Title: *Aerococcus urinae* causing infective endocarditis in a patient with Down's syndrome with ventricular septal defect

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Key Clinical Message

We report a Down's syndrom with unknown ventricular septal defect with infective endocarditis due to *Aerococcus urinae*. It is a rare cause associated with high risk of embolic event. Risk factors are advanced age and urogenital comorbidities

Introduction

Aerococcus urinae is a gram-positive cocci rare in infective endocarditis[1]. It is associated with a high risk of an embolic event[2]. Its isolation and identification can be tricky and its impact probably underestimated. The best known risk factors are advanced age and urogenital comorbidities[1].

We report the case of a 46-year-old male with Down's syndrom referred for a prolonged fever for 6 weeks. Transthoracic ultrasound reveals the presence of mitral vegetation suggestive of infective endocarditis. Aerobic and anaerobic blood cultures return positive for *A. urinae*, cytobacteriological examination of urine remains sterile. The patient underwent antibiotic treatment with amoxicillin and heart surgery with valve replacement. He had an unknown ventricular septal defect.

Clinical report

A 46-year-old patient with trisomy 21 was referred by his attending physician and admitted to the hospital for prolonged fever and biological inflammatory syndrome. For 6 weeks he has had persistent fever, chills and sweats without diagnostic. Empirical antibiotic treatment using ciprofloxacin failed. The patient has a history of Down's syndrome, grade 3 obesity, benign systolic murmur and hyperuricemia with acute gout attack. The patient does not present with any identified cardiac pathology, the last cardiac ultrasound dating from 2018 was normal. The patient works in a specialized institute, is independent and lives with his parents. He weighs 123kg with a body mass index of 42.

The clinical examination on admission found: hyperthermia at 38 °, a grade 2 systolic murmur. He was dyspneic on exertion and described sternal chest pain during peaks of hyperthermia. The patient does not present any functional urinary or digestive signs. The examination does not find any sign of severe sepsis or cardiac decompensation. ECG on admission was normal.

The biological assessment of entry finds an inflammatory syndrome with a CRP at 170 mg / l without hyperleukocytosis, a fibrinogen at 4.70 g / l, D-dimers increased to 2.76 ng / l (laboratory standard <0.7 ng / l), troponin increased to 45 ng / l (laboratory standard <17 ng / l) with BNP at 97 pg / ml (laboratory standard at <100 pg / ml).

In the first 48 hours, 9 series of blood cultures were taken during fever peaks or systematically (BactAlert Virtuo, bioMerieux). All the aerobic and anaerobic vials showed bacterial development of *A. urinae* with time-to-positivity between 28 and 35h. Identification was carried out by MALDITOFF-type mass spectrometry (Microflex, Brucker Daltonics coupled with FlexControl software).

The antibiogram confirms a sensitivity to penicillin G (MIC <0.016 mg / L), amoxicillin (MIC <0.016 mg / L), cefotaxime (MIC <0.016 mg / L) and tetracyclines, macrolides, vancomycin, ciprofloxacin, aminoglycosides. The cytobacteriological urinalysis performed on admission was sterile. The search for emerging uropathogens was carried out by inoculating a blood agar incubated 48 hours under CO_2.

Transthoracic echocardiography finds a 23 mm mobile mitral valve vegetation with grade 2 mitral regurgitation.

The computed tomography pulmonary angiogram did not find pulmonary emboli or pleural effusion. Contrast computed tomography of abdomen and pelvis found hepatic steatosis and thickened bladder walls suggesting cystitis. Contrast computed tomography of the brain did not find septic emboli. Transesophageal echocardiography confirms the presence of 25mm mitral vegetation, mitral regurgitation with ventricular septal defect.

Therapeutic:

Initial antibiotic treatment with amoxicillin 9g / 24h + amoxicillin / clavulanic acid 6g / 24h + gentamycin 360 mg / 24h was initiated. In front of a mitral dysfunction with a large mouthpiece, the patient was transferred to cardiac surgery for surgical management.

On day 4, the patient had a myocardial infarction with obstruction of the right coronary artery. He benefited from a cardiac stent insertion.

