Case report

Rhodococcus hoagii bloodstream infection in an allogeneic hematopoietic stem cell transplantation patient: Case report and review of literature

Pedro da Silva Campana\textsuperscript{a}, Lorena Zaine Matos Martinho\textsuperscript{b}, Marjorie Vieira Batista\textsuperscript{b}, Hermes Higashino\textsuperscript{b}, Camila Rizek\textsuperscript{c}, Flavia Rossi\textsuperscript{d}, Fernando Nivaldo Oliveira\textsuperscript{e}, Vanderson Rocha\textsuperscript{f}, Silvia Figueiredo Costa\textsuperscript{g,*}

\textsuperscript{a}Instituto de Infectologia Emilio Ribas, São Paulo, Brazil
\textsuperscript{b}Infectious Diseases Division of Hospital das Clínicas of University of São Paulo, São Paulo, Brazil
\textsuperscript{c}UMT-Instituto de Medicina Tropical of University of São Paulo, São Paulo, Brazil
\textsuperscript{d}Laboratory of Microbiology of Hospital das Clínicas of University of São Paulo, São Paulo, Brazil
\textsuperscript{e}Infectious Diseases Department of Hospital das Clínicas of University of São Paulo, São Paulo, Brazil
\textsuperscript{f}Bone Marrow Transplantation Unit of Hospital das Clínicas of University of São Paulo, São Paulo, Brazil
\textsuperscript{g}Department of Infectious Diseases of Faculdade de Medicina of University of São Paulo, São Paulo, Brazil

\textbf{A R T I C L E   I N F O}

Article history:
Received 25 September 2019
Received in revised form 10 February 2020
Accepted 18 February 2020

Keywords:
Rhodococcus hoagii
Bacteremia
Hematopoietic stem cell transplantation

\textbf{A B S T R A C T}

We report a case of bloodstream infection caused by \textit{R. hoagii} in a woman with acute myeloid leukemia, 37-years-old, who received an allogeneic hematopoietic stem cell transplant. She developed cutaneous and gastrointestinal tract graft versus host disease, respectively on day 29 and day 69. On day 157 she developed to acute severe respiratory failure. \textit{Rhodococcus sp} was identified by MALDI-TOF and 16S rRNA sequencing from blood culture as \textit{Rhodococcus hoagii}. The patient was a nurse that lived in urban areas, and stated no recent trips to countryside areas neither contacted with animals. Despite of the treatment with antibiotics action against \textit{R. hoagii} such as linezolid and meropenem the patient evolved to multiorgan dysfunction and death. Our case-report emphasizes the importance of early diagnosis and the use of 16S rRNA sequencing to confirmed the identification of species of \textit{Rhodococcus} infection.

© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

\textit{Rhodococcus} is a Gram-positive coccobacillus that belongs to the \textit{Actinomycetaceae} order [1] This microorganism has been described as cause of infection in immunocompromised host such as Human Immunodeficiency Virus (HIV) and solid organ transplantation patients [1,2]. Moreover, few cases have been reported in hematopoietic stem cell transplantation (HSCT) patients, mostly in allogeneic (allo) patients with graft versus host diseases (GVHD) [3].

Case report

We present the case of a 37-year-old woman with acute myeloid leukemia (AML), colonized by vancomycin-resistant Enterococcus (VRE) who received an allo-HSCT from HLA compatible donor 5 months prior to admission. Bulsuphan, Fludarabine and Alemtuzumab were used as conditioning agents. The patient developed cutaneous and gastrointestinal tract GVHD, respectively on day 29 and 69. On day 69, she presented reactivation of cytomegalovirus (CMV) (RT-PCR CMV 6027 UI/mL, negativation within 3 weeks).

