A rare infectious agent: *Rhodococcus equi*, a case report and literature review of soft tissue infections in immunocompetent patients

Nadir bir etken: *Rhodococcus equi*, immünkompetan hastalarda yumuşak doku enfeksiyonlarına ilişkin bir vaka sunumu ve literatür incelemesi

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Abstract

Rhodococcus equi (R. equi) is a microorganism that was first identified in horses. Afterward, it was found to cause opportunistic infections in immunosuppressed patients. It causes especially pulmonary infections in immunocompromised patients while it rarely causes diseases such as septic arthritis and soft tissue infections. It is important to question epidemiological risk factors for the diagnosis of the disease. Also, the clinician-microbiologist relationship is important in the laboratory diagnosis of the microorganism because it is possible to be missed as part of normal flora or contaminant or to be confused with microorganisms with similar phenotypic features (Nocardia species or rapidly growing mycobacteria). Rarely, it has been reported in immunocompetent patients, as in our case. MEDLINE, SCOPUS, Google Scholar, and Cochrane searches were performed using the keywords *Rhodococcus equi* and *Corynebacterium equi* from 1945 to July 2021. A total of 582 articles were determined. Articles containing these keywords were then scanned for the words "humans", "soft tissue infections", and "cellulite" and a total of 42 articles were listed in the end. A total of 14 case reports of soft tissue infection/cellulitis in immunocompetent patients related to *R. equi* were detected in the literature. In our case, there was a soft tissue infection and *R. equi* was detected in the abscess culture. Obtaining culture and determining the factor is very important in the treatment of infections. In this report, soft tissue infections caused by *R. equi* in immunocompetent patients are reviewed.

Keywords: Immunocompetence; human; *Rhodococcus equi*; soft tissue infections

Öz

Rhodococcus equi (R. equi) ilk olarak atlarda tanımlanan ve daha sonra bağışıklığı baskılanmış hastalarda fırsatçı enfeksiyonlara neden olduğu anlaşılan bir mikroorganizmadır. Özellikle bağışıklığı baskılanmış hastalarda akciğer enfeksiyonlarına neden olurken nadiren septik artrit ve yumuşak doku enfeksiyonları gibi hastalıklara neden olur. Hastalığın tanısı için epidemiyolojik risk faktörlerinin sorgulanması önemlidir. Klinisyen-mikrobiyolog ilişkisi de mikroorganizmanın laboratuvar tanısında önemlidir çünkü normal floranın veya kontaminantın bir parçası olarak gözden kaçabilir veya benzer fenotipik özelliklere sahip mikroorganizmalarla (Nocardia türleri veya hızla büyüyen mikobakteriler) karıştırılabilir. Nadiren de olsa bizim olgumuzda olduğu gibi immunkompetan hastalarda da bildirilmeye başlanmıştır. MEDLINE, SCOPUS, Google Akademik ve Cochrane aramaları, 1945'ten Temmuz 2021'e kadar *Rhodococcus equi* ve *Corynebacterium equi* anahtar kelimeleri kullanılarak yapıldı. Toplam 582 makale belirlendi. Bu anahtar kelimeleri içeren makaleler daha sonra "insan", "yumuşak doku enfeksiyonları" ve "selülit" kelimeleri için tarandı ve sonunda toplam 42 makale listelendi. Literatürde *R. equi* ile ilgili bağışıklığı sağlam hastalarda yumuşak doku enfeksiyonu/selülit ile ilgili toplam 14 vaka raporu tespit edilmiştir. Bizim olgumuzda yumuşak doku enfeksiyonu mevcuttu ve apse kültüründe *R. equi* saptandı. Enfeksiyonların tedavisinde kültür alınması ve etkenin belirlenmesi çok önemlidir. Bu raporda, bağışıklık sistemi sağlam hastalarda *R. equi*'nin neden olduğu yumuşak doku enfeksiyonları gözden geçirilmiştir.

Anahtar Sözcükler: Bağışıklık yeterliliği; insan; *Rhodococcus equi*; yumuşak doku enfeksiyonları

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INTRODUCTION

Rhodococcus equi (R.equi) is an intracellular, Gram-positive, immobilized coccobacillus, which forms smooth-surfaced, mucoid-red-salmon-colored colonies in nonselective media. It is commonly found in nature, especially in soil. It has been detected and described as the causative agent of pneumonia in foals in 1923 (1). In humans, it was first detected as an infectious agent in an immunosuppressed patient who received steroid treatment in 1967 (2). Although it is frequently seen in immunosuppressive patients, it may rarely cause an infection in immunocompetent patients (3). Therefore it is rarely recognized. This agent is usually detected in patients with epidemiological risk factors (those in contact with horses, etc.). However, it has also been reported as a causative agent of infections in people without known exposure. To determine the possible factors in patients better, a detailed anamnesis should be provided and a culture sample should be taken from the infection site. As presented in our review, we should also consider rare factors in immunocompromised patients who have intense exposure to the external environment.

