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Ralstonia mannitolilytica Bacteremia in an Immunocompromised Patient: Case Report and Review

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ABSTRACT: *Ralstonia mannitolilytica* is an emerging opportunist pathogen reported in many healthcare facilities over the years. We report a case with *R. mannitolilytica* bacteraemia in breast carcinoma patient with chemo port. Identification of this non fermentative, Gram negative bacilli was done by Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI TOF MS). A minireview of cases of *R. mannitolilytica* bacteremia in the recent years with special reference to those reported in India is done.

KEYWORDS: Chemo Port, Central Venous Catheter, MALDI-TOF, Opportunistic Pathogen, *R. mannitolilytica* Bacteraemia.

INTRODUCTION

The genus *Ralstonia* comprises a group of non-fermentative, Gram-negative bacteria (NFGN) found in moist environments, such as water, soil, and plants [1]. The genus Ralstonia has six species, of which *Ralstonia pickettii, Ralstonia insidiosa and Ralstonia mannitolilytica* have been recognized as opportunistic human pathogens [1]. Their relevance has been currently re-evaluated because of their ability to survive in different types of disinfectants and to pass through 0.2 µm filters that are used to sterilize solutions [1, 2]. Multidrug resistance in NFGN is widely reported in the literature and is causing increasing concern because such bacteria may have a role not only as human pathogens but also as potential reservoirs of resistance genes, particularly when they are found in hospital settings [1]. Clinical isolation of *Ralstonia* is rare in India and thus the lack of sufficient experience with its diagnosis and treatment. A case of *R. mannitolilytica* bacteraemia in post operative carcinoma breast patient is presented here along with a review of *R. mannitolilytica* bacteraemia cases and outbreaks reported in recent years to highlight the clinical, diagnostic, prognostic, and microbiologic features of this emerging pathogen for its better management in Indian setup.

CASE

A 38 years old female patient was admitted with history of one day high grade fever. She was a diagnosed case of a right sided carcinoma breast stage II and had undergone modified radical mastectomy six months before. She had one indwelling chemo port for adjuvant combination chemotherapy since four months. Patient had developed fever with chills one day after her fourth chemotherapy cycle completion. She appeared toxic, with temperature 102.8^0 F, pulse rate 106 /min, respiratory rate 28/min and blood pressure 100/60 mm Hg. Systemic examination was unremarkable. Investigations revealed a total count of 15,763/mm^3 with a neutrophilic leucocytosis 9865/mm^3, haemoglobin of 9 g/dl, platelet count of 229,000/mm^3. C-reactive protein was 9.1 mg/dL. Liver function tests, Renal function tests and urine routine examination did not show any significant abnormality. Chest-X ray showed no lung infiltration. Abdominal ultrasound revealed no alterations suggestive for infectious foci. Two sets of blood cultures were taken from the peripheral vein and chemo port. She was then put on Piperacillin-tazobactam empirically, but fever spikes persisted.

After 24 hours of incubation in automated blood culture system (BD BACTEC ™ FX Instrument, Becton Dickinson, USA), blood culture bottles flagged positive for growth. The differential time to positivity (DTP) between blood taken from chemo port and the peripheral vein was 6 hours 35 minutes. The Gram stain smears from blood culture bottles showed Gram negative, slender bacteria. Catheter tip of chemo port was processed by rolling the tip back and forth on the surface of a Columbia agar plate supplemented with 5% sheep blood, essentially as described by Maki DG, et al [3]. After 24 hours of incubation at 37°C, on sheep blood agar colonies were non hemolytic, small pinpoint, opaque, circular, and convex. Non lactose fermenting, small, convex colonies were

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observed on MacConkey agar. The isolate was motile, catalase and oxidase positive. On further biochemical testing, glucose was oxidized, urea was hydrolysed and nitrates were not reduced to nitrites. It was presumptively reported as Gram negative Nonfermenter as it was unidentified by Vitek 2 (bioMérieux, France). Subsequently, it was identified as *Ralstonia mannitolilytica* by Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI TOF MS) (bioMérieux, France) with 99.9% confidence value. Diagnosis of catheter related blood stream infection (CRBSI) caused by *Ralstonia mannitolilytica* was made. Piperacillin-tazobactam was discontinued and Imipenem was added to the treatment protocol.