On day 119, she was admitted to the hospital with dyspnea and cough, the baseline liver enzymes were normal (ALT 10 U/L and AST 15 U/L) and blood count (Hb = 7.0 gm/dL; Ht = 20.9%; leukocytes 940 cells/m3; neutrophils 790 cells/m3 and platelets 159,000). The chest computer tomography (CT) revealed opacities in the upper lobe of right lung and absence of halo sign, both galactomannan on bronchoalveolar lavage fluid and serum were positives (0.5 OD1 and 0.73 OD1 respectively) (Fig. 1). Thus, she started voriconazole (200 mg IV q 12 h), that was replaced later on

https://doi.org/10.1016/j.idcr.2020.e00724
2214-2509/© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
by liposomal Amphotericin B (LAmB) 300 mg/d because of increased rates of liver enzymes (ALT 166 U/L and AST 85 U/L). Voriconazole was reintroduced (200 mg IV q12 h) when the liver enzymes were normal. There was improvement of pulmonary symptoms and radiological images with non-invasive ventilation after 23 days of antifungal drugs and GVHD treatment (methylprednisolone 90 mg/d) (Fig. 1). The patient was discharged from the hospital on day 142.

On day 145, three days after she was discharged, the patient was hospitalized with dyspnea, acute kidney injury and CMV reactivation (RT-PCR CMV 401 UI/mL) that was treated with ganciclovir (2.5 mg/kg/d IV q 12 h) adjusted for kidney function (KDIGO II). Blood cultures were collected, voriconazole was replaced by LAmB (3 mg/kg/d) and piperacillin-tazobactam (4.0 mg IV q6h) was introduced. On day 157 she evolved to acute severe respiratory failure and renal replacement therapy. She was transfer to the intensive care unit and mechanic ventilation was started. In this context, cultures were collected and trimethoprim/sulfamethoxazole (trimethoprim 15 mg/kg/d IV q6h), meropenem (1g IV q12h), colistin 2.5 mg/kg/d IV qDay), amikacin (15 mg/kg/d q24h) and linezolid (600 mg q12h) were given. Bronchoalveolar lavage was performed and Ziehl-Neelsen staining, bacteria and fungi cultures, Multiplex PCR for virus and galactomannan were negatives. Pulmonary CT before HSCT showed sparse and bilateral micronodules, measuring up to 0.3 cm and stable calcifications. Pulmonary CT on day 119 HSCT showed sparse nodules and micronodules, pneumonic foci in organization and opacity in frosted glass (Fig. 1).

After five days, blood cultures were positive for Achromobacter sp. and Rhodococcus sp. using VITEK® Biomerieux-France and matrix-assisted laser desorption ionization with time of flight (MALDI-TOF-Biomerieux-France). We performed the sequencing of 16S ribosomal RNA gene (16S rRNA gene) of Rhodococcus sp to confirm the identification that revealed 100% of identity with Rhodococcus hoagii according to the National Center for Biotechnology Information (NCBI) database. Genebank access number SUB4217796 Seq1 MH539885.

The central venous catheter was removed, moreover, despite the treatment with active antibiotics against R. hoagii as linezolid, amikacin and meropenem for 14 days, the patient evolved with multi organ dysfunction syndrome and death on day 172 (Fig. 2).

**Discussion**

We present here a case report of a bloodstream infection (BSI) caused by R. hoagii in an allo-HSCT patient who evolved to death. This bacterium has been associated with severe infections such as BSI and pneumonia with high mortality in this population of patient; mainly allo-HSCT patients (Table 1).

**Rhodococcus** has been associated to exposure to rural areas. It transmission usually occurs by inhalation of contaminated soils; as the soils of horses ‘s farmers contains highly concentration of this bacteria [1,4,5]. Recently its taxonomy changed based on sequencing methods, thus, *Rhodococcus equi* was named as *R. hoagii* according to the rules of the Bacteriological Code [14]. Although the 16S rRNA gene sequencing analysis is an useful method to identify the Rhococcus; this gene is unable to differentiate some of Rhodococcus species [15,16]. Thus, this technique can result in misidentification of species. Up to now, whole genome sequencing (WGS) analysis is consider the trustworthy method to identify the species in this genus [15–17]. Moreover, the WGS is not available as routine in most of low income countries. In our case report the 16S rRNA sequencing revealed 100% of identity with *Rhodococcus hoagii* according to NCBI database.

