Case Report

Rare and persistent Rhodococcus equi infection in a diffuse large B cell lymphoma patient: case report and review of the literature

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Abstract: Rhodococcus equi (R. equi) is an uncommon gram positive organism. It is a rare but recognized pathogen in humans and has emerged as an important cause of morbidity and mortality among immunocompromised patients. Generally, R. equi infection needs combined treatment with effective antibiotics, and often requires the immune adjuvant therapy. Here we reported a 49-year-old man presented dyspnea with fever, skin ulcer for 5 months, and the final diagnosis was diffuse large B cell lymphoma with R. equi septicemia and pneumonia, the treatment was failure, the blood culture was always positive during the course of disease, though he was given combined treatment with effective antibiotics, perhaps the immune reconstitution or immune supportive treatment was more important.

Keywords: Rhodococcus equi (R. equi); diffuse large B cell lymphoma; immunologic reconstitution; combined treatment

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Introduction

Rhodococcus equi (R. equi) formerly corynebacterium equi (C. equi), is an uncommon gram positive organism. It has been collected from soil, water, horses, cattle, swines and wild birds. R. equi is a rare but recognized pathogen in humans and has emerged as an important cause of morbidity and mortality among immunocompromised patients. It need combined treatment with effective antibiotics, and often requires the immune adjuvant therapy, due to survival inside histiocytes, immunocompromised, the site(s) and extent of infection, the duration of treatment is uncertain. A minimum of 6 months of antibiotic therapy is typically required for immunocompromised patients. Here we reported a 49-year-old man presented dyspnea with fever, skin ulcer for 5 months and the final diagnosis was diffuse large B cell lymphoma with R. equi septicemia and pneumonia, the treatment was failure, the blood culture was always positive during the course of disease, though he was given combined treatment with effective antibiotics.

Perhaps the immune reconstitution or immune supportive treatment is more important.

Case report

In this article, the patient’s history was divided into four parts to describe according to the treatment course and the change of disease.

The local hospital—February

A 49-year-old man presented dyspnea with fever, skin ulcer for 5 months. He had hewed out the stones for 8 years and then operated “meat pie shop” to now more than 10 years, denying that smoking and the history of tuberculosis. About 5 months ago, he had a temperature of almost 39 degrees, accompanied by shortness of breath, left cape side skin itching (a thumb nail sized red lesions with 4-5 gibbous red papules, no damage, and purulent), no
cough and expectoration. White blood cell, neutrophils were normal, but lymphocytes decreased significantly: 0.2-0.7 (1.1×10^9-3.2×10^9/L), T-SPOT.TB and cryptococcal latex agglutination test, LDH were negative. Left lip pathology: ulcer with hyperplasia of squamous epithelium.

Lung CT (Figure 1): multiple lesions in both sides with left lower lobe mass, cancer with two multiple pulmonary metastases may be; two pulmonary diffuse military and small nodules. Pathology of the left lower mass (the local hospital): suppurative granulomatous inflammation; pathology consultation of The First Hospital of Zhejiang Province: suppurative granulomatous inflammation, morphology of fungal infection was first considered. Twice-positive blood cultures were corynebacterium jeikeium: sensitive to vancomycin, imipenem, cefepime, ciprofloxacin, SMZ-TMP, cefotaxime, linezolid, and erythromycin.

The patient's condition did not improve after two weeks' treatment of vancomycin, levofloxacin and voriconazole, and review the lung CT (Figure 1B): lung lesions progress than before.

**The First Affiliated Hospital of Zhejiang University—March-May**

Then to The First Hospital of Zhejiang Province for further diagnosis. Pathology of bronchoscopy (Figure 2): (lower left dorsal segment) mucosa of chronic inflammation with granuloma formation. Bone marrow routine: granulocyte increased active. It did not improve after two weeks' empirical anti-infective therapy of moxifloxacin and voriconazole. After that, many times of culture were R. equi: blood culture (twice), bone marrow culture (once),

![Figure 1](https://example.com/figure1.png)

**Figure 1** (A) Lung CT at the onset of the first (multiple lesions in both sides of the lung; lung mass in left lower lobe); (B) lung CT after 2 weeks treatment in local hospital; (C) after 43 days treatment in The First Hospital of Zhejiang Province, better than before treatment; (D) 2 weeks after the treatments of methylprednisolone and immunoglobulin, further improvement than (C); (E) a week after the discontinuation of hormone and immunoglobulin, pulmonary lesions deteriorated again; (F-H) lung imaging showed pulmonary lesions progressive deterioration in SRRSH. SRRSH, Sir Run Run Shaw Hospital.
sputum culture (once), sensitive to ceftriaxone, vancomycin, moxifloxacin, clindamycin, and erythromycin. He was then treated with moxifloxacin and vancomycin, the patient’s condition improved after 5 days’ treatment: no fever; breath better; but left lip ulcer did not improve, and after 43 days’ treatment, lung CT (Figure 1C): better than before. However, blood cultures remained positive during the treatment: after 2 weeks and 43 days respectively.