Antimicrobial susceptibility testing by broth microdilution was done and interpreted as per Clinical and Laboratory Standards Institute (CLSI) M100 recommendations for ATCC *Pseudomonas aeruginosa* 27853. The isolate was found to be susceptible to Imipenem (MIC 4 μg/mL), Cefepime (MIC 4 μg/mL) and Cefoperazone/ Sulbactam (MIC $\leq$8 μg/mL). Resistance was noted for Ticarcillin/Clavulanic acid (MIC $\geq$128 μg/mL), Piperacillin/Tazobactam (MIC $\geq$128 μg/mL), Amikacin (MIC $\geq$ 64 μg/mL), Gentamicin (MIC $\geq$ 16 μg/mL), Ciprofloxacin (MIC $\geq$ 4 μg/mL), Levofloxacin (MIC $\geq$ 4 μg/mL) Colistin (MIC $\geq$ 16 μg/mL) and Intermediate susceptibility was observed for Ceftazidime (MIC 16 μg/mL). Based upon the sensitivity pattern observed, Imipenem was continued in treatment protocol. Two follow-up blood cultures were collected in the subsequent week which were negative for any bacterial growth. The patient recovered 10 days after starting therapy and bacteraemia due to the same pathogen had not recurred for more than six months.

To elucidate a source of *R. mannitolilytica* infection and to avoid outbreaks, a comprehensive environmental sampling was done including from in-use parental solutions, filled syringes, disinfectants, medical devices and water in the wards to which the patient had been admitted. Swabs were cultured in Tryptic Soy Broth, incubated for 48 hours at 37°C, and plated on chocolate agar and blood agar but yielded negative results. All microbiological data of hospital were reviewed, but no *Ralstonia spp*. have been matched in the last two years.

DISCUSSION

Nonfermenting Gram-negative rods are one of the commonest causes of nosocomial infections in clinical environments. The major opportunistic pathogens in this group are *Acinetobacter baumanii*; *Stenotrophomonas maltophilia* and other oxidase-positive bacteria such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* [4]. *R. mannitolilytica* is another emerging opportunistic pathogen which was previously referred as *Pseudomonas thomasii* and *R. pickettii biovar 3/thomasii* [4]. It has been reported in nosocomial outbreaks secondary to medical devices, equipment, water, or parenteral solutions contamination [5, 6]. It has been isolated in newborns and in patients with solid cancer, hematological disease, ventriculoatrial draining for hydrocephalus, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus and scleroderma [7]. Globally, the first reported outbreak of *R. mannitolilytica* was of 30 patients from USA in 2005 [8]. Since then, many outbreaks and cases have been reported. In India, very few cases of bacteremia with *R. mannitolytica* have been reported. The first case reported in India was in a renal transplant patient by Mukhopadhyay et al in 2003 [9].

R. mannitolilytica grows readily on routine culture media i.e. trypticase soy agar with 5% sheep blood or Mac Conkey agar. However, when both biochemical tests and automated identification systems are used, *Ralstonia spp*. can be misidentified as *Burkholderia spp*. or non-aeruginosa *Pseudomonas spp*. [10]. *R. mannitolilytica* can be differentiated from *Pseudomonas spp*. and *Burkholderia spp*. by arginine dihydrolase test and pyrrolidonyl peptidase test [11]. The diagnostic methods used for identification are either ViTek 2 system with 16sRNA gene sequencing (molecular methods), PFGE or MALDI-TOF [12]. We identified *Ralstonia mannitolilytica* by MALDI TOF MS.

The most important source of infection is contaminated medical products during the manufacturing phase as the bacteria can pass through 0.2 µm filters during the sterilization process [1]. Colonization of medical devices like hemodialysis machine, bronchoscope, etc. and contamination of tap water, sterile water, saline solution, etc. are also major reasons for infections cases caused by *Ralstonia spp*. [11, 13]. Use of contaminated solution leading to biofilm formation which allowed adherence to central venous catheter (CVC) followed by its dissemination during the flushing process might be a possible cause of infection. In the cases reported by Lucarelli et al, Lim et al and Boattini et al, CVC was found to be the source of infection [5,13,14]. Whereas, in the study by Shankar et al the use of sterile water for IV drug preparation was the culprit [12]. Said M et al reported water in the dialysis system as the source of *R. mannitolilytica* [15]. In our case, as all the samples from disinfectants, antiseptics and saline solutions

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were not available for microbiological investigation when the isolate was identified, we probably missed the exact source of infection. However, vigilant monitoring for successive months prevented further cases.

