

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.

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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

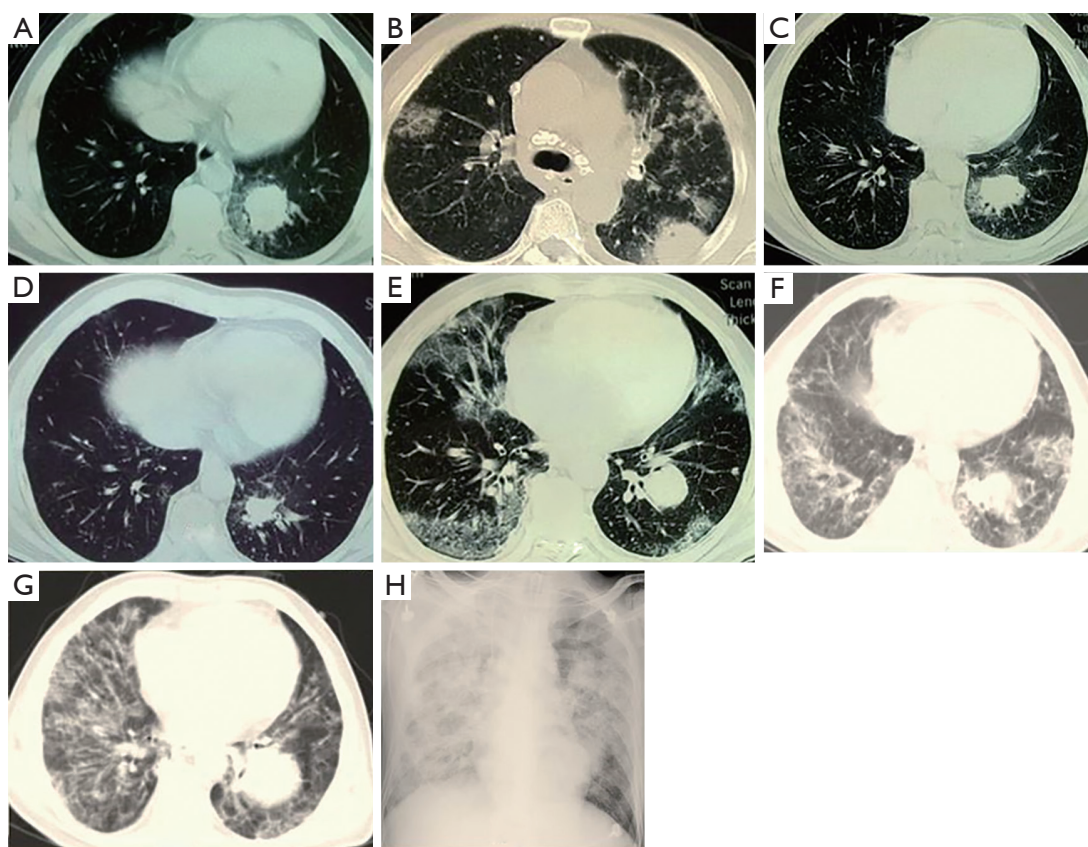


Figure 1 (A) Lung CT at the onset of the first (multiple lesions in both sides of the lung; lung mass in left lower lobe); (B) lung CT after 2 weeks treatment in local hospital; (C) after 43 days treatment in The First Hospital of Zhejiang Province, better than before treatment; (D) 2 weeks after the 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.

cough and expectoration. White blood cell, neutrophils were normal, but lymphocytes decreased significantly: $0.2-0.7 (1.1 \times 10^9 - 3.2 \times 10^9/L)$, 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),

