

First Report of *Granulicatella* sp. Endocarditis in a Kidney Transplant Patient

Relato do primeiro caso de Endocardite por *Granulicatella* sp. em transplantado renal

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ABSTRACT

Granulicatella and *Abiotrophia* are genera of fastidious Gram-positive cocci commensal of the oral, genitourinary, and intestinal flora. We report the first case of infective endocarditis caused by *Granulicatella* sp. in a kidney transplant recipient. A 67-year-old male kidney transplant recipient was admitted to the hospital for investigation of fever, abdominal pain, and diarrhea. On physical examination, he was dehydrated. Laboratory tests identified impaired renal function (creatinine level of 15.5 mg/dl; reference, 3.0 mg/dl), metabolic acidosis, and electrolyte disturbances. *Cryptosporidium* sp. was identified as the cause of the diarrhea, and the infection was treated with nitazoxanide. On admission, cultures of blood, urine, and stool samples were negative. Echocardiography results were normal. Despite the antimicrobial treatment, the fever persisted. A transthoracic echocardiogram revealed infective endocarditis of the mitral valve, and *Granulicatella* spp. were isolated in blood cultures. Although the patient was treated with penicillin and amikacin, he evolved to septic shock of pulmonary origin and died. Infective endocarditis caused by *Granulicatella* sp. should be suspected in cases of culture-negative endocarditis.

Keywords: endocarditis; endocarditis, bacterial; kidney transplantation.

RESUMO

Granulicatella e *Abiotrophia* são gêneros de cocos gram-positivos fastidiosos comensais das floras oral, genitourinária e intestinal. Relatamos o primeiro caso de endocardite infecciosa por *Granulicatella* sp. em paciente transplantado renal. Paciente do sexo masculino, 67 anos, foi admitido no hospital para investigação de febre, dor abdominal e diarreia. Ao exame físico encontrava-se desidratado. Exames laboratoriais identificaram piora de função renal (creatinina: 15,5mg/dL – níveis basais: 3mg/dL), acidose metabólica e distúrbios eletrolíticos. *Cryptosporidium* sp foi identificado como causa da diarreia e tal germe foi tratado com nitazoxanida. À admissão, hemoculturas, urocultura e coprocultura negativas além de ecocardiograma normal. A despeito do tratamento antimicrobiano, paciente persistiu febril. Um ecocardiograma transtorácico posterior foi realizado, revelando endocardite em válvula mitral, sendo então identificada em hemocultura *Granulicatella* sp. Apesar do tratamento com penicilina e amicacina, o paciente evoluiu com quadro de choque séptico de foco pulmonar e óbito. Endocardite infecciosa por *Granulicatella* sp. deve ser suspeitada em casos de endocardite com hemoculturas negativas.

Palavras-chave: endocardite; endocardite bacteriana; transplante de rim.

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INTRODUCTION

The genera *Granulicatella* and *Abiotrophia* are fastidious Gram-positive cocci previously classified as nutritionally variant streptococci (NVS).¹⁻⁵ These bacteria belong to commensal flora of the oral cavity, genitourinary tract, and intestinal tract, potentially producing severe infections in immunocompetent and immunosuppressed patients.^{1,2} Here, we report the first case of infective endocarditis caused by *Granulicatella* sp. in a kidney transplant recipient.

CASE REPORT

A 67-year-old man with arterial hypertension, dyslipidemia, coronary disease, and chronic renal failure received a kidney transplant from a deceased donor in 2008. In the first post-transplant year, he was treated three times for invasive cytomegalovirus reactivation (esophagitis, colitis, and viral replication at the graft site). He subsequently developed graft dysfunction and had a basal creatinine level of 3.4 mg/dl (Modification of Diet in Renal Disease equation-estimated glomerular filtration rate, 19 ml/min/1.73m²).

Six years after transplantation, while under maintenance immunosuppression therapy with prednisone, tacrolimus, and everolimus, he was admitted to the emergency room with a two-week history of aqueous diarrhea (20 movements per day), together with abdominal pain, loss of appetite, nausea, vomiting, and episodes of fever up to 38.6°C. On physical examination, the patient was dehydrated and tachycardic (heart rate, 120 beats per minute), with an arterial pressure of 125/95 mmHg, diffuse abdominal pain, and no signs of peritonitis.

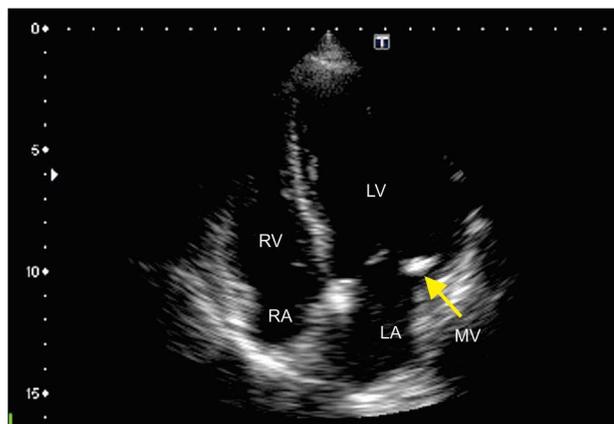
Laboratory tests showed the following: creatinine, 15.5 mg/dl (reference value, 3.0 mg/dl); urea, 149 mg/dl; severe metabolic acidosis (pH, 7.16; HCO₃, 3.6 mmol/L; base excess, -24.2 mmol/L); sodium, 141 mEq/L; potassium, 3.2 mEq/L; chloride, 111 mEq/L; ionic calcium, 4.3 mg/dl; phosphorus, 9.2 mg/dl; magnesium, 1.91 mg/dl; C-reactive protein, 57.2 mg/L; hemoglobin, 8.2 g/dl; leukocyte count, 7350 cells/mm³; and platelet count, 185,000 cells/mm³. Urinalysis revealed no hematuria, leukocyturia, or proteinuria. The patient was started on empirical antimicrobial therapy with ciprofloxacin and metronidazole. Cultures of blood, urine, and stool

samples were negative. An initial transthoracic echocardiogram was normal.