The comprehensive minireview of literature of *R. mannitolilytica* bacteraemia in recent years was performed and depicted in the table 1 which shows demographic, clinical, diagnostic and prognostic features of 84 cases of *R. mannitolilytica* bacteraemia. No age or gender predilection was found. *R. mannitolytica* bacteremia presents with symptoms of sepsis like any other pathogenic organism i.e. high grade fever, chills and neutrophilic leukocytosis. Majority of the patients were neonates, immunodeficient with frequent hospital visits or indwelling devices [4,5,10, 12-23].

R. mannitolilytica is known to have multidrug resistance although carbapenem resistance is not reported enough [24]. A combination of ciprofloxacin and trimethoprim-sulfamethoxazole is considered as the first-choice antibiotics in the treatment of *R. mannitolilytica* infection. Other treatment recommendations include third- generation cephalosporins or carbapenems [18]. In a case of infective endocarditis by *R. mannitolilytica*, carbapenems were found resistant and isolate was susceptible to only ciprofloxacin and co-trimoxazole. After two weeks of therapy, ciprofloxacin was found resistant thus showing the capacity of the organism to acquire resistance [19]. The isolate in our case was found susceptible to imipenem, cefepime and cefoperazone/ sulbactam. Similar susceptibility pattern was reported by Souza DC et al and Zhou S et al [17,20]. On the contrary, the strains identified in oncology ward of Italy were resistant to ceftazidime, meropenem, fluoroquinolones, aminoglycosides but were susceptible to piperacillin/tazobactum [13]. Certain studies did molecular testing for resistant genes. Lucarelli et al found the *R. mannitolilytica* strains to be having AmpC B-lactamase, OXA-443 and OXA-444 [13]. Whole Genome Sequencing (WGS) of *R. mannitolilytica* strain isolated in Basso et al had OXA-22, OXA-443 and OXA-444 genes [18]. Persistent fever even after adding antibiotics mandated removal of chemo port in some studies like Chitre et al [23]. This hints towards biofilm formation in the chemo port and the need towards checking long standing indwelling devices. Biofilm provides a protective environment which helps in evasion from bactericidal effects of the antibiotics. Although, reported isolates were multidrug resistant, it was found that cases of *R. mannitolilytica* bacteraemia show favorable prognosis as in our case and the review table (81/84 recovered).

It is now evident that there is increased incidence of *Ralstonia* infections in healthcare settings, particularly in vulnerable patients who need continuous IV access, hemodialysis, nebulisations, etc. This is a major concern especially for Indian setup is underreporting of such cases due to inability of routine microbiological methods to identify *Ralstonia spp.* and further emergence of multi-resistant strains of *R.mannitolytica* add to the existing burden.

Table 1– Demographic, Clinical, Diagnostic and Prognostic Findings

Reference	Country	Age	Clinical presentation	Healthcare setting	Identification system	Source of infection	Treatment	Outcome
Liu CX et.al. 2016 [16]	China	3 cases	Fever with chills, septic shock	Oncology ward	VITEK Compact-2 (bioMerieux Inc., Marcy L'Etoile, France), PFGE	Not found	Cotrimoxazole ,Ceftriaxone, Tazocin	Recovered
Lucarelli et al. 2017 [13]	Italy	22 cases	Cancer treatment	Oncology ward	Vitek 2 (bioMérieux, Florence, Italy), 16S rDNA sequencing	CVC (18 patients) Undetermined (4 patients)	Piperacillin/ tazobactum	Recovered