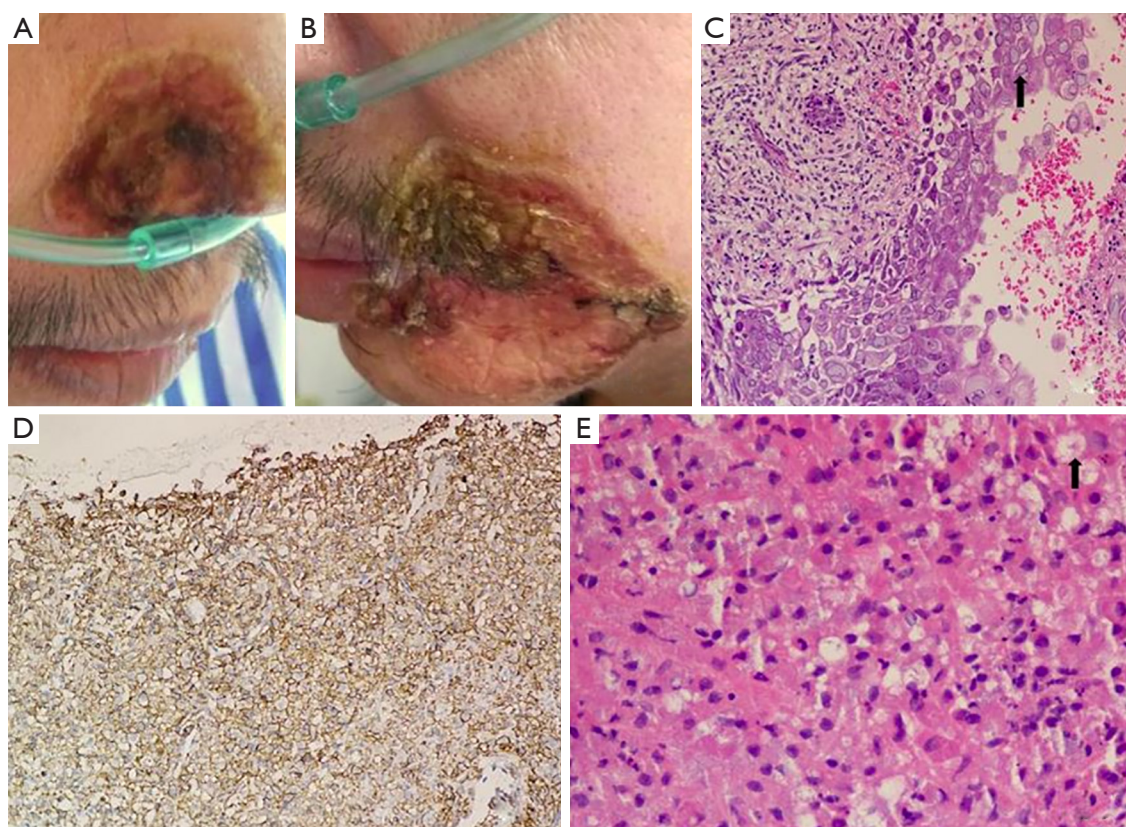


Figure 2 (A,B) Skin ulcer: left lip (d =4-5 cm), the right wing of the nose (d =2 cm); (C) pathology of the left lip (40×): chronic inflammation with necrosis of skin, with virus infection (black arrow: purple blue viral inclusion body in the cytoplasm of epidermal cells); (D) immunohistochemistry (100×): CD20+, consistent with this diagnosis diffuse large B cell lymphoma; (E) pathology of bronchoscopy (20 Mar, The First Hospital of Zhejiang Province) (HE 400×): the cytoplasm is full of purple dot (black arrow: gram positive cocci, *R. equi*), but were described only mucosa of chronic inflammation with granuloma formation by the front hospitals. *R. equi*, *Rhodococcus equi*.

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 skin 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 disabled 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

