Rothia mucilaginosa, an important cause of invasive disease in children with leukemia: Report of 2 cases and review of the literature

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Abstract

Rothia mucilaginosa is an opportunistic agent detected in the upper respiratory tract and oral cavity in humans. Immunocompromised hosts have more risk to develop severe infections. We present a short review and two clinical cases of Rothia mucilaginosa bloodstream infection in children with leukemia, one of them with endocarditis. Both were completely recovered. Predisposing factors for Rothia mucilaginosa infection include profound and prolonged neutropenia, use of central venous catheter, mucositis and high dose steroid. It is important to consider this bacterium as an emerging causative agent of severe infection in immunocompromised patients, especially in the presence of the mentioned factors.

INTRODUCTION

Rothia mucilaginosa is a facultative anaerobic, gram-positive, coagulase-negative bacterium from the genus *Rothia* , which belongs to the *Micrococcae* family. It can be detected as part of the oral cavity and upper respiratory tract as normal flora in humans[1].

In immunocompromised hosts, it has been implicated in serious infections, such as bacteremia, endocarditis and meningitis[2].

CASE 1

A 3 years old boy with high risk acute lymphoblastic leukemia (ALL), presented with 48 hours of fever without a source at emergency room. Three weeks earlier, he experienced febrile neutropenia and grade III mucositis (WHO scale) and persisted with profound neutropenia since then. Six days before admission, he received third consolidation cycle of chemotherapy. Laboratory tests revealed leucocytes count of 120 cells/µL (reference range, 5.5–14.5 $\times$ 10^3 cells/µL) with an absolute neutrophil count of 20 cells/µL. Hemoglobin level was 7.2 g/dL (reference range, 10.2–12.7 g/dL) and platelet count was 8 x 10^3 cells/µL (reference range, 150 – 450 x 10^3 cells/µL). C-reactive protein (CRP) level was 88.32 mg/L (reference range, <5 mg/L). He was admitted to Pediatric Intensive Care Unit (PICU) and was commenced on vancomycin and piperacillin/tazobactam after blood cultures were drawn. Peripheral blood culture was positive at 14 hours. The quantitative central and peripheral blood cultures were positive for 8 and 32 colony forming units (CFU) respectively, each for *Rothia mucilaginosa* (Figure 1). Echocardiogram showed an image suggestive of vegetation in the right atrium (11.6 mm x 15.6 mm) in relation to the central venous catheter (CVC) tip in the interatrial septum (Figure 2). CVC was removed. CVC tip and peripheral concomitant blood cultures were negative. Susceptibility evaluation was performed in Mueller Hinton Blood (MHB) Broth medium and epsilometry. *Rothia mucilaginosa* was resistant to sulphamethoxazole/trimethoprim and susceptible to penicillin, ceftriaxone, vancomycin (MIC [?] 0.5), erythromycin and clarithromycin. Piperacillin/tazobactam

was replaced by ceftriaxone. On third day of hospitalization he was transferred to the Oncology Unit. As he persisted febrile until day eight of hospitalization a bone scintigram, abdominal ultrasound and a cerebral magnetic resonance image (MRI) were performed, all resulted normal. The patient completed 6 weeks of intravenous vancomycin plus ceftriaxone with no evidence of vegetation at 38 days of treatment.

CASE 2

A 10 years old girl with early T acute lymphoblastic leukemia presented at emergency room with fever and headache. Five days before admission, she received chemotherapy corresponding to the third consolidation cycle and was neutropenic since then. Laboratory values revealed that the leucocytes count was 60 cells/µL with an absolute neutrophil count of 0 cells/µL. Hemoglobin level was 7.2 g/dL, and platelet count was 2 x 10^3 cells/µL. CRP level was 27.5 mg/L. She evolved with hypotension and was admitted to PICU. Due to previous carbapenems-resistant *Pseudomonas aeruginosa* urinary tract infection, vancomycin, meropenem and amikacin were prescribed. Peripheral blood culture was positive at 10 hours of incubation. The quantitative central and peripheral blood cultures were positive for >100 CFU, each for *Rothia mucilaginosa.*Echocardiogram was normal. Susceptibility in MHB Broth medium showed that *Rothia* was resistant to sulphamethoxazole/trimethoprim, intermediate to penicillin, and susceptible to vancomycin (MIC [?] 0.5), erythromycin and clarithromycin. She was transferred to Oncology Unit 48 hours after admission. She was afebrile after 24 hours, with negative blood cultures at 72 hours of treatment. She completed 10 days with intravenous vancomycin with no complications.