In this report, an immunocompetent patient who developed facial cellulitis due to *R. equi* was presented. It is intended to collect data to draw attention to the microorganism which often causes disease in animals, and despite being under-recognized, it also causes disease in humans over the years.

METHODS

Data sources

Electronic database system research is readily based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (Preferred Reporting Items for Systematic Reviews and Meta-Analysis - PRISMA). The online search of published reports was conducted in MEDLINE (Pubmed coverage from 1945 to present) and The Cochrane Central Register of Controlled Trials (Central) (Wiley Online Library, coverage from 1966 to present), Scopus, and Google Scholar. The most extensive search strategy was made on the MEDLINE database: (*Rhodococcus equi* OR (*Corynebacterium equi)* AND (humans OR soft tissue infections OR abscess OR osteomyelitis OR cellulite) AND (case OR report OR series OR observational OR cohort OR case-control OR cross-sectional OR clinical trial) NOT (immunosuppressive OR HIV positive OR animals OR "in vitro"

Study eligibility criteria and participants

The inclusion criteria were as follows: type of study – observational study (cohort and cross-sectional), case series and case report; characteristics of participants – patients of all ages and of both sexes from which they have been isolated and identified by any diagnostic method, isolating *R. equi* as the sole microorganism in their body fluids or tissues. Studies in any language were eligible for inclusion. The exclusion criteria were: cases of *R. equ*i infections in immunosuppressive patients, cases of *R. equi* infections in HIV-positive patients cases, cases of *R. equi* infections in non-human species, and studies with incomplete data.

Interventions

The data from publications included in the review were extracted to an Excel table with the following columns: publication ID; report ID; citation and contact details; age and sex of patients; source; immune status; site of isolation of R. equi (bodily fluid or tissue); sampling method; antibiotic regimen used treatment; duration of the antibiotic regimen used; outcomes of the antibiotic treatment.

Data analysis

The following outcomes were categorical: gender of patients, the method for *R. equi* identification, outcomes of antibiotic treatment, and antibiotics used. The following outcomes were continuous: the age of patients and the total number of patients. Assessment of heterogeneity was not applicable to this type of systematic review. Clinical trials were not found for quantitative data synthesis. Narrative summation and tabulation of findings from individual publications were made.

RESULTS

A total of 582 articles were determined. Articles containing these keywords were then scanned for the words "humans", "soft tissue infections", and "cellulite" and a total of 42 articles were listed in the end. A to-

Table 1. Demographic and epidemiological features, diagnosis, treatment, and outcomes of soft tissue infections related to Rhodococcus equi in immunocompetent patients reported in the literature.

Number	Year, reference	Age/gender	Source	Specimen source	Diagnosis	Treatment	Treatment duration	Surgery	Relaps/ outcome
1	1988 (3)	13/M	Car accident	Joint aspirate	Cellulite	No antibiotic, drain with iodophor and fusidic acid	1 week	Surgical debridasyon	cured
2	1990 (5)	35/F	Self inoculsyon	Blood and tissue	Leg ulcer	More than once, different antibiotic	Different times	No	relaps
3	1994 (6)	4/M	Nail puncture	Joint aspirate	Septic knee arthtiris	Cefazolin	2 days	Knee joint irrigation	cured
4	1994 (6)	9/M	Unknown	Wound	Lymphangit	Cephalexin	2 weeks	No	cured
5	1995 (7)	76/M	Horse breeder	Biopsy	Mandibular osteitis	Ciprofloxacin + rifampicin	8 months	No	cured
6	2001 (8)	16/M	Exposure to livestock	Biopsy	Soft tissue infectious	Erythromycin+ rifampicin	3 months	Debridement+ graft+ muscle flap	cured
7	2002 (9)	76/F	Unknown	Aspirate	Left thigh abscess	Ciprofloxacin + rifampicin	6 weeks	Debridement	cured
8	2003 (10)	25/F	Motor accident	Wound	Cellulite	Ciprofloxacin + rifampicin	3 weeks	Amputation	cured
9	2009 (11)	15/M	Car accident	Wound	Acut osteomyelitis	Erythromycin	4 weeks	Drainage	cured
10	2011 (12)	26 days/M	Parents exposure to livestock	Blood	Cellulite	Amikacin	1 week	No	cured
11	2011 (13)	31/F	Breast operation	Biopsy	Right breast cellulitis	Moxifloxacin+rifampicin	6 weeks	Drainage	cured
12	2011 (10)	42/M	Unknown	Wound	Cellulite	Moxifloxacin+rifampicin	1 month	Amputation	cured
13	2013 (14)	38/F	Trauma	Aspirate	Breast cellulitis	Amoxicillin clavulanate	10 days	Drainage	cured
14	2013 (15)	37/F	Exposure to livestock	Aspirate	Granulomatous mastititis		4 weeks	Excisional biopsy	cured