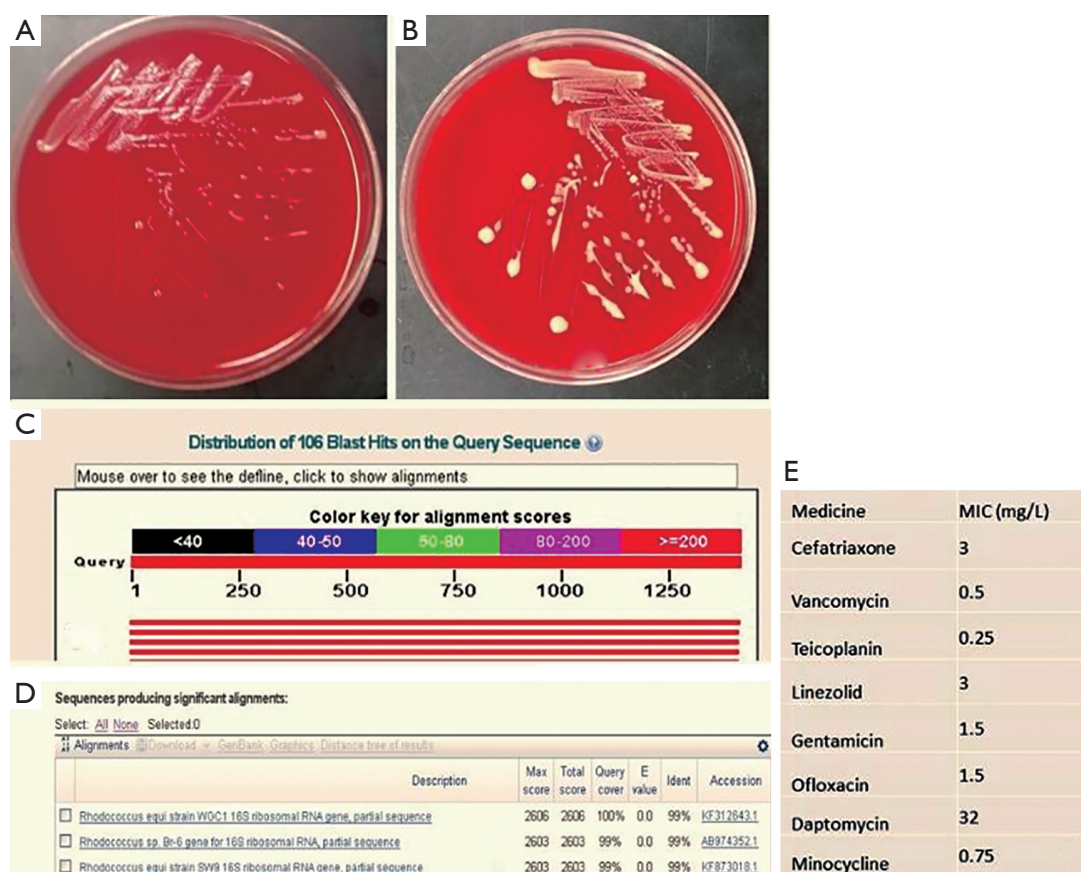


Figure 3 (A,B) Colonies on blood plate, incubation for 24 and 48 hours respectively; (C,D) we confirmed the isolate was *R. equi* by 16S RNA sequencing; (E) MIC of *R. equi*. *R. equi*, *Rhodococcus equi*.

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

Date	Hospital	Symptoms	Blood culture	Lung imaging CT/X	Pathology	Treatment
Feb 14	The local hospital	Fever, dyspnea, left lip skin ulcer (d =2 cm)	Corynebacterium jejkeium x twice	Before the treatment: lung CT (Figure 1A), after 2 weeks treatment: lung CT (Figure 1B)	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	2 weeks: vancomycin + levofloxacin + voriconazole
Mar 2014- May 2014	The First Hospital of Zhejiang Province	No fever; breath better; left lip skin ulcer (d =3 cm); after 43 days of therapy, appear serious systemic rash, disable all medication	R. equi: before this treatment, blood culture x2, bone marrow culture x1, sputum culture x1; treatment for 2 weeks x1; treatment for 43 days x1	Treatment for 43 days: lung CT (Figure 1C)	Bronchoscopy (Figure 2E): (lower left dorsal segment) mucosa of chronic inflammation with granuloma formation	2 weeks: moxifloxacin + voriconazole; 43 days: moxifloxacin + vancomycin
Jun 14	The local hospital	Fever dyspnea skin ulcer: left lip (d =4 cm), the right wing of the nose (d =2 cm), rash: whole body Symptoms ibid, rash worsened Symptoms ibid, rash subsided	- - - -	- Lung CT (Figure 1D) improve Lung CT (Figure 1E): pulmonary lesions progress	- - -	2 weeks: moxifloxacin + rifampicin+ SMZ-TMP Methylprednisolone + immunoglobulin (3 days); methylprednisolone (oral) + loratadine (10 days) Caspofungin 3 days; moxifloxacin + rifampicin 3 days; sulperazone 2 days
Jul 14	SRRSH: Department of Respiration of Infectious Disease	Fever, dyspnea, skin ulcer: left lip (d =4 cm) (Figure 2B), the right wing of the nose (d =2 cm) (Figure 2A) Symptoms ibid	- - R. equi: blood culture x3 (Figure 3A-E)	Lung CT (Figure 1F): the left lower pulmonary mass, tumor? patchy exudation: progress Lung CT (Figure 1G): pulmonary lesions progress; lung X-ray (Figure 1H): pulmonary lesions progress	The left Lip (Figure 2C): chronic inflammation with necrosis of skin, with virus infection Left lung puncture (Figure 2D): diffuse large B cell lymphoma	Moxifloxacin + teicoplanin: 2 days; cefoperazone sulbactam + ciprofloxacin + fluconazole: 4 days; the family refused to continue the current treatment 10 days: amphotericin B + imipenem + linezolid + methylprednisolone
C. equi, corynebacterium equi; R. equi, Rhodococcus equi; SRRSH, Sir Run Run Shaw Hospital.						