The local hospital—June

They disable all medication because he appeared serious systemic rash after 43 days’ therapy of “moxifloxacin and vancomycin”. Rash slightly, but symptoms of fever and dyspnea began from 1 week after discontinuance, and he got a new ulcer in the right alar (2 cm in diameter). Hence to treated with moxifloxacin, rifampicin and SMZ-TMP. Symptoms ibid, rash worsened, so removed all drugs, then gave methylprednisolone and immunoglobulin for 3 days, sequential oral methylprednisolone and loratadine for 10 days, rash subsided, lung CT (Figure 1D) improved, but still have a fever, shortness of breath with skin ulcer (Figure 2A,B), blood culture was also R. equi. Then treated with caspofungin 3 days, moxifloxacin and rifampicin 3 days, sulperazone 2 days, but symptoms ibid, and review the lung CT (Figure 1E): pulmonary lesions progress.

Sir Run Run Shaw Hospital (SRRSH)—July

Department of respiration: lung CT (Figure 1F) showed pulmonary lesions progress obviously: the left lower pulmonary mass, tumor? The fuzzy patch scattered in both sides of the lung. Pathology of the left corner of the mouth (Figure 2C): chronic inflammation with necrosis
of skin, with virus infection. Treated with moxifloxacin and teicoplanin for 2 days; cefoperazone sulbactam, ciprofloxacin and fluconazole for 4 days, levofloxacin combined with methylprednisolone for 10 days, because the patient's condition did not improve, and the family refused to continue the current treatment, so to department of infectious disease for further treatment. Combined with the local data, we can't exclude that histoplasmosis infection and R. equi infection, but had no malignant basis at least. He was given 10 days treatment with amphotericin B, imipenem, linezolid, methylprednisolone, and lung biopsy again. However, in the 10 days' treatment of our department, patients with progressive dyspnea and fever, lung CT (Figure 1G) and X-ray (Figure 1H) showed pulmonary diffuse lesions progress obviously and finally died of respiratory failure. To our surprised, the final pathology result was diffuse large B cell lymphoma (Figure 2D), the last 3 times blood cultures were all positive, and the isolate was identified as corynebacterium by BioMérieux Vitek2 (Figure 3A,B), 16S RNA sequencing was further performed and finally confirmed the isolate was R. equi (Figure 3C,D). We borrow patient's pathology slices outside the hospital, the full field of vision were plenty of gram positive cocci (Figure 2E), but were not described by the front two hospitals. The summary of main clinical, laboratory and imaging findings from patient was shown in Tables 1, 2.

**Discussion**

R. equi, formerly C. equi, is an uncommon gram positive organism belonging to the group of mycolata (mycolic acid containing bacteria), that also incorporates the genera nocardia, corynebacterium and so on, it's hard to treat mostly owing to the establishment of intracellular niches (1,2). Colonies form on solid media appears irregularly round,
Table 1 Summary of main clinical, laboratory and imaging findings from patient