On day 6, acute mitral dysfunction with a large embolus, lead to cardiac surgery with prosthetic mitral valve implementation (figure 1).

On day 10, the patient presented third-degree atrioventricular block treated permanent pacemaker implantation.

The antibiotic treatment was adapted on day 12 with amoxicillin 15g / 24h.

Discussion

A. urinae is generally non-virulent and involved in 0.15 - 0.8% of urogenital infections[3,4]. The predisposing factors are male sex, an age over 65 and urogenital pathology (enlarged prostate, history of urinary tract infection or urological surgery)[3,5,6]. The natural habitat of the aerococci pathogen is unknown but it is considered to be part of the commensal flora of the urinary tract [5].

More than 50% of patients with Down's syndrome are carriers of a congenital heart defect. The most common is atrial septal defect followed by ventricular septal defect (25% of congenital heart disease)[7]. Patients with ventricular septal defect are 11 to 15 times more likely to have infective endocarditis compared to the general population[8].

Ventricular septal defect is responsible for a left-to-right shunt causing pulmonary hypertension with the risk of pulmonary arterial hypertension. This malformation is at moderate risk of endocarditis and antibiotic prophylaxis is not recommended[7]. Good skin and dental hygiene remains essential for patients with ventricular septal defect[7].

Few cases of endocarditis caused by *A. urinae* are described: 50 cases described in the literature[9], around 2 new case reports per year on Medline and Pubmed[1]. However its incidence is often underestimated because this pathogen can be confused by these microscopic characteristics with a staphylococcus or a streptococcus[3,5,6]. We recall the importance of the realization of blood cultures by respecting the rules of asepsis and filling of vials, only guarantors of a sensitivity and specificity of detection of bacterium. In case of negative blood culture *A.urinae* can be detected by genomic detection of 16sRNA[1,4]. Genomic sequencing of 16S ribosomal RNA is the gold standard for identifying *A. urinae*, but this technique is expensive, slow, and impractical by most laboratories in clinical practice[5]. Endocarditis caused by *A. urinae* is rare and associated with high mortality[4]. Its virulence is explained by its ability to form a biofilm and by its platelet aggregating action[1,2]. The damage is mainly to the aortic valve followed by the mitral valve[5]. Because of the high risk of embolism, prompt

treatment should be initiated. There is no consensus regarding the antibiotic treatment, its duration and its doses. *A. urinae* is almost always sensitive to penicillin, amoxicillin, carbapenems and aminoglycosides[4]. According to the literature, patients with native valve endocarditis should be treated with intravenous beta-lactams[1] for 4 weeks and aminoglycosides for at least the first 14 days[5]. In case of penicillin allergy, vancomycin or daptomycin can be used in combination with gentamycin[5]. Cardiac surgery should be performed as soon as possible if indicated[1]. The indications are: infectious endocarditis on prosthetic valve, severe valve dysfunction, large vegetation, abscess.

Conclusion

A.urinae is a rare pathogen involved in infectious endocarditis[3,5]. Its frequency is underestimated because its detection can be tricky[3]. The main risk factors are age and urogenital pathologies[3,4]. More studies are needed to determine the true incidence, optimal treatment, and prognosis of systemic *A.urinae* infections. Interventricular communication is present in more than 25% of patients with Down's syndrome, this congenital heart disease makes them particularly vulnerable to infectious endocarditis[8, 10]. It is the role of the attending physician to carefully monitor any sepsis or bacteremia in these patients.

Conflict of interest

No declared

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Author contribution

Valentine LIETAERT : drafted and wrote the article

Georgeta CORNEA: reviewed the article and provided guidance and helpful feedback on the draft

Perrine KUCZERA-NAESSENS : reviewed the article

Alexandre MONTMUREAU : reviewed the article

Gisèle DEWULF : reviewed the article, particularly the microbiological aspects

Arnaud DZEING ELLA : Revised it critically and provided suggestions for final preparation of the manuscript.

All the authors agreed the final version of the draft

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Figure legend

Figure 1 : Mitral vegetation ablation