The development of the infection by *Rhodococcus* occurred later than day 100 in most cases of HSCT [4,6–15]. Regarding risk factors; it has recently been shown, in a case-control study that 02 conditions (diabetes mellitus and a prior opportunistic infection) might increase the risk of infection caused by *Rhodococcus* [3]. Other authors, however, did not evidence any risk factors [4,6–15]. In our report, the patient was a nurse that lived in urban areas, and stated no recent trips to countryside areas neither contact with animals. Infections caused by *Rhodococcus* are underreported and

---

**Fig. 1.** Pulmonary CT before HSCT. Pulmonary CT day 119 HSCT.

**Fig. 2.** Timeline showing main events that occurred during patient treatment.
Table 1
Cases of Rhodococcus in allo-HSCT patients described in the literature.

| Year (Reference) | Age years | Gender | Rhodococcus species | Comorbidities | Clinical diagnosis | Treatment | Outcome |
|------------------|-----------|--------|---------------------|---------------|-------------------|-----------|---------|
| 1995 (10)        | 29        | Male   | R. equi             |               | Lymphoma          | Pneumonia | Not reported |
|                  |           |        |                     |               | Lymphoma          | Pneumonia | Vancomycin (treatment failure); ertapenem and rifampin  |
| 2008 (4)         | 61        | Male   | R. equi             |               |                   | Lung nass, pleural malakopla    | Right upperlobe lobectomy     | Death |
| 2012 (11)        | 60        | Male   | R. equi             |               | T-cell           | Bacteremia | Cefepime and cefozopran      | Death |
|                  |           |        |                     |               | prolymphocytic   |           |                     |       |
|                  |           |        |                     |               | Leukemia         |           |                     |       |
|                  |           |        |                     |               | Not Informed     | Bacteremia | Vancomycin and ciprofloxacin  | Not reported |
|                  |           |        |                     |               | Acute            |           | Vancomycin and ciprofloxacin  | Not reported |
|                  |           |        |                     |               | Myelomonocytic   |           |                     |       |
|                  |           |        |                     |               | Leukemia         |           |                     |       |
| 2012 (5)         | 64        | Male   | R. corynbcateoides  |               |                   | Bacteremia | Cefepime and cefozopran      | Death |
| 2012 (8)         | 68        | Male   | R. equi             |               |                   | Bacteremia | Cefepime and cefozopran      | Death |
| 2013 (7)         | 61        | Male   | R. globulus         |               |                   | Bacteremia | Cefepime and cefozopran      | Death |
| 2017 (present case) | 37       | Female | R. equi             |               |                   | Pneumonia  | Moropenin, amicakin and linezolid | Death |

probably misdiagnosed because of a conjunction of factors that include the difficult of identification of genus and species by traditional techniques, and the importance of history as previous exposure to rural area, contact with animal as horse which should always prompt investigation. In addition, Rhodococcus is a diverse spectrum of disease [17]. Immuno compromised patients can present pneumonia, BSI, malakopla and mediastinitis caused by Rhodococcus [17]. This clinician characteristic makes the diagnostic hypothesis even more challenging. Most of the cases reported in transplantation patients described the lung as the mainly route of infection [4,6–17]. Around 80% developed pulmonary cavity, and among immunocompromised populations, it is often observed disseminated disease as well [1]. Our patient presented respiratory symptoms but the respiratory cultures were negative. Although, she received a multidrug treatment including antibiotics with action against Rhococcus such as linezolid, amikacin and meropenem [13,14] she evolved to death. The literature recommends at least combination of two antibiotics such as vancomycin, carbapenem, aminoglycosides and quinolones, to treat infections caused by this microorganism [4,6–15]. As for systemic infections, monotherapy might result in emergence of resistance [4,6–17]. But, there is no robust data to establish the proper antibiotic regime to treat infections caused by this organism.

Conclusion
Our case-report emphasizes the importance of early diagnosis and the use of 16S rRNA sequencing as a tool to confirmed the identification of species of Rhodococcus infection.

Author contribution
PSC and L ZMM data collection analysis and writing; MV B; HH and FNO data collection; FR and CR laboratory and sequencing data; VR data collection and SFC data analysis and writing.

Funding
This study was supported by the laboratory funding.

Declaration of Competing Interest
All authors declare that they have no conflict of interest.