<table>
<thead>
<tr>
<th>Date</th>
<th>Hospital</th>
<th>Symptoms</th>
<th>Blood culture</th>
<th>Lung imaging CT/X</th>
<th>Pathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 14</td>
<td>The local hospital</td>
<td>Fever, dyspnea, left lip skin ulcer (d = 2 cm)</td>
<td>Corynebacterium jeikeium × twice</td>
<td>Before the treatment: lung CT (Figure 1A), after 2 weeks treatment: lung CT (Figure 1B)</td>
<td>The left lower lung: the local hospital, suppurative granulomatous inflammation; The First Hospital of Zhejiang Province pathology consultation, suppurative granulomatous inflammation (PAS+, methenamine silver staining+), morphology of fungal infection was first considered</td>
<td>2 weeks: vancomycin + levofloxacin + voriconazole</td>
</tr>
<tr>
<td>Mar 2014-</td>
<td>The First Hospital of Zhejiang Province</td>
<td>No fever; breath better; left lip skin ulcer (d = 3 cm); after 43 days of therapy; appear serious systemic rash, disable all medication</td>
<td>R. equi: before this treatment, blood culture × 2, bone marrow culture × 1, sputum culture × 1; treatment for 2 weeks × 1; treatment for 43 days × 1</td>
<td>Treatment for 43 days: lung CT (Figure 1C)</td>
<td>Bronchoscopy (Figure 2E): (lower left dorsal segment) mucosa of chronic inflammation with granuloma formation</td>
<td>2 weeks: moxifloxacin + voriconazole; 43 days: moxifloxacin + vancomycin</td>
</tr>
<tr>
<td>May 2014</td>
<td></td>
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<td></td>
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<tr>
<td>Jun 14</td>
<td>The local hospital</td>
<td>Fever dyspnea skin ulcer: left lip (d = 4 cm), the right wing of the nose (d = 2 cm), rash: whole body</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2 weeks: moxifloxacin + rifampicin + SMZ-TMP</td>
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<td></td>
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<tr>
<td></td>
<td>Symptoms ibid, rash worsened</td>
<td></td>
<td></td>
<td>Lung CT (Figure 1D): improve</td>
<td>–</td>
<td>Methylprednisolone + immunoglobulin (3 days); methylprednisolone (oral) + loratadine (10 days)</td>
</tr>
<tr>
<td></td>
<td>Symptoms ibid, rash subsided</td>
<td></td>
<td></td>
<td>Lung CT (Figure 1E): pulmonary lesions progress</td>
<td>–</td>
<td>Caspofungin 3 days; moxifloxacin + rifampicin 3 days; sulperazone 2 days</td>
</tr>
<tr>
<td>Jul 14</td>
<td>SRRSH: Department of Respiration</td>
<td>Fever, dyspnea, skin ulcer: left lip (d = 4 cm) (Figure 2B), the right wing of the nose (d = 2 cm) (Figure 2A)</td>
<td>–</td>
<td>Lung CT (Figure 1F): the left lower pulmonary mass, tumor? patchy exudation: progress</td>
<td>The left Lip (Figure 2C): chronic inflammation with necrosis of skin, with virus infection</td>
<td>Moxifloxacin + teicoplanin: 2 days; cefoperazone sulbactam + ciprofloxacin + fluconazole: 4 days; the family refused to continue the current treatment</td>
</tr>
<tr>
<td></td>
<td>Department of Infectious Disease</td>
<td>R. equi: blood culture × 3 (Figure 3A-E)</td>
<td></td>
<td>Lung CT (Figure 1G): pulmonary lesions progress; lung X-ray (Figure 1H): pulmonary lesions progress</td>
<td>Left lung puncture (Figure 2D): diffuse large B cell lymphoma</td>
<td>10 days: amphotericin B + imipenem + linezolid + methylprednisolone</td>
</tr>
</tbody>
</table>

C. equi, corynebacterium equi; R. equi, Rhodococcus equi; SRRSH, Sir Run Run Shaw Hospital.
smooth, semitransparent, glistening and mucoid (3) after incubation for 24 and 48 hours respectively (Figure 3A,B). R. equi has been collected from soil, water, horses, cattle, swines and wild birds, and concentrations are high in horse feces (1,2). However, the transmission of R. equi is not entirely clear; the patient of this case had no history of exposure to livestock obvious. It can cause dangerous opportunistic infections.

R. equi was first reported in 1923 in foals with pyogranulomatous pneumonia (4), with the first human infection being diagnosed in 1967 (5). The vast majority of patients infected with R. equi are immunocompromised, and more than 60% have human immunodeficiency virus infection (1,6,7), some have transplant recipient (8,9), only a few suffering from lymphoma, and most of them are Hodgkin’s lymphoma, there are no reports of R. equi infection in diffuse large B cell lymphoma patients. Unlike the case, they were all secondary infection after chemotherapy in many of these lymphoma patients, most can be cured after treated by antibiotic plus chemotherapy, immune supportive treatment such as IVIG.

