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Ralstonia mannitollylitica endocarditis: A case report

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ABSTRACT

Ralstonia mannitolilytica (*R. mannitolilytica.*) is an emerging aerobic Gram-negative bacteria causing infection among immunocompromised patients. *R. mannitolilytica*, has been described in hospital outbreaks, mainly as bloodstream infection, but also as meningitis, hemoperitoneum infection and post renal transplant infection. We describe the first reported case of *R. mannitolilytica* infective endocarditis.

Introduction

Ralstonia spp. are aerobic Gram-negative non-fermentative bacteria that can be found in water and soil, now emerging as an opportunistic pathogen causing infection among immunocompromised patients [1]. *Ralstonia mannitolilytica (R. mannitolilytica)* has been previously associated with bloodstream infection [2–4]

We report a rare case of persistent *R. mannitolytica* bacteremia which lead to the diagnosis of infective endocarditis (IE).

Case

A 60 year-old man with a past medical history of alcoholism and chronic liver disease (Child-Pugh A), secondary insulin-dependent diabetes *mellitus* and diabetic nephropathy with end-stage renal disease (ESRD), began intermittent hemodialysis eight months before admission, initially through a right jugular central venous dialysis catheter. Since he presented fever, blood cultures were performed and *R. mannitolilytica* was isolated. The patient was treated with ceftazidime for two weeks and central venous catheter was removed, presenting then a functional right brachial arteriovenous fistula. Transthoracic and transesophageal echocardiograms were negative for signs of endocarditis. However, fever persisted, as well as positive blood cultures for Gram-negative bacilli, so the patient was admitted to further investigation.

The patient reported no complaints, physical examination was unremarkable, and chest radiograph and abdominal ultrasound showed no signs of infection. Another transesophageal echocardiogram (Fig. 1) was performed, presenting now a large and fistulized abscess located close to the left coronary cusp, with a continuous shunt directed towards the left atrium and part of its content protruding on the left ventricle outflow tract. The aortic valve was functionally bicuspid and showed moderate regurgitation. As such, the diagnosis of infective endocarditis was established, according to the modified Duke criteria.

The persistently isolated *R. mannitolilytica* was resistant to beta-lactam antibiotics (including carbapenems) and colistin, being only sensitive to trimethoprim/sulfamethoxazole (TMP-SMX) and ciprofloxacin. The patient was treated with ciprofloxacin (400 mg after dialysis on dialysis days) and TMP-SMX (5 mg/kg/day of the TMP component, after dialysis on dialysis days) in combination for two weeks, with decreasing fever spikes, but maintaining positive blood cultures. In subsequent blood cultures, sensitivity tests showed resistance to ciprofloxacin (minimum inhibitory concentration = 4 mg/L, EUCAST breakpoint) but still susceptibility to TMP-SMX (minimum inhibitory concentration of 0,5 mg/L, EUCAST breakpoint). The patient continued treatment exclusively with a higher dose of TMP-SMX of 15 mg/kg/day of the TMP component after dialysis, on dialysis days.

Contrast-enhanced cardiac computed tomography (Fig. 2) suggested a contained rupture of a pseudoaneurysm in the aortic angle, measuring 27 × 15 mm on axial and 25 mm on coronal planes, in close relation to the left sinus of Valsalva (immediately inferior), its neck located 16 mm from left coronary ostium origin. The patient was referred for cardiothoracic surgery, which was performed at 36th day in-hospital, with incision and drainage of perivalvular abscess, closure of fistula to the left atrium, closure of abscess with bovine pericardium and replacement of the aortic valve with bioprosthetic valve. Aortic valve culture isolated *R. mannitolilytica* with similar MIC for TMP-SMX. After surgery, three