The patient received intravenous hydration, and acid-base disturbances were corrected. *Cryptosporidium* sp. was detected in stool samples by ELISA, and the patient was treated with nitazoxanide (500 mg bid) for 7 days, which resulted in remission of the diarrhea and partial recovery of renal function (creatinine, 6 mg/dl), without uremia or other hydrolytic disturbances. However, the fever persisted. The antimicrobial regimen was switched to piperacillin and tazobactam.

The investigation also included polymerase chain reaction and detection of antigenemia, both of which were negative for cytomegalovirus, and upper digestive endoscopy, which revealed an esophageal ulcer. Biopsy showed that it was intestinal metaplasia without signs of infection. A transthoracic echocardiogram, performed 10 days after the first, revealed thickening of the posterior leaflet of the mitral valve and a mobile filament adhered to the atrial surface, consistent with vegetation (Figure 1).

Figure 1. Transthoracic echocardiogram showing thickening of the posterior leaflet of the mitral valve (yellow arrow), consistent with endocardial vegetation.



Blood cultures incubated in chocolate agar medium showed growth identified as that of *Granulicatella* sp. He was then started on crystalline penicillin G at 12,000 IU/day (dose corrected for renal function), together with gentamicin at 200 mg/day. After 7 days of that treatment, the patient suddenly presented delirium, respiratory distress, and hypotension, progressing to a decreased level of consciousness and cardiac arrest in asystole. He did not respond to resuscitation.

DISCUSSION

To grow *Granulicatella* sp. and *Abiotrophia* sp., it is necessary to supplement the culture medium with cysteine or active forms of vitamin B6 (e.g., pyridoxine), and these streptococci can be also identified because they present satellitism.^{4,6} Although they belong to the normal microbiota of the oral cavity, genitourinary tract, and gastrointestinal tract,^{2,4} NVS are associated with severe infections that produce significant morbidity and mortality, such as endocarditis, ocular infections, pneumonia, central nervous system infections, and osteomyelitis, in immunocompetent and immunosuppressed patients.⁶

It is estimated that NVS are currently responsible for 5-6% of all cases of infective endocarditis.^{4,7} When *Granulicatella* sp. is the cause, the clinical course of endocarditis tends to be more indolent, the disease generally presenting as the subacute or chronic form.¹ Although it typically affects individuals with a history of cardiac disease, case series have shown that infective endocarditis can occur in patients with no such history.^{2,3,6} The most common site of infection is the aortic valve,¹ followed by the mitral valve. Two-dimensional transthoracic echocardiography is capable of diagnosing the disease in 64% of cases.³

As previously mentioned, *Granulicatella* spp. are found in the normal flora of the gastrointestinal tract. In the case presented here, it seems that the gut mucosal barrier was broken due to the *Cryptosporidium* infection, which provoked the diarrhea, or to the esophageal ulcer, given that the first echocardiogram did not reveal the vegetation (although transesophageal echocardiography was not performed until later). Cases of bacteremia due to *Granulicatella* sp. have been associated with predisposing factors such as mucositis and neutropenia^{2,5} and have also been reported abdominal infection.⁸

NVS can be identified through biochemical analysis after culture in media enriched with thiols or active forms of vitamin B6 (e.g., pyridoxine). The gold standard method of identifying NVS is sequencing the 16S rRNA gene from blood or valve samples.^{2,7} In the present case, we experienced difficulty in making the diagnosis, because the patient was immunosuppressed and had persistently negative cultures. Unfortunately, we could not identify the causative species. Infective *Granulicatella* endocarditis is mainly caused by the species *G. adiacens*, followed by *G. elegans*.^{7,9}

Our patient had an unfortunate outcome, and the cause of the final event that led to death was unknown. He was under the treatment recommended by the European Society of Cardiology and the American Heart Association.^{10,11} We hypothesize that he may have presented a disturbance in the cardiac conduction provoked by the vegetation or a possible valve abscess.

Infective endocarditis caused by NVS is associated with a high frequency of adverse effects such as septic emboli, which occurs in approximately one third of cases.^{2,4} Vegetations greater than 15 mm in diameter have also been associated with a greater risk of embolization and mortality in the first year after diagnosis.¹ Other related complications include acute cardiac failure requiring surgery for valve replacement, as well as distal embolization and cerebral mycotic aneurysm, although vascular and immunological events rarely occur.^{1,7} Among patients with infective endocarditis caused by NVS, the estimated mortality is 17%.^{1,5}

In conclusion, infective endocarditis caused by *Granulicatella* sp. is a rare, severe condition that should be suspected in cases of culture-negative endocarditis. Unfavorable outcomes can occur when the diagnosis or treatment is delayed, especially in immunosuppressed patients.

AUTHORS' CONTRIBUTIONS

FJP provided clinical care for the patient, performed literature searches and revised the article. PDMMN provided clinical care for the patient, performed literature searches, drafted and revised the article. RAB provided clinical care for the patient, performed literature searches, drafted and revised the article. ATWS provided clinical care for the patient, performed literature searches, drafted and revised the article. EDN provided clinical care for the patient and revised the article. All authors read and approved the final manuscript.

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