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Case Report

Primary retroperitoneal abscesses due to *Rhodococcus equi* in a patient with severe nephrotic syndrome: successful antibiotic treatment with linezolid and tigecycline

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ABSTRACT

We present a case of *Rhodococcus equi* primary retroperitoneal abscesses without pulmonary involvement in an immunocompromised patient with severe nephrotic syndrome. No risk factors for exposure to *R. equi* were present. The infection was successfully treated with long-term combination antibiotic treatment including linezolid and tigecycline.

1. Introduction

Rhodococcus equi is a facultative, intracellular, Gram-positive coccobacillus which primarily causes pyogranulomatous bronchopneumonia in foals.[1] Over the last few years, *R. equi* has emerged as a human opportunistic pathogen in immunocompromised patients, especially those with AIDS.[2–4] With the introduction of potent antiretroviral therapy, cases related to HIV immunodeficiency have decreased. However *R. equi* infections are increasingly reported in transplant recipients and in patients receiving immunosuppressive and/or prolonged corticosteroid treatment.[5–7]

The first site of infection is commonly the lung, and it results in a necrotizing pneumonia (80% of cases), which clinically resembles mycobacterial, fungal or nocardial pulmonary infections.[2] Primary extrapulmonary manifestations are unusual and mainly secondary to hematogenous dissemination from a silent lung infection. We describe herein a case of *R. equi* primary retroperitoneal abscesses with no evidence of either pulmonary involvement or hematogenous dissemination, in an immunocompromised patient with severe nephrotic syndrome. The infection was successfully treated with long-term combination antibiotic treatment including linezolid and tigecycline.

2. Case report

A 44-year-old man with nephrotic syndrome and focal-segmental glomerulosclerosis treated with brief cycles of cyclosporine and long-term dexamethasone for 6 years, presented with a 2-week history of severe lumbar pain involving the left leg. On admission, he was afebrile and was unable to walk or maintain a standing position. He underwent magnetic resonance imaging (MRI), which showed a voluminous fluid mass (18 × 8 cm) in the left psoas muscle. A chest X-ray was normal and a total body computed tomography (CT) scan revealed no disease localization in lung or other extrapulmonary sites. Laboratory tests showed leukocytosis (white blood cell count 27.3 × 10^9 cells/l, 98% of neutrophils), high inflammatory index (C-reactive protein (CRP) 25.7 mg/dl), serum creatinine of 1.6 mg/dl, proteinuria (22.5 g/24 h), decreased creatinine clearance (59.3 ml/min), and serum albumin of 1.6 g/dl. A surgical drainage of the abscess was done and bacterioscopic examination showed partially acid-fast coccobacilli consistent with

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Rhodococcus spp. Empiric combined therapy with rifampin, imipenem and tetracycline was started. Serology for HIV infection was negative, however lymphopenia ($<0.5 \times 10^9$ cells/l) associated with low levels of both CD4+ T-cells ($<0.2 \times 10^9$ cells/l) and low total circulating IgG (204 mg/dl) was found. After a week of treatment, a control MRI showed a new voluminous fluid mass (10×8 cm) in the medial region of the right thigh and another involving the homolateral gastrocnemius muscle. Two new drainage catheters were placed. After 48 h the drainage fluid culture grew *Rhodococcus spp*, identified by Gram stain reaction, microscopic and colony morphology, growth characteristics, and a synergistic hemolysis test using *Corynebacterium pseudotuberculosis*.[8] The biochemical profile of the isolate was defined using the API Coryne System (BioMerieux, Marcy l'Etoile, France) confirming the strain identification as *R. equi*. Antibiotic susceptibility testing was performed through broth microdilution, E-test strips, and disk diffusion, as previously reported.[9,10] No risk factors for environmental exposure to *R. equi* were identified.