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Lim CTS et al. 2017 [5]	Malaysia	65/F	Fever with chills and rigors	Hemodialysis unit	Not reported	CVC	Ceftazidime	Recovered
Shankar et. al. 2018 [12]	India	5 cases	Fever with chills, tachycardia, hypertension, fatigue, loss of appetite	Hemodialysis unit	Not given	Sterile water for IV drug preparation	Fluoroquinolones, Cefepime, cefoperazone/ sulbactum	Recovered 1 died
Souza DC et.al. 2018 [17]	Brasil	3 cases	Sepsis	NICU	Vitek 2, 16S rDNA sequencing and PFGE	Not found	Cefepime, Meropenem, Vancomycin	Recovered
Boattini et al. 2018 [14]	Italy	44/M	Fever with chills	ICU	16S rRNA sequencing	CVC	Cefepime25	Recovered
Basso M et.al. 2019 [18]	Italy	46/F	Fever	ICU	MALDI TOF MS (bioMérieux), 16S rDNA gene sequencing	Not found	Cotrimoxazole, ciprofloxacin	Recovered
Owusu M et.al. 2019 [4]	Ghana	2/F	Sepsis	OPD	API-20NE (bioMérieux, Florence, Italy), 16S rDNA sequencing	Not given	Cefuroxime	Recovered
Chitre G et al. 2019 [23]	India	6 cases	Fever with chills, loss of appetite, generalized weakness	Oncology ward	VITEK 2 system (BioMérieux)	Not found	Piperacillin tazobactum, Levofloxacin	Recovered
Said M et.al. 2020 [15]	South Africa	16 cases	Sepsis	Hemodialysis center	Vitek 2 (bioMérieux, Florence, Italy), ERIC-PCR	Water in dialysis system	Not reported	15 recovered, 1 died
Carreira M et.al. 2020 [19]	Portugal	60/ M	Infective Endocarditis	Hemodialysis center	Not given	CVC or aortic valve	Cotrimoxazole, Ciprofloxacin (later found resistant)	Died (co-morbidities and co-infections)

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Zhou S et.al. 2021 [20]	China	25/ F	Fever, hypotension, sepsis	ICU	Not given	Not found	Imipenem/ cilastatin, cefoperazone/ sulbactum	Recovered
Rajendran UD et al. 2021 [21]	India	4 cases	Sepsis	NICU	-	Not found	Fluoroquinolones, cotrimoxazole	Recovered
Tu J et.al. 2021 [22]	China	48/ M	Sepsis and multiple organ dysfuntion syndrome	Proctology department	Bruker MALDI-TOF MS	Not found	Levofloxacin, ceftriaxone	Recovered
Ramani VK, et al. 2021 [10]	India	17 cases	Chemotherapy cycle	Oncology hospital	ViTek 2 Compact system (Biomeriux)	Not found	Cefoperazone sulbactum, ceftazidime, meropenem	Recovered
Present study	India	38/F	Chemotherapy cycle	Oncology hospital	MALDI-TOF MS	Not found	Imipenem	Recovered

CVC: Central venous catheter; ICU: Intensive care unit; NICU- Neonatal Intensive care unit; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry.

CONCLUSION

R. mannitolilytica might be more widely distributed than previously thought and targets the immunocompromised and in-vivo device patients. The chemo port was probably inhabited with the strain. Although the source of infection was not sought, correct identification and antimicrobial susceptibility pattern was found essential in the recovery of patient. Active surveillance and multicentric studies to standardise the MICs for *Ralstonia spp*. are therefore recommended.

REFERENCES

1. Ryan MP, Adley CC. 2014. Ralstonia spp.: emerging global opportunistic pathogens. Eur J Clin Microbiol Infect Dis.
2. Gröbner S. 2002. Monoclonal outbreak of catheter-related bacteraemia by Ralstonia mannitolilytica on two haemato-oncology wards. *J Infect.*
3. Maki DG, Weise CE, Sarafin HW. 1977. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med.
4. Owusu M, Acheampong G, Annan A, Marfo KS, Osei I, Amuasi J, et al. 2019. *Ralstonia mannitolilytica* sepsis: a case report. Journal of Medical Case Reports.
5. Lim CTS, Lee SE. 2017. A rare case of *Ralstonia mannitolilytica* infection in an end stage renal patient on maintenance dialysis during municipal water contamination. *Pak. J. Med. Sci.*
6. Block C., Ergaz-Shaltiel Z., Valinsky L., et al. 2013. Déjà vu: *Ralstonia mannitolilytica* infection associated with a humidifying respiratory therapy device, Israel, June to July 2011. *Euro. Surveill.*
7. Coman I., Bilodeau L., Lavoie A., et al. 2016. *Ralstonia mannitolilytica* in cystic fibrosis: A new predictor of worse outcomes. *Respir. Med. Case. Rep*.
8. Jhung MA, Sunenshine RH, Noble-Wang J, Coffin SE, St John K, Lewis FM, et al. 2007. A national outbreak of *Ralstonia mannitolilytica* associated with use of a contaminated oxygen-delivery device among pediatric patients. *Pediatrics.*
9. Mukhopadhyay C., Bhargava A., Ayyagari A. 2003. Ralstonia mannitolilytica infection in renal transplant recipient: first report. *Indian J Med Microbiol.*