DISCUSSION

Rothia mucilaginosa was formerly known as *Staphylococcus salivarius* , *Micrococcus mucilaginosus* , and *Stomatococcus mucilaginosus* . Reclassified into a new genus belonging to the family*Micrococcaceae* in 2000 based on 16S rRNA sequencing[3]. It is an oxidase-negative, catalase-variable gram-positive coccus bacterium. Gram staining reveals non-spore-forming, encapsulated gram-positive cocci that can appear in pairs, tetrads, or irregular clusters. It is facultative anaerobic that grows well on most nonselective media and in standard blood culture systems. On sheep blood and chocolate agar, forms clear to gray/white, nonhemolytic, mucoid or sticky colonies that adhere to the agar surface[4]. Usually, it only causes dental plaque and periodontal disease[1]. Recently, cases of opportunistic infections in immunocompromised patients have been reported, including bacteremia, endocarditis, pneumonia, meningitis , peritonitis and dermatitis[2,5]. Remarkably, it has shown prominent adherence properties, which increase the colonization risk of catheters, damaged or prosthetic cardiac valves in bacteremic patients[4]. The main portal of entry is the oral cavity after mucosal disruption secondary to chemotherapy-induced mucositis or mild oral infections[6]. There are only a few reports on*Rothia mucilaginosa* infections in immunocompromised children[7]. *Chavan et al* reported that those infections were associated with profound and prolonged neutropenia, use of CVC and mucositis. 40% had active or relapsed ALL[2]. *Poyer et al* . reported the same with the addition of steroids use[1]. In pediatric patients,*Rothia mucilaginosa* bacteremia has been associated to complications in up to 45%, including meningitis, pneumonia and respiratory failure and with a 36% mortality rate in one serie[2]. In other report, there were no complications and one patient died secondary to oncology disease relapse[1]. In adults, a mortality rate of 7% has been described[8].

Rothia mucilaginosa is generally susceptible to penicillin, ampicillin, cefotaxime, imipenem, and vancomycin. It is frequently resistant to clindamycin, aminoglycosides, sulfamethoxazole/trimethoprim and ciprofloxacin. However, partial resistance to penicillin has also been reported in the literature[4,9]. Therefore, vancomycin is recommended as empirical therapy[7]. The duration of treatment will depend of the diagnosis. Bacteremia alone with good clinical response is treated for at least ten days[2].

Endocarditis has been reported in 1/29 adults with *Rothia mucilaginosa* bacteremia [8] and in prosthetic devices users[4,6]. Treatment is valve replacement and intravenous vancomycin for six weeks[4]. If valve replacement is not performed, vancomycin has been associated to gentamicin or rifampin[4]. In other *Rothia* severe infections like meningitis or septic shock, vancomycin and concomitant betalactams has been used[2].

In our first case, the patient had high risk ALL, prolonged neutropenia associated with CVC use and three

weeks of mucositis. In the context of endocarditis with persistent fever, antibiotic regimen was changed to vancomycin plus ceftriaxone. We did not use rifampin or gentamicin because the patient had a native valve endocarditis. To our knowledge, this is the first report of *Rothia* endocarditis in pediatric patients. In the second case, ALL profound neutropenia and CVC use were the predisposing factors. There was a rapid clearance of blood cultures and clinical improvement with the initial treatment. Both patients had recent use of high steroids dose and the presence of predisposing factors for *Rothia mucilaginosa* infection. However, only the first case presented with prolonged grade III mucositis, which is crucial in the physiopathology of *Rothia* bacteremia. This may influenced the complication with endocarditis.

