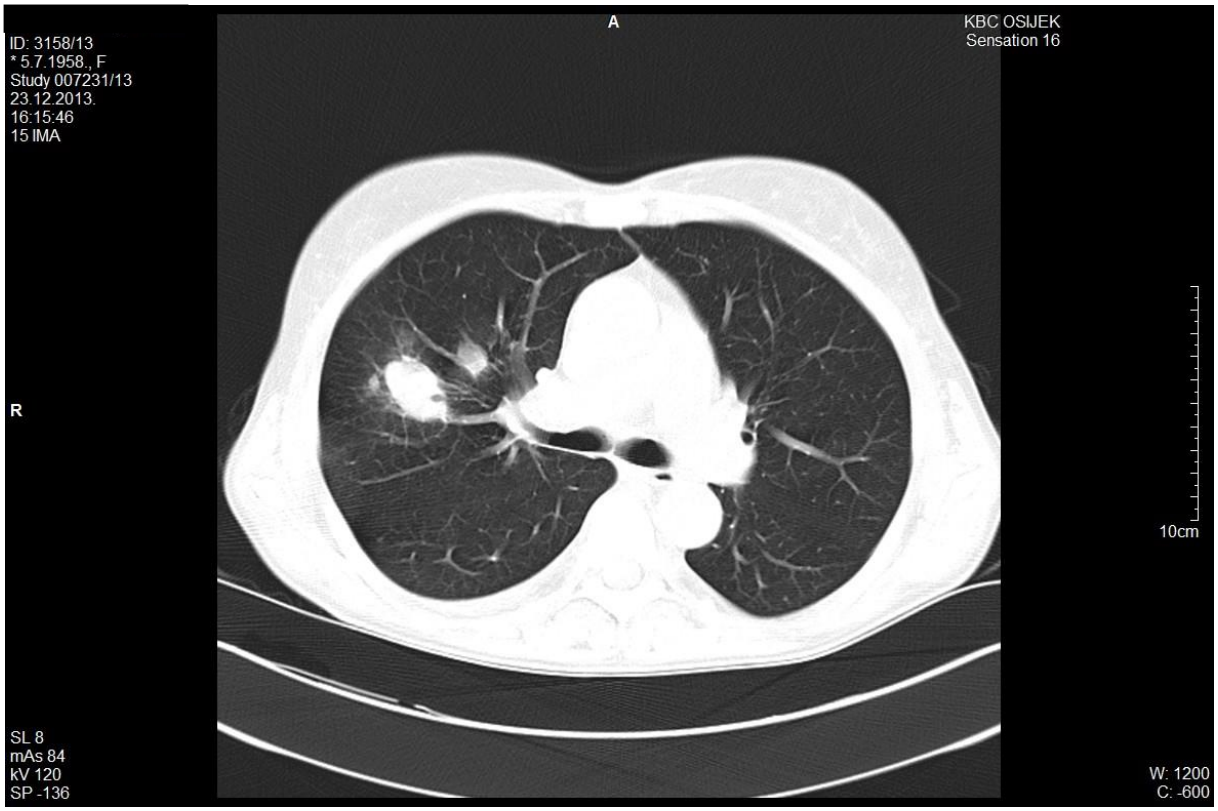

Figure 1 CT image of the patient's thorax with a solid soft tissue opacity in the right middle zone of the lungs

Slika 1. CT slika toraksa pacijenta s čvrstom neprozirnošću mekog tkiva u desnoj srednjoj zoni pluća

CT was performed only then and not earlier, supposedly due to many various doctors and departments that she had changed during the course of the illness and, obviously, everyone had started the diagnostics and empirical therapy from the beginning. The culture of the CT-guided aspirate was sterile while cytology showed inflammation. Two months upon admission, a new empirical therapeutic strategy was established, consisting of ceftriaxone, trimethoprim/ sulfamethoxazole and meropenem. Different antimicrobials were empirically included to cover common bacterial pneumonia, other opportunistic interstitial pneumonia and tuberculosis. Pulmologists administered an *ex iuvantibus* antituberculotic treatment with isoniazid, ethambutol, pyrazinamide and rifampicin. Vancomycin, ciprofloxacin and azithromycin followed. A sputum sample collected three months upon admission showed cultures that grew after the seventh day. The incubation process was prolonged to enable the growth of slower-growing cultures. Gram positive cocci and coccobacilli were found. Tests for *Staphylococcus, Corynebacterium* and atypical mycobacteria were negative. Automated identification system VITEK® 2 (bioMérieux, Inc., Durham, NC, USA) suggested *Rodococcus equi* or *Kocuria kristinae*. *Rhodococcus* was identified with MALDI-TOF Mass Spectrometry. The strain was susceptible to macrolides, vancomycin, linezolid, meropenem and ciprofloxacin. The patient was discharged from the hospital two weeks after the diagnosis, three and a half months after the initial admission.