References
[1] Yamschikov AV, Schuetz A, Lyon GM. Rhodococcus equi infection. Lancet Infect Dis 2010;10(5):350–5. doi:10.1016/S1473-3099(10)70068-2.
[2] Weinstock DM, Brown AE. Rhodococcus equi: an emerging pathogen. Clin Infect Dis 2002;34(10):137–45.
[3] Vergidis P, Ariza-heredia EF, Nellore A, et al. Rhodococcus infection in solid organ and hematopoietic stem cell transplant recipients. Emerg Infect Dis 2017;23(3):21–3.
[4] Cronin SM, Abidi MH, Shearer CJ, Chandrasekar PH, Ibrahim RB. Rhodococcus equi lung infection in an allogeneic hematopoietic stem cell transplant patient. Transpl Infect Dis 2008;10(1):48–51.
[5] Kitamura Y, Sawabe E, Ohkusu K, Tojo N, Tohda S. First report of sepsis caused by Rhodococcus corynebacteroides in a patient with myelodysplastic syndrome. J Clin Microbiol 2012;50(3):1089–91.
[6] Shahani L. Rhodococcus equi pneumonia and sepsis in an allogeneic hematopoietic stem cell transplant recipient. BMJ Case Rep 2014;1–3.
[7] Ramanan P, Desiel PJ, Razonable RR. Rhodococcus globulovarius bacteremia in an allogeneic hematopoietic stem cell transplant recipient: report of the first transplant case and review of the literature. Transpl Infect Dis 2014;16(3):484–8.
[8] Bhardwaj R, Swaminathan S, Salimnia H, Fairfax M, Frey A, Chandrasekar PH. Clinical impact of the use of 16S rRNA sequencing method for the identification of “difficult-to-identify” bacteria in immunocompromised hosts. Transpl Infect Dis 2012;14(2):206–12.
[9] Graham DW. MALDI-TOF mass spectrometry: an emerging technology for microbial identification and diagnosis. Front Microbiol 2015;6(August):1–16.
[10] Scott MA, Graham BS, Vertall R, Dixon R, Schaffner W, Tham KT. Rhodococcus equi – an increasingly recognized opportunistic pathogen. Report of 12 cases and review of 65 cases in the literature. Am J Clin Pathol 1995;103(5):649–55.
[11] Behnes CL, Neumann S, Schweyer S, Radzun HJ. Pleural malakopla caused by Rhodococcus equi infection in a patient after stem cell transplantation. Diagn Pathol 2012;7:20.
[12] Russo G, Lichtner M, Carnellini M, Mascellino MT, Mengoni F, Oliva A, et al. Primary retroperitoneal abscesses due to Rhodococcus equi in a patient with severe nephrologic syndrome: successful antibiotic treatment with linezolid and tigecycline. Int J Infect Dis 2010;14(6):e531–535.
[13] Muñoz P, Palomo J, Guinée J, Yañez J, Giannella R, Bouza E. Relapsing Rhodococcus equi infection in a heart transplant recipient successfully treated with long-term linezolid. Diagn Microbiol Infect Dis 2008;60(2):197–9.
[14] Kämpfer P, Dott W, Martin K, Glaeser SP. Rhodococcus defluviu sp. nov., isolated from wastewater of a bioreactor and formal proposal to reclassify Corynebacterium hoagii and Rhodococcus equi as Rhodococcus hoagii comb. nov. Int J Syst Evol Microbiol 2014;64(Pt 3):755–61.
[15] Majdzadeh M, Fatahi-Rafghi M. Current taxonomy of Rhodococcus species and their role in infections. Eur J Clin Microbiol Infect Dis 2018;37(11):2045–62.
[16] Sangal V, Goodfellow M, Jones AL, Schwalbe EC, Blom J, Hoskisson PA, et al. Next-generation systematics: an innovative approach to resolve the structure of complex prokaryotic taxa. Sci Rep 2016;7(6):38392.
[17] Vergidis P, Ariza-Heredia EF, Nellore A, Kotton CN, Kaul DR, Morris MI, et al. Rhodococcus infection in solid organ and hematopoietic stem cell transplant recipients. Emerg Infect Dis 2017;23(3):510–2.