Table 2 T-lymphocyte subsets

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

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.

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 transbronchial 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

- Weinstock DM, Brown AE. *Rhodococcus equi*: an emerging pathogen. *Clin Infect Dis* 2002;34:1379-85.
- Savini V, Salutati P, Sborgia M, et al. Brief Tale of a Bacteraemia by *Rhodococcus equi*, With Concomitant Lung Mass: What Came First, the Chicken or The Egg? *Mediterr J Hematol Infect Dis* 2011;3:e2011006.
- Yamshchikov AV, Schuetz A, Lyon GM. *Rhodococcus equi* infection. *Lancet Infect Dis* 2010;10:350-9.
- Magnusson H. Spezifische infektiöse pneumonie beim fohlen: ein neuer eitererreger beim pferd. *Arch Wiss Prakt Tierheilkd* 1923;50:22-38.
- Golub B, Falk G, Spink WW. Lung abscess due to *Corynebacterium equi*. Report of first human infection. *Ann Intern Med* 1967;66:1174-7.
- Ferretti F, Boschini A, Iabichino C, et al. Disseminated *Rhodococcus equi* infection in HIV infection despite highly active antiretroviral therapy. *BMC Infect Dis* 2011;11:343.
- Topino S, Galati V, Grilli E, et al. *Rhodococcus equi* infection in HIV-infected individuals: case reports and review of the literature. *AIDS Patient Care STDS* 2010;24:211-22.
- Hayes D Jr, Diaz-Guzman E, Hoopes CW. *Rhodococcus equi* infection after lung transplantation. *Respir Care* 2011;56:1605-7.
- Behnes CL, Neumann S, Schwyer S, et al. Pleural malakoplakia caused by *Rhodococcus equi* infection in a patient after stem cell transplantation. *Diagn Pathol* 2012;7:20.
- Gallant JE, Ko AH. Cavitary pulmonary lesions in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1996;22:671-82.
- Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al. Prognosis and clinical evaluation of infection caused by *Rhodococcus equi* in HIV-infected patients: a multicenter study of 67 cases. *Chest* 2003;123:1970-6.
- Takai S, Sasaki Y, Ikeda T, et al. Virulence of *Rhodococcus equi* isolates from patients with and without AIDS. *J Clin Microbiol* 1994;32:457-60.
- Ng S, King CS, Hang J, et al. Severe cavitary pneumonia caused by a non-*equi* *Rhodococcus* species in an immunocompetent patient. *Respir Care* 2013;58:e47-50.
- Akilesh S, Cross S, Kimmelshue K, et al. Pseudotumor of the tracheal-laryngeal junction with unusual morphologic features caused by *Rhodococcus equi* infection. *Head Neck Pathol* 2011;5:395-400.
- El-Mofty SK, Akilesh S. Infectious pseudotumors: red herrings in head and neck pathology. *Head Neck Pathol* 2012;6:58-63.
- Russo G, Lichtner M, Carnevalini M, et al. Primary retroperitoneal abscesses due to *Rhodococcus equi* in a patient with severe nephrotic syndrome: successful antibiotic treatment with linezolid and tigecycline. *Int J Infect Dis* 2010;14:e533-5.
- Denes E, Peignon-Orsoni D, Terrade FX. Nonhealing wound due to *Rhodococcus equi* in an apparently immunocompetent patient, revealing CD8+ T-lymphocyte deficiency. *J Clin Microbiol* 2010;48:4658-60.
- Capalbo E, Peli M, Lovisatti M, et al. Trans-thoracic biopsy of lung lesions: FNAB or CNB? Our experience

- and review of the literature. *Radiol Med* 2014;119:572-94.
19. Boskovic T, Stanic J, Pena-Karan S, et al. Pneumothorax after transthoracic needle biopsy of lung lesions under CT guidance. *J Thorac Dis* 2014;6:S99-107.
 20. Vollmer T, Hinse D, Kleesiek K, et al. Interactions between endocarditis-derived *Streptococcus gallolyticus* subsp. *gallolyticus* isolates and human endothelial cells. *BMC Microbiology* 2010;10:78.
 21. Boleij A, van Gelder MM, Swinkels DW, et al. Clinical Importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clin Infect Dis* 2011;53:870-8.

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