The established therapeutic regimen consisted of one-week intravenous vancomycin 2 × 500 mg daily, with 2 months peroral azithromycin 2 × 500 mg daily. After the two-month period, azithromycin was reduced to 1 × 250 mg daily and the therapy continued for additional 10 months. For the first 6 months of the peroral treatment with levofloxacin 500 mg once daily was also administered. Levofloxacin was administered due to our empirical clinical assessment, since both levofloxacin and ciprofloxacin were found to be effective against *R. equi*. The whole regimen ended 1 year after the beginning of the therapy. One month after the initiation of the therapy, a spirometry found a low stage restrictive lung disorder. The patient reported feeling much better 6 weeks after the administration of the therapy. By that time, her appetite improved and her cough was less frequent but still productive. A radiographic regression was seen 4

months after the start of the therapy. One year after the start of the therapy, the patient was feeling well. Her chest X-ray showed no pathological changes. During the whole episode, the graft function was sufficient and unchanged with the reduced IS therapy. The findings implied that she was free of the disease and that the administered antibiotic regimen with vancomycin, azithromycin and levofloxacin had successfully cured the *R. equi* pneumonia in the renal transplant patient.

Discussion

In this case, the report we presented is the first case of *R. equi* infection in a transplant patient in Croatia. The increasing rate of kidney TX warrants a serious consideration of rare infections within the differential diagnosis of morbidity in this population.

Our patient was exposed to horses in her neighborhood. *R. equi* is found in the soil of 50 – 95% of farms, and only one-third of infected patients had a history of exposure to horses or pigs.[6] The infection is commonly acquired by soil inhalation, inoculation into a wound or mucous membrane, ingestion, direct animal contact, but also *via* nasal colonization and interhuman contact.[6,14]

The mortality rate among immunocompetent patients is around 11%, 50 – 55% among the HIV-infected and 20 – 25% among non–HIV-infected immunocompromised patients.[6,15]

R. equi infections present as pulmonary in 80%, as was the case with our patient.[6,13-17] The patient presented with malaise and productive cough, with sputum colored from white, yellow to brown. Other possible symptoms include dyspnea, nonproductive cough, pleuritic chest pain, fever, chills, weight loss, anorexia and hemoptysis. The infection can be subtle and misleading for days to months, and is often chronic and recurrent. The usual histopathological finding is necrotizing granulomatous pneumonia with inflammatory pseudotumors, intracellular Gram-positive coccobacilli, and granulomatous and fibrinous pleuritis. The infection in our patient was complicated by cavities, as seen by radiologic imaging. Cavitations occur in 54 – 69% of cases 2 – 4 weeks after the initial infection. Complications may also include pleural effusion, empyema, and invasion into the chest wall. Relapses may occur at extrapulmonary sites such as the brain or subcutis.[1,13,15,17,18]

Other possible manifestations include gastro-intestinal infections, pericarditis, meningitis, mastoiditis, abscesses in the liver, brain, kidney, psoas muscles, and cutaneous wounds, with other presenting symptoms such as lymphadenopathy, eye drainage and pain, altered consciousness, and joint pain.[9,15,19]

R. equi is a Gram-positive coccobacillus that belongs to nocardiform actinomycetes. This group includes, among others, the genera *Mycobacterium*, *Nocardia* and *Corynebacterium*, with which it is often confused.[12,14,15,20]

The best diagnostic method is isolation of bacteria in cultures from the infection site - mostly sputum or blood, our specimen was identified from the sputum sample.[13,20]