*F: Female, M: Male

tal of 14 case reports of soft tissue infection/cellulitis in immunocompetent patients related to *R. equi* were detected in the literature (4-15) (**Table 1**). When examined in detail, the vast majority of cases were immunosuppressed and HIV-positive individuals, and approximately 10% of cases were immunocompetent patients (16).

The oldest patient reported with *R. equi* soft tissue infection had 76 years while the youngest was a newborn, the mean age is 30. There were 6 (43%) female and 8 (57%) male patients. The source of the disease is unknown in 6 (43%), trauma in 4 (28.5%), and 4 (28.5%) patients exposed to livestock. All patients were immunocompromised patients.

The sampling methods were aspirate in 5 (%36), biopsy in 3 (%21), wound in 4 (%29), and blood and tissue in 2 (%14) patients. In the treatment, a single agent regimen in 5 (%36) patients and combination therapy in 7 (%50) patients were used as the antibiotic regimen. The most commonly used antibiotics were rifampicin, ciprofloxacin, moxifloxacin, erythromycin, and beta-lactam group antibiotics, respectively. The mean duration of treatment of the antibiotic regimen was found to be 43 days (min 2 days - max 240 days). No patient died, a complete cure was achieved in 13 (93%) patients, and relapse occurred in 1 (%7) patient.

Our Case Presentation

A 38-year-old male peddler without known chronic disease was admitted to the emergency department with complaints of redness and swelling around the left eye. The patient stated that he had hordeolum in

his eyelid for a week and he had tried to empty the contents of the hordeolum with the needle four days ago. In computed tomography, it was detected that the eyeballs were natural, while there were fluid levels and thickening of the subcutaneous fat at preorbital and buccal levels. He was consulted to the department of infectious diseases for further investigation and treatment. He had a fever of 37 °C, hyperemia, and edema starting from the left eye to the middle of the face. In laboratory testing, leukocytes were 11500/mm3, neutrophil 63%, and CRP 67 mg/L (normal range: 0-5 mg/L). The anti-HIV test was negative. After obtaining a culture from the abscess, empirical treatment of intravenous ampicillin-sulbactam and oral ciprofloxacin was prescribed. Local dressing with saline was also performed. On the second day of hospitalization mucoid, hemolysis-free, pinkish salmon-colored colonies were detected on the blood agar prepared from the culture obtained from the discharge in the lesion area under the eye. Gram-positive coccobacilli were detected in the preparations from colonies. Catalase was positive and oxidase negative colonies were identified as R. equi by Matrix-Assisted Laser Desorption and Ionization Time-Of-Flight Mass Spectrometry (MALDI Tof MS) (Bruker/Germany). The antimicrobial therapy of the patient was revised to rifampicin and ciprofloxacin. The patient recovered and was discharged with a recommendation of completion of the treatment in 14 days. On the follow-up, it was observed that the lesion completely recovered at the end of the treatment.

DISCUSSION AND CONCLUSION

When the literature is reviewed, the mean age of the immunocompetent patients with soft tissue infections is 30 (min 26 days-max 76 years) (Table 1). Our patient was 38 years old and shows similar features to the reported cases. Six of the reported 14 patients in the literature are children and the other patients being predominantly young led to the thought that it may be related to their exposure to trauma and external factors more often. *Rhodococcus equi*, is an aerobe, carbohydrate non-fermenting, catalase-positive, usually urease-positive, and oxidase-negative microorganism causing zoonotic infections. It can be confused with *Mycobacterium tuberculosis* and *Nocardia* spp. because

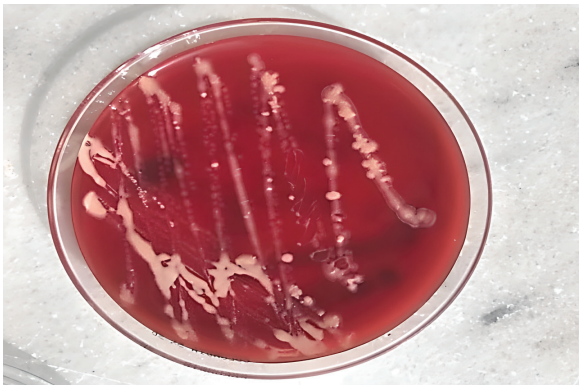

Figure 1. *Rhodococcus equi* on blood agar

it shows weak positivity in modified acid-fast staining (17). In automated systems, it can be identified easily. Likewise, it can be quickly and accurately determined in MaldiT-of MS.

In the diagnosis of the disease and the identification of the microorganism, it is usually necessary to take a sample from the infection site. Similarly, in the literature, it was reported that the agent was detected in the samples taken from the primary infection site (Table 1). In a study evaluating blood cultures, the growth rate in immunosuppressed patients was 54%, while the reproduction rate was found 10% in the immunocompetent host (6,17). One of the most important factors in the early diagnosis of *R equi* infection is the effective communication between clinicians and laboratory staff. Although the microorganism is easy to reproduce, considering that it is seen as a diphtheroid, it can easily be evaluated as contamination. In our case, a culture sample was obtained from the primary infection site. Due to having a partial response to current therapy, and the detection of Gram-positive coccobacilli that was mucoid on blood agar, with no hemolysis, salmon-colored colony-forming, catalase-positive, and oxidase negative, it was thought to be *R.equi* and its accurate identification was made with MaldiT-of MS (Figure 1). Exposure to soil contaminated by animal waste and contact with farm animals, especially horses, plays an important role in the development of *R.equi* infections epidemiologically, for causing pneumonia or gastrointestinal tract infections commonly in horses it is thought that infection can occur with inhalation of the contaminated aerosols or consumption of contaminated food (6,18,19). In an

Australian study, it was reported that *R. equi* was isolated from 18 of 19 horse farms and 54% of the examined land areas (20). Being in horse farms and stables is among the major risk factors for infection (21,22). Infection may also develop with trauma and superinfection of wounds (Table 1). In accordance with the literature, in our case, it is thought that the infection developed as a post-traumatic superinfection. Since our patient was a peddler, it was thought that frequent exposure to soil and dust outdoors may have brought about the development of infection.

The agent may often cause infection in patients with immunosuppressive diseases such as AIDS, solid organ transplant recipients, and diabetes (23). Most of the *R.equi*-associated pneumonia cases reported in the literature occur in immunocompromised patients, particularly in solid organ and hematopoietic stem cell transplant recipients (23,24). In immunosuppressed patients, extrapulmonary involvement such as subcutaneous and brain abscesses, and kidney and bone involvement can be seen, together with pneumonia (6,25-27). Extrapulmonary infections, including septic arthritis, cellulitis, post-traumatic endophthalmitis, osteomyelitis, central venous catheter, and peritoneal catheter-related infections are reported in approximately 25% of patients with *R.equi* infection (6,16,28-32). Nevertheless, extrapulmonary infections are rare in immunocompetent patients (6,21,33,34). Demographic and epidemiological features, diagnosis, treatment, and outcomes of soft tissue infections related to R. equi in immunocompetent patients reported in the literature were summarized in Table 1.

When we review the literature, an increase in soft tissue infections of *R.equi* is observed over the years. This may be due to advances in laboratory identification, however, considering the chance of not recognizing the rare agent in differential diagnosis and the difficulty of treatment, we believe that it will be more problematic in the coming years.

In vitro studies using disk diffusion testing and/or minimum inhibitory concentration (MIC) techniques report that *R.equi* is usually sensitive to rifampin, macrolides, fluoroquinolones, aminoglycosides, glycopeptides, linezolid, and imipenem (35,36). For the treatment, combination therapy is recommended, primarily rifampin together with macrolides or fluoroquinolones (37,38). Treatment recommendations are based on cases and reviews in the literature and there is no definite consensus, and the treatment should be individualized depending on the patient's condition. Treatment in immunocompromised individuals should be a minimum of two months (19), and a minimum of two weeks of treatment is recommended in immunocompetent patients (21). When the cases in the literature (Table 1) are examined, it is seen that this period is usually followed. In our case, antibiotic treatment was completed in 14 days and the lesion was completely resolved.

To the best of our knowledge, this is the first case report of an *R.equi*-related abscess in an immunocompetent patient from Turkey. In this study, along with our case, 14 cases with soft tissue infections in immunocompetent patients were evaluated in the literature. *R.equi*, which rarely comes to mind in immunocompetent patients, has increased the probability of detection with the use of the MALDI-TOF MS automated system today. With the use of new microbiological techniques, the right treatment can be initiated as soon as possible. However, in cases in which rapid and advanced diagnostic methods cannot be used, particularly in immunocompetent patients with recurrent infections or when there is no response to empirical therapy, epidemiological history should be detailed and *R.equi* should be kept in mind.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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