Clinical manifestation of R. equi infection are protean, includes fever, chills, nonproductive cough, dyspnea, weight loss, hemoptysis, and pleuritic pain etc. (3,8,10), although pulmonary infection is present up to 80% and bacteremia occurs in >80% cases (11). May be associated with invasion of the mononuclear phagocyte system, perhaps the ability of continued destruction of alveolar macrophages is the foundation of its pathogenicity, often accompanied by granuloma formation (1,11,12), caused sub-acute pneumonia with cavity and bacteremia. The mortality rate as high as 60% in immunocompromised people, infection serious degree and scavenging ability were closely associated with CD4 lymphocyte count, that is, you can improve the therapeutic effect by inducing immune reconstitution (2,6,11,13). Combination antibiotic therapy is the mainstay of treatment; R. equi is usually susceptible to erythromycin, rifampin, fluoroquinolones, aminoglycosides, glycopeptides and imipenem. Susceptibility to cotrimoxazole, tetracycline and clindamycin is variable (1,2,11), some studies such as tygecycline, vancomycin and linezolid have also successfully been used in patients (2,14-16). Like most have reported cases, due to survival inside histiocytes, immunocompromised, the site(s) and extent of infection, diseases are commonly chronic and recurrent (2), and the duration of treatment is uncertain. A minimum of 6 months of antibiotic therapy is typically required for immunocompromised patients with pulmonary, bone or multi-system infection (1,2,11,13,17).

In our study, the patients had been successively applied vancomycin, rifampin, moxifloxacin, cotrimoxazole, and when to our department, we give patient with linezolid, vancomycin, imipenem, levofloxacin, but there still were positive blood cultures during and after the whole combined treatment. The total T lymphocyte and T helper/inducer cell of the patients were very low at the onset of the first, but improved obviously after the application of methylprednisolone and immunoglobulin because of rashes, and at the same time we also found the pulmonary lesions improved than before, perhaps the immune reconstitution or immune supportive treatment more important. On the other hand, if we noticed a change of these, and further to look for the underlying diseases more actively, then given the long-term immune supportive treatment or chemotherapy, perhaps these aggressive treatment strategies can cure or significantly prolong the life of patient.

In addition, the patient of this case suffered from repeated puncture, however, we should know the positive rate of percutaneous lung biopsy is closely related with operator level of experience, distance of the lesion from the pleural surface, target lesion size, needle type, guide positioning map, pathology expert’s experience (18,19). I hope we should do what we can as far as possible to improve the positive rate of puncture, which can provide the basis for clinical diagnosis as early as possible, and increase the survival rate of the patients.

### Table 2 T-lymphocyte subsets

<table>
<thead>
<tr>
<th>Date</th>
<th>Hospital</th>
<th>Total T lymphocyte (50-84%)</th>
<th>T Helper/inducer cell (27-51%)</th>
<th>T suppressor/cytotoxic cell (15-44%)</th>
<th>CD4/CD8 (1.4-2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb</td>
<td>Local hospital</td>
<td>19.2</td>
<td>1.8</td>
<td>13.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Mar</td>
<td>The First Hospital</td>
<td>20.4</td>
<td>2.9</td>
<td>14.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Jul</td>
<td>SRRSH</td>
<td>86.79</td>
<td>24.32</td>
<td>21.99</td>
<td>1.11</td>
</tr>
</tbody>
</table>

SRRSH, Sir Run Run Shaw Hospital.
Conclusions

In areas of the world where laboratory facilities are lacking, and for immunocompromised patients, R. equi infection should be considered in the differential diagnosis of a “mycobacterium-like” illness with negative smear results. And R. equi should always be considered as a potential pathogen in any immunocompromised patient and especially with cavitary pneumonia (10), like the first reaction when saw pneumocystis carinii, we need to learn what causes the immune-suppression, and further studies and procedures are often required, including CT, BAL, and transbrachial or percutaneous biopsy.

In addition, when the treatment effect is not good in immunocompromised patients, we must clearly know the importance of an effective immune recovery. Most importantly, Isolation of any of rare pathogens in practice should require a thorough search for possible malignant diseases, for example, the association between group bovis bacteremia and colon carcinoma (20,21).

Because the experience of pathology and microbiology doctors is very different, incompetent physicians will cause a high rate of misdiagnosis. We would increase clinicians’ awareness of this pathogen’s morbidity in compromised people and to improve the likelihood of its accurate and timely diagnosis. Further clinical and laboratory research is needed to better define the routes of acquisition and the mechanisms of pathogenesis of R. equi infection and the appropriate treatments for it.

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References