The *R. equi* strain was resistant to erythromycin (minimum inhibitory concentration (MIC) >6 μg/ml), rifampin (MIC >128 μg/ml), and tetracycline (MIC >16 μg/ml). Antibiotic therapy was changed to intravenous levofloxacin (MIC = 0.25 μg/ml), vancomycin (MIC = 4 μg/ml), and imipenem (MIC < 1 μg/ml), with dose adjustment for creatinine clearance. Laboratory tests showed persistence of neutrophil leukocytosis, lymphopenia, and a severe circulating IgG deficit. After 4 weeks of treatment there was no significant reduction of the abscesses. The inflammation index decreased (CRP 2.5 mg/dl), but renal function was worsening. In order to improve treatment efficacy and reduce the nephrotoxicity risk of antimicrobial therapy, we tested the susceptibility of the isolated *R. equi* to linezolid (MIC = 1 μg/ml)[9] and tigecycline (23 mm inhibition diameter using agar disk diffusion method corresponding to a MIC of <2 μg/ml).[11] Considering the lack of nephrotoxicity of these two antibiotics and their in vitro activity, treatment was then switched to intravenous linezolid and tigecycline. A marked reduction of fluid mass was seen without any impairment of kidney function. Two weeks later, the patient was discharged with oral linezolid. Under this treatment his clinical condition improved, neutrophil leukocytosis decreased, and a drainage catheter was removed. After one month, the patient was again hospitalized because of the onset of generalized seizures; a brain MRI revealed lesions compatible with cerebritis. A new culture of drainage fluid from a retroperitoneal site grew *Serratia marcescens*, but *R. equi* was not isolated. Antibiotic therapy was changed to intravenous linezolid and meropenem, which were administered for a total of 12 weeks. The clinical and laboratory parameters improved. All microbiological cultures from blood and drainage catheters were sterile. A brain MRI showed disappearance of the cerebritic lesions. A control CT scan revealed that all abscesses had almost disappeared, and the remaining drainage catheters were removed (Figure 1). The patient did not at any time suspend the steroid treatment for his nephrotic syndrome. In order to prevent a relapse of the *R. equi* infection, secondary antibiotic prophylaxis with moxifloxacin (MIC <0.25 μg/ml) was administered for 4 months; this was interrupted when the patient stopped steroid treatment and underwent hemodialysis because of the worsening of his renal disease. After 6 months of regular hemodialysis the immunologic condition had improved and a control CT scan showed no relapse of infection.

3. Discussion

R. equi has become increasingly recognized as a cause of severe infections in immunocompromised patients without HIV disease.[5–7] The infection mortality rate is still high (20–25%)[12] and disease relapses are common.[13] A wide range of clinical manifestations have been reported, although pneumonia is present in about 80% of *R. equi* infections.[2] Our case represents a primary extrapulmonary manifestation of *R. equi* infection presenting as retroperitoneal abscesses, with no evidence of pulmonary involvement or hematogenous dissemination. It is interesting to note that there were no environmental exposures that may have predisposed this patient to acquiring *R. equi*. Bacterial virulence factors and host immunity play an important role in the pathogenesis of *R. equi* infections. The presence of the well-known virulence-associated antigens was not found to be essential for the development of *R. equi* infection in humans.[14] On the other hand, both cellular and humoral immunity play a crucial role in the host response against *R. equi*.[15,16] In the present patient, the main

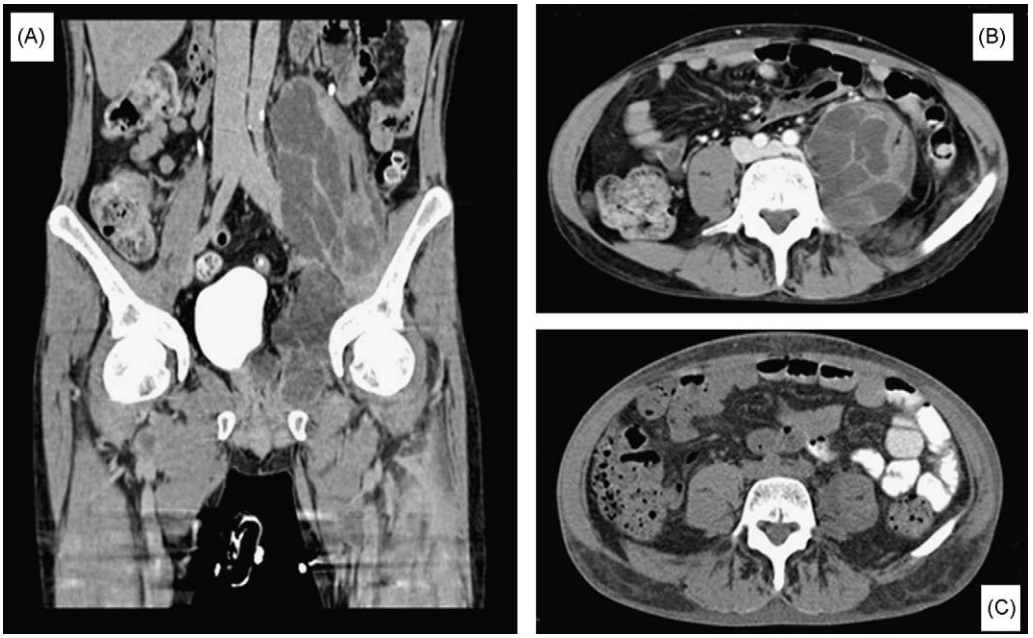

Figure 1. Computed tomography scan of *Rhodococcus equi* retroperitoneal psoas abscess: A and B: pre-therapy scan showing fluid mass (18×10 cm) in the left psoas major muscle; C: control scan showing complete resolution after successful treatment.

predisposing factor was the severe immunocompromise due to nephrotic syndrome treated with prolonged steroid therapy. He had an immunoglobulin deficit due to persistent proteinuria (22–30 g/24 h) and also a severe lymphopenia, which might have contributed to the development of the disease.

Surgical drainage and antibiotic therapy are the gold standard for the management of retroperitoneal abscesses. There is no standardized antibiotic treatment for *R. equi* infection. *R. equi* is usually susceptible in vitro to macrolides, rifampin, aminoglycosides, fluoroquinolones, glycopeptides, and carbapenems; susceptibility to co-trimoxazole, tetracycline, clindamycin, chloramphenicol, and cephalosporins is variable.[2] It is suggested that more serious infections should initially be treated intravenously using a combination of two or three drugs, such as vancomycin, imipenem, rifampin, quinolones, and macrolides.[2,12,17] A long-term maintenance treatment with antibiotics having good intracellular penetration (i.e., macrolides plus rifampin or quinolones) is required in order to fully eradicate the infection and prevent disease relapses. A secondary prophylaxis with a single agent that has in vitro activity should be strongly considered for patients with ongoing immunosuppression.[2]

Antibiotic susceptibility testing was performed in our case through broth microdilution, E-test strips and disk diffusion: all methods were comparable, with good reproducibility. The E-test is a simple method, which does not require special equipment, allowing the measurement of MIC values. Moreover the interpretation of MIC categories by E-test method highly correlates with those of either microdilution or disk-diffusion when testing coryneform bacteria.[18] Antimicrobial susceptibility testing of *R. equi* remains problematic because the criteria for defining the susceptibility breakpoints of the different antibiotics are still controversial. Our data in the present study are based on the standards reported by other authors in the literature.[9,10,19] The *R. equi* strain of our patient was resistant to macrolides, rifampin, and tetracycline, but susceptible to quinolones, vancomycin, and carbapenems. Although this sensitivity pattern is unusual, it was seen in a case series of invasive *R. equi* infections showing emergence of multidrug-resistant strains.[20] The resistance pattern of our strain, which involved three antibiotic classes with intracellular activity, should be taken into account in the selection of a therapeutic regimen for rhodococcal infections. After a 4-week treatment with imipenem, levofloxacin, and vancomycin we did not observe significant clinical improvement. All the antibiotics used had a high renal excretion and required dose adjustment, possibly resulting in sub-therapeutic plasma concentrations. The antibiotic plasma protein binding (PPB) was another crucial issue in our case, because of a persistent and irreversible serum albumin deficit that could have affected drug pharmacokinetics. On the basis of these considerations, we decided to modify the antibiotic treatment, switching to linezolid and tigecycline. Little is known about the efficacy of these two antibiotics in the treatment of *R. equi* infections. Linezolid has some in vitro activity[9] and a successful treatment of *R. equi* pneumonia in a heart transplant recipient has been described.[21] Tigecycline has been reported to show good in vitro activity against *R. equi*,[22] but clinical experience is still lacking. In our case, the combination of linezolid and tigecycline induced a rapid clinical improvement and reduction of retroperitoneal abscesses. Tigecycline was used for 14 days, while linezolid was administered for a total of 18 weeks without any impact on kidney function. Considering the patient's immune system impairment due to the severity of his nephrotic syndrome, a secondary prophylaxis with moxifloxacin was administered until steroid therapy was stopped and a regular hemodialysis treatment was started.

In conclusion our case indicates the increasing clinical relevance of *R. equi* as a cause of extrapulmonary manifestations in immunocompromised patients. The combination of tigecycline and linezolid may represent a reasonable therapeutic alternative for *R. equi* infections, especially in selected patients with severe comorbidities.

Conflict of interest: No conflict of interest to declare.

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