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10. Ramani VK, Ganesha DV, Sarathy V, Bhattacharjee S, Ganeshan S and Naik R. 2021. Outbreak of *Ralstonia mannitolilytica* infection at a Tertiary care Oncology Center in South India: A case series. Asian Pacific Journal of Cancer biology.
11. Vaneechoutte M., De Baere T., Wauters G., Steyaert S., Claeys G., et al. 2001. One Case Each of Recurrent Meningitis and Hemoperitoneum Infection with Ralstonia mannitolilytica. Journal of Clinical Microbiology.
12. Shankar M, Rampure S, Siddhi V and Ballal HS. 2018. Outbreak of *Ralstonia mannitolilytica* in hemodialysis unit: A case Series. Indian Journal of Nephrology.
13. Lucarelli C., Di Domenico E.G., Toma L., et al. 2017. *Ralstonia mannitolilytica* infections in an oncologic day ward: description of a cluster among high-risk patients. Antimicrobial Resistance & Infection Control.
14. Boattini M, Bianco G, Biancone L, Cavallo R and Costa C. 2018. Ralstonia mannitolilytica bacteraemia: a case report and literature review. *Infez Med.*
15. Said M, Tulleken WH, Naidoo R, Mbelle N and Ismail F. 2020. Outbreak of *Ralstonia mannitolilytica* bacteremia in patients undergoing haemodialysis at a tertiary hospital in Pretoria, South Africa. Antimicrobial Resistance & Infection Control.
16. Liu CX, Yan C, Zhang P, Li FQ, Yang JH, Li XY. 2016. *Ralstonia mannitolilytica*-induced septicemia and homology analysis in infected patients: 3 Case Reports. *Jundishapur. J. Microbiol.*
17. Souza DC, Palmeiro JK, Maestri AC, Cogo LL, Rauen CH, Graaf ME, et al. 2018. *Ralstonia mannitolilytica* bacteremia in a neonatal intensive care unit. Journal of Brazilian Society of Tropical Medicine.
18. Basso M, Venditti C, Raponi G, Navazio AS, Alessandri F, Giombini E, et al. 2019. A case of bacteraemia by *Ralstonia mannitolilytica* and *Ralstonia picketti* in an intensive care unit. Infection and Drug Resistance.
19. Carreira M, Gomes C, Silva M and Duro R. 2020. *Ralstonia mannitolilytica* endocarditis: A case report. ID Cases.
20. Zhou S, Tang D, Wei S, Hu Z, Wang X and Luo D. 2021. *Ralstonia mannitolilytica* sepsis after elective caesarean delivery: a case report. BMC Pregnancy and Childbirth.
21. Rajendran UD, Sundaramoorthy S and Sethuraman G. 2021. *Ralstonia mannitolilytica* sepsis in neonatal intensive care unit – Be(a)ware of the multidrug resistant nosocomial bug. Tropical Doctor.
22. Tu J, Tu L, Jiang Y, Fu H, Mai Z, Wu X and Xu B. 2021. Sepsis due to bloodstream *Ralstonia mannitolilytica* treatment of parianal abscess: A case report. Infection and Drug Resistance.
23. Chitre G, Sirsath N. 2019. Ralstonia mannitolilytica outbreak in a day care oncology ward. J Patient Saf Infect Control.
24. Dotis J, Printza N, Orfanou A, Papathanasiou E, Papachristou F. 2012. Peritonitis due to Ralstonia mannitolilytica in a pediatric peritoneal dialysis patient. *New Microbiol.*

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