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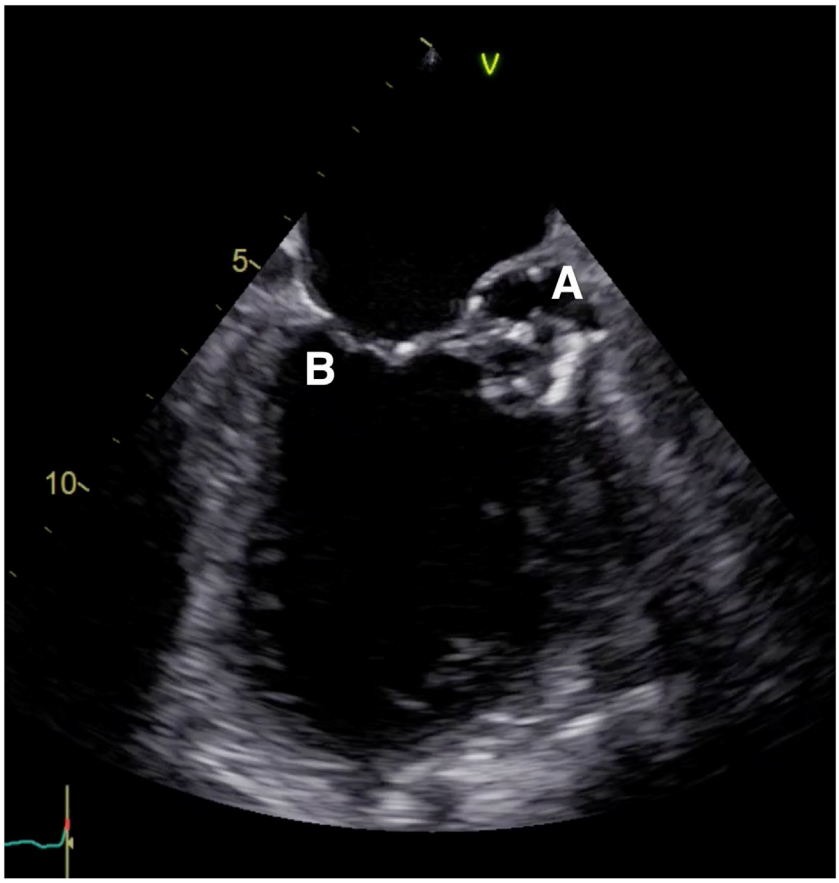

Fig. 1. Transesophageal echocardiogram (TTE) in Midesophageal Long-Axis view (ME LAX) showing an aortic valve involved by endocarditis (A). Note that the mitral apparatus (B) doesn't show any signs of involvement.

sets of blood cultures were negative. Because of large-volume pericardial effusion with cardiac tamponade, the patient was submitted to pericardiotomy nine days later and transesophageal echocardiogram performed during surgery showed a normofunctioning aortic valve and no vegetations or fistulas. Although he had persistently negative blood cultures after the first surgical intervention, he could not be weaned off vasopressors nor continuous venovenous hemofiltration, maintaining high serum inflammatory markers and altered mental status. Blood cultures collected on 23rd day of antibiotics after the first negative blood cultures, showed growth of yeasts, later identified as *Candida albicans*. The patient started treatment with caspofungin but died two days later.

Discussion

Infection due to *Ralstonia* spp. is becoming more prevalent mainly due to three bacterial species: *Ralstonia pickettii, Ralstonia insidiosa and Ralstonia mannitolilytica* [1]. Usually isolated in water and soil samples, these bacteria are widespread in many different types of water supplies, including hospital water supplies [1]. *Ralstonia* spp. persists in sterile solutions due to its ability to grow and survive over a wide range of temperatures (15–42 °C) and pass through both 0.2 and 0.45 μm filters, which are used to filter-sterilize medical solutions [5].

R. mannitolilytica, has been described in a few hospital outbreaks, mainly as bloodstream infection [2–4], but also as meningitis [6], hemoperitoneum infection [6] and post renal transplant infection [7]. All patients with previously reported *R. mannitolytica* infection recovered completely [2–4,6,7].

There have been only two previous reports of endocarditis associated with *Ralstonia* spp [8,9]. Both patients had bloodstream infection thought to be associated to an indwelling catheter or intravenous drug abuse. Both patients died. To the best of our knowledge this is the first reported case of *R. mannitolilytica* infective endocarditis

Risk factors for *Ralstonia* infection are not well established but appear to include immunocompromised patients, indwelling devices and neonates [1]. Our patient had a few predisposing factors that could facilitate *Ralstonia* infection Firstly, he was diabetic, presented chronic liver disease Child-Pugh A and had a central venous catheter placed for intermittent hemodialysis eight months earlier. Although previous outbreaks have implicated hemodialysis machines, this was an isolated case. On the other hand, he was later found to have a bicuspid aortic valve which is a well-known risk factor for infective endocarditis and associated complications such as valve destruction and abscess formation [10].

There is no standardized empirical treatment for *Ralstonia* infection and data about antimicrobial susceptibility is scarce. *R. mannitolilytica* is intrinsically resistant to colistin with variable susceptibility to ceftazidime, cefepime, carbapenem and aminoglycosides [11]. In previously reported cases, all *R. mannitolilytica* associated bloodstream infection showed susceptibility to sulfamethoxazole-trimethoprim and most of the strains appeared susceptible to fluoroquinolones, cefotaxime and piperacillin-tazobactam [11].

When the patient first presented to our hospital he had already been treated with ceftazidime for two weeks. Isolated *R. mannitolilytica* was resistant to all beta-lactam antibiotics, being

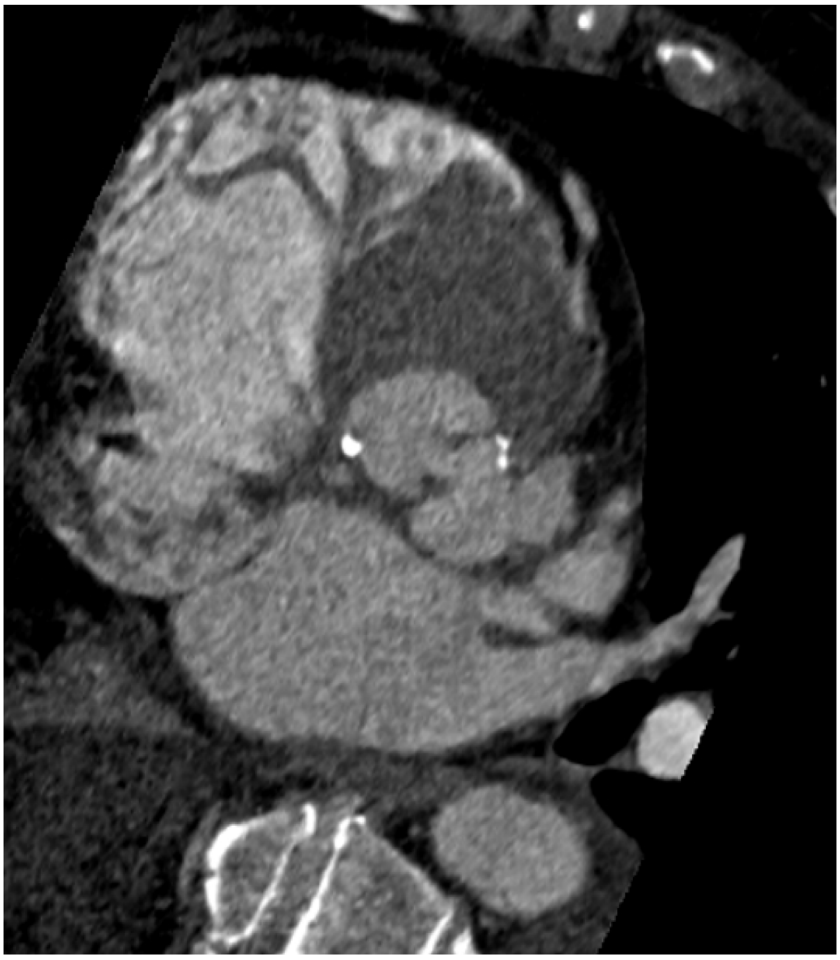

Fig. 2. Contrast-enhanced cardiac computed tomography showing a contained rupture of a pseudoaneurysm in the aortic angle.

only sensitive to TMP-SMX and ciprofloxacin. Similarly to standardized Gram negative infective endocarditis treatment we chose to treat the patient with two antibiotics, each from a different antimicrobial class, which allows for two different mechanisms of bacterial killing. TMP-SMX is a combination antibiotic comprised of a dihydrofolate reductase inhibitor and a folic acid synthesis inhibitor that block sequential steps in folic acid synthesis in susceptible bacteria. The usual dose is 5–10 mg/kg q6–12 hours, based on the TMP component, although higher doses are recommend when treating nocardiosis or *Pneumocystis* pneumonia. In dialysis patients the usual dose is 5–10 mg/kg q24hours after dialysis on dialysis days. We chose to start with a smaller dose giving the risk of intolerance and the uncertainty of the correct dosage. However, once resistance to ciprofloxacin was documented and considering the high risk of failure, we adjusted to a higher dose to improve the chances of cure with close monitoring of possible side effects.

Surgery was initially delayed for it was perceived to be of high risk due to the patient's functional status and comorbidities (ESRD and chronic liver disease).

However, *R. mannitolilytica* easily acquires antimicrobial resistance, as emphasized by our case in which it gained resistance to ceftazidime and ciprofloxacin after being exposed to these drugs for two weeks. Persistent bacteremia despite appropriate treatment prompted surgery, which appeared to efficiently control infection. Unfortunately the patient died due to complications of surgery and fungemia.

This case highlights a very rare form of infection due to *Ralstonia* spp. Endocarditis was initially deemed unlikely because ETT had no evidence of vegetations or *de novo* valvular changes and *Ralstonia* spp is not a typical agent of IE. However, the diagnosis of IE was later established and *R. mannitolilytica* acquired progressive resistance to the antibiotics. This case illustrates that despite its rarity *Ralstonia* infection should be considered and managed appropriately, especially in ESRD patients.

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Ethical approval

Patient family's written consent has been obtained before writing and submitting this manuscript.

CRediT authorship contribution statement

Marta Carreira: Writing - original draft, Writing - review & editing. **Clara Gomes:** Writing - review & editing. **Margarida Silva:** Writing - review & editing. **Raquel Duro:** Supervision.

Declaration of Competing Interest

The authors of this manuscript have no conflicts of interests.

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