It can be easily cultivated when incubated aerobically at 37°C in the majority of nonselective culture media. It forms irregular, smooth, semi-transparent mucoid colonies that turn salmon-pink after 4 - 7 days of incubation.[1,6,12,17,20]

Recent research has shown that human *R. equi* infections are not as infrequent as it is usually thought.[20] The illusion of rarity lies in the misdiagnosis of *R. equi* infections. Differential diagnosis of pulmonary *R. equi* infections includes cavitating malignancy and cavitating infections (such as tuberculosis, aspergilloma, nocardiosis, pulmonary abscess and *Pneumocystis jiroveci* pneumonia). That was the reason for performing numerous diagnostic tests, including tumor markers, CT, sputum and bronchial aspirate cytology, multiple microbiological cultures, microscopic examinations and QuantiFERON tests, before setting the right diagnosis. The reason one often must repeat microbiological tests is the small concentration of *R. equi* in the sputum samples, which, in turn, leads to a failure to successfully grow microbiological cultures.

Our patient's radiographic images showed opacity in the right middle zone that changed through time. The most common radiological presentation of pulmonary *R. equi* infection is consolidation with cavitation, with or without air-fluid levels, most commonly affecting the upper lobes. Attention is needed, since the finding may suggest other diseases, the majority of them much more common than *R. equi* infection. CT is better for revealing key features of diagnostic relevance, such as cavitary lesions, centrilobular nodules, ground glass opacities, areas of bronchiolar obstruction, minor pleural effusion and mediastinal lymph node enlargement that might not be seen on chest radiograph.[19,21] Since a CT guided aspiration can also be performed, this method can be very important, as the bronchial aspirate is a much better sample for both microbiological and cytological analysis. Due to its relative rarity in causing infections in humans, the treatment for *R. equi* infections has not been standardized.[1,13]

A prolonged regimen with vancomycin, azithromycin and levofloxacin was elected for our patient.

Empiric therapy of *R. equi* infection includes erythromycin, rifampicin, and/or ciprofloxacin which should be adjusted once the results of susceptibility tests are available.[6]

For immunocompromised and patients with serious infections, a minimum of 6 months of combined 2- or 3-drug therapy that includes vancomycin, imipenem, aminoglycosides, ciprofloxacin, rifampin, and/or erythromycin is appropriate. Transplant recipients who receive calcineurin inhibitors should not be given rifampicin or clarithromycin as the first-line treatment, because of the potential drug interactions.[13]

Due to the possible side-effects and an increasing resistance to erythromycin, it is advised to consider newer and safer macrolides, such as azithromycin and clarithromycin. These drugs have shown to be more effective than erythromycin in pneumonia caused by *R. equi* and azithromycin monotherapy was nearly as effective as a combination with rifampicin.[18] Since *R. equi* is present intracellularly in alveolar macrophages and neutrophils, it is essential for anti-rhodococcal activity that the antibiotic reaches high intracellular concentration. Therapy must be given intravenously for at least two weeks, followed by prolonged oral treatment.[1,9,17] Our patient's strain was susceptible to macrolides, vancomycin, linezolid, meropenem and ciprofloxacin. It is usually susceptible to macrolides, rifampicin, fluoroquinolones, aminoglycosides, glycolpeptides, meropenem, and imipenem. Susceptibility to cotrimoxazole, tetracycline, chloramphenicol, clindamycin, and cephalosporins is variable, and *R. equi* is typically resistant to penicillins and cefazolin.[6,19]

Drainage of abscesses should be performed when possible; but resection surgery should be limited to selected patients who do not respond to drugs. In our patient, a CT aspiration had been performed, primarily for diagnostic purposes.[12]

Conclusion

R. equi is an opportunistic microorganism, usually causing pulmonary infections in immunocompromised patients. Since the clinical presentation and diagnostic results can be unspecific and misleading, *R. equi* infections are often misdiagnosed and might be more frequent than usually thought. This case deserves attention as it reminds us of a rare but important etiology of pulmonary infiltrate in immunocompromised patients. Common empirical antimicrobials do not provide efficient treatment for the infection. There is a need for establishing treatment guidelines, as inconsistent antimicrobial combinations of various duration were reported in literature. Detailed epidemiological history, including contact with animals, seems not to be forgotten.

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