In summary, although traditionally believed to be an organism of low virulence, *Rothia mucilaginosa* is increasingly being recognized as an emerging opportunistic pathogen in immunocompromised patients. Predisposing factors has been described. If *Rothia mucilaginosa*is isolated in blood cultures, we recommend the initial use of vancomycin until susceptibility testing results and the performance of an echocardiogram, because even if is infrequent, endocarditis is a severe complication that needs to be ruled out. Pediatricians should be aware of this organism when treating oncology pediatric patients, especially with predisposing described factors and in the context of a gram-positive bacteria bacteremia.

DECLARATION OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

REFERENCES

1. Poyer F, Friesenbichler W, Hutter C, et al. *Rothia mucilaginosa* bacteremia: A 10-year experience of a pediatric tertiary care cancer center. *Pediatric Blood & Cancer* . 2019;66(7):e27691. doi:10.1002/pbc.27691

2. Chavan RS, Pannaraj PS, Luna RA, et al. Significant Morbidity and Mortality Attributable to *Rothia Mucilaginosa* Infections in Children with Hematological Malignancies or Following Hematopoietic Stem Cell Transplantation. *Pediatric Hematology and Oncology* . 2013;30(5):445-454. doi:10.3109/08880018.2013.783893

3. Collins MD, Hutson RA, Baverud V, Falsen E. Characterization of a Rothia-like organism from a mouse: description of Rothia nasimurium sp. nov. and reclassification of Stomatococcus mucilaginosus as Rothia mucilaginosa comb. nov. *INTERNATIONAL JOURNAL OF SYSTEMATIC AND EVOLUTIONARY MICROBIOLOGY* . 2000;50(3):1247-1251. doi:10.1099/00207713-50-3-1247

4. Bruminhent J, Tokarczyk MJ, Jungkind D, DeSimone JA. Rothia mucilaginosa Prosthetic Device Infections: a Case of Prosthetic Valve Endocarditis. *Journal of Clinical Microbiology* . 2013;51(5):1629-1632. doi:10.1128/JCM.03173-12

5. Morgan EA, Henrich TJ, Jarell AD, et al. Infectious Granulomatous Dermatitis Associated With Rothia mucilaginosa Bacteremia: A Case Report: *The American Journal of Dermatopathology* . 2010;32(2):175-179. doi:10.1097/DAD.0b013e3181b1c5ad

6. Pérez-Vega C, Narváez J, Calvo G, Castro-Bohorquez FJ, Falgueras MT, Vilaseca-Momplet J. Cerebral Mycotic Aneurysm Complicating Stomatococcus mucilaginosus Infective Endocarditis. *Scandinavian Journal of Infectious Diseases* . 2002;34(11):863-866. doi:10.1080/0036554021000026956

7. Ochi F, Tauchi H, Moritani K, et al. *Rothia mucilaginosa*infection in a child with acute lymphoblastic leukemia: Ochi et al.*Pediatric Blood & Cancer* . 2017;64(1):205-206. doi:10.1002/pbc.26145

8. Abidi MZ, Ledeboer N, Banerjee A, Hari P. Morbidity and mortality attributable to Rothia bacteremia in neutropenic and nonneutropenic patients. *Diagnostic Microbiology and Infectious Disease* . 2016;85(1):116-120. doi:10.1016/j.diagmicrobio.2016.01.005

9. Pinsky RL, Piscitelli V, Patterson JE. Endocarditis caused by relatively penicillin-resistant Stomatococcus mucilaginosus.*Journal of Clinical Microbiology* . 1989;27(1):215-216. doi:10.1128/JCM.27.1.215-216.1989

LEGENDS

Figure 1 Macroscopic and microscopic appearance of *Rothia mucilaginosa.* (A) Gram staining smears from blood sample bottle cultured at 37°C for 24 hours. (B) Macroscopic appearance of *R. mucilaginosa* colonies following isolation from the patient and culture on a blood agar plate incubated at 37°C for 24 hours in CO2 atmosphere.

Figure 2 Echocardiogram that shows vegetation in the right atrium.