



Case report

Trivalvular infective endocarditis secondary to *Granulicatella adiacens* and *Peptostreptococcus spp*



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ABSTRACT

We present a case of a 42-year-old Caucasian man that came to our facility complaining of dyspnea and subjective fevers and was found to have infective endocarditis. His blood cultures initially grew *Peptostreptococcus spp* and he was started on penicillin and gentamicin. Repeat blood cultures, drawn 48 h later, became positive for *Granulicatella adiacens*. Vancomycin was added at this point, given reports of growing penicillin resistance of *Granulicatella spp*. Transthoracic echocardiogram showed multiple vegetations on the aortic, mitral and tricuspid valves. The patient's final antibacterial regimen consisted of intravenous penicillin G 24 million units daily and vancomycin (goal trough of 15–20) for a total of 6 weeks. The first 2 weeks of his regimen also included gentamicin. The patient was not considered for valve replacement surgery given concern for continued use of illicit intravenous drugs. *Peptostreptococcus* species are anaerobic, non-spore forming, gram-positive cocci, thought to generally have a subacute clinical presentation. *Granulicatella* genus is nutritionally deficient bacteria which require a supplemented media in order to grow. Both of these bacteria are present in the mouth and gastrointestinal flora. The rate of infective endocarditis from anaerobic species has been reported up to 16%, which includes multiple species. While on nutritionally deficient bacteria are reported to be involved on infective endocarditis in the range of 3–8%. Antimicrobial resistance is on the rise for both of these species, which makes the appropriate choice of antimicrobials quite important.

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Introduction

Infective endocarditis (IE) caused by anaerobic bacteria is an uncommon event, accounting for only 16% of all cases of infective endocarditis over the past three to four decades [1]. IE has a high burden for society worldwide; in the United States alone, the incidence is about 40,000 cases per year - an increase from 15,000 just 40–50 years ago [2]. Cases of anaerobic IE has been linked to a higher incidence of thromboembolic events, higher morbidity rate, and higher mortality compared to IE caused by aerobic bacteria [1,3]. Potential complications include valvular destruction, perivalvular abscess, aortitis, cardiogenic shock, dysrhythmias, and septic shock. The mortality rate for patients with anaerobic IE ranges from 21 to 43% [1,3]. *Peptostreptococcus spp.* are anaerobic, non-spore forming, gram-positive cocci. They are part of the normal microbial flora of the mouth, upper respiratory tract, gastrointestinal tract, female genitourinary system, and skin [4]. *Granulicatella* species are known to be part of the normal oral flora, gastrointestinal, and urogenital

tract [5]. Currently, there are no other cases of infective endocarditis reported in the literature that are caused by the combination of these two organisms, which gives proof of rarity for this case.

Case report

A 42-year-old Caucasian man presented to our facility complaining of dyspnea and subjective fevers. His past medical history included hypertension and chronic hepatitis C. He admitted to active intravenous illicit drug use, as well as smoking crack cocaine and marijuana. He reported that the dyspnea started 3 days prior to admission, and described it as exertional in nature. Other associated symptoms included left-sided chest pain and palpitations. On admission, blood pressure was 140/75 mmHg, heart rate was 117 beats/min, respiratory rate was 26 breaths/min, the temperature was 97 °F, and his oxygen saturation was 100% on room air. Initial laboratory studies showed 8570 leukocytes/uL, a hemoglobin of 8.5 g/dL, platelets of 176,000 uL, and normal liver enzymes.

The patient's physical exam was notable for poor dentition and a prominent grade 3/6 holosystolic murmur heard best over the left lower sternal border. Additionally, the patient was noted to

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display head bobbing with arterial pulsations consistent with de Musset's sign. There were no splinter hemorrhages, Osler nodes, or Janeway lesions observed. Blood cultures collected on admission were positive for *Peptostreptococcus spp.* A transthoracic echocardiogram was obtained and showed multiple vegetations on the aortic, mitral, and tricuspid valves (Figs. 1–3). His reported ejection fraction was 30–35% with global hypokinesis, as well as severe aortic regurgitation, moderate to severe mitral regurgitation, and torrential tricuspid regurgitation. There was no prior echocardiogram on file to compare. Computed tomography imaging of his abdomen and pelvis did not show any evidence of septic emboli or other infection. He was initially treated with intravenous penicillin G 24 million units by continuous infusion and gentamicin. Blood cultures were repeated 48 h later and grew *Granulicatella adiacens*. Vancomycin was added to his regimen at this point. Antimicrobial susceptibility testing for *Granulicatella adiacens* showed only intermediate susceptibility to penicillin (Fig. 4). Cardiothoracic surgery was consulted for valvular replacement; however, no surgical intervention was performed given concern for continuous illicit intravenous drug use. Six days after admission, the patient cleared his blood cultures. During his hospital stay, the patient's clinical status improved with resolution of his dyspnea and chest pain. The patient's final antibiotic regimen consisted of intravenous penicillin G 24 million units daily and vancomycin (goal trough of 15–20) for a total of 6 weeks. The first 2 weeks of this regimen also included gentamicin. The patient finished his course of antibiotics in the hospital and was discharged home. He was scheduled for outpatient to follow up with a possibility of valve replacement surgery in the future if he remained drug-free for at minimum six months.

Discussion

Infective endocarditis caused by anaerobic organisms accounts only for 16% of cases of IE in total. Majority of these cases are related to *Propionibacterium species* and *Bacteroides species* [3]. *Peptostreptococcus species* are anaerobic, non-spore forming, gram-positive cocci that are part of the normal microbial flora of the mouth, upper respiratory and gastrointestinal tract, female genitourinary system and skin [4]. *Peptostreptococcus* endocarditis is thought to generally have a subacute clinical presentation [3]. Pre-existing cardiac valve pathology is a major risk factor [1]. Procedures that may be predisposing to these types of infections are periodontal surgery, followed by tooth extraction and tonsillectomy [3]. This comes as no surprise since anaerobic bacteria are found in the oral cavity. There are multiple barriers

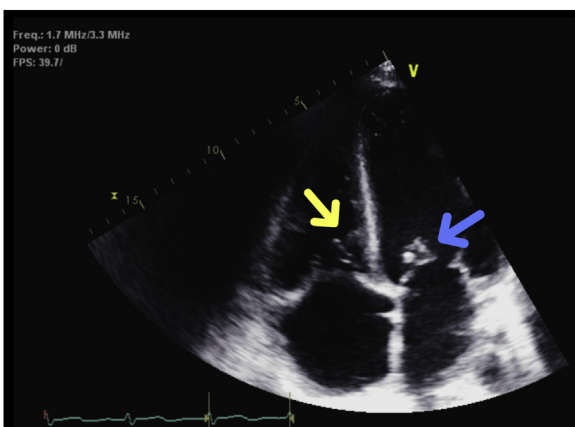


Fig. 1. Transthoracic echocardiogram – apical view showing vegetations on the mitral [blue arrow] and tricuspid valves [yellow arrow].

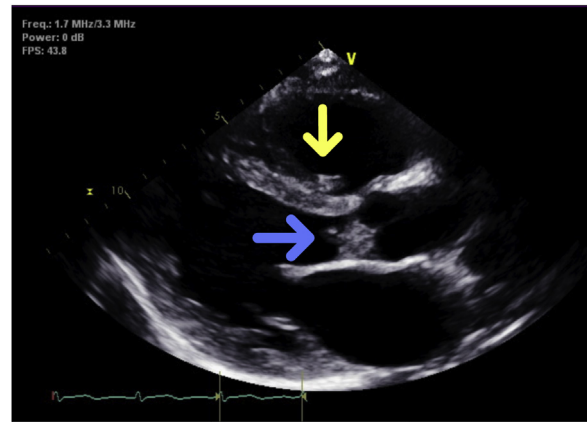


Fig. 2. Transthoracic echocardiogram – parasternal long axis view showing vegetation on the aortic valve [blue arrow] as well as vegetation inside the right ventricle [yellow arrow].

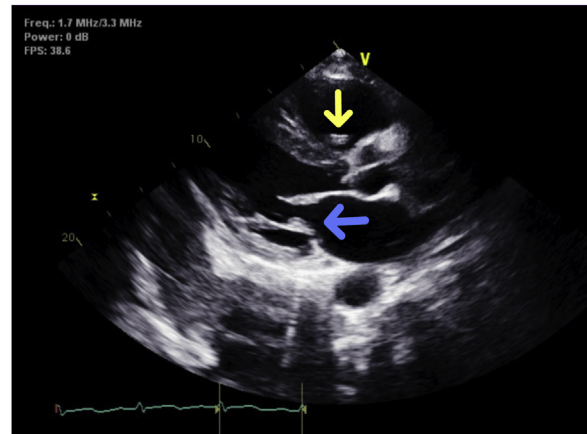


Fig. 3. Transthoracic echocardiogram – parasternal long axis view showing vegetation on the mitral valve [blue arrow] as well as in the right ventricle [yellow arrow].

that impede the timely identification of *Peptostreptococcus spp* and other anaerobic bacteria. These include mixed culture samples, slow growth pattern, and poor sensitivity of standard culture media [1,3].

The mortality rate for anaerobic IE has been reported since the 1970s to be 21–43%, but in a more recent retrospective study that included 21 cases, the mortality rate was found to be around 10% [1,3]. We can speculate that this study coincides with the reported more favorable prognosis of *Peptostreptococcus* as compared to patients with other types of anaerobic IE such as *B. fragilis* or *Fusobacterium species* [3]. The majority of reported cases were treated with penicillin G for six weeks, and in a few cases, gentamicin was used as well [1,3,6]. In cases of penicillin-resistant anaerobic infections, metronidazole is considered the drug of choice. However, resistance to metronidazole is also on the rise, so it is imperative that antimicrobial susceptibilities are always obtained [3,6].

Granulicatella adiacens is part of the class of nutritional variant streptococci [NVS] [7–12]. This class is composed of two genera that came from the discovery of 16S rRNA gene sequencing data in 1995 and 2000 [8,8,9,10,11,12]. The two genera are *Abiotrophia* and *Granulicatella* – the latter having 3 species: *G. adiacens*, *G. elegans* and *G. balaenopterae* [8,12]. NVS was first described by Frenkle and Hirsh in 1961 in a case of infectious endocarditis [7,10,11]. *Abiotrophia defectiva* is the most common of the two genera to

SUSCEPTIBILITY, AEROBIC BACTERIA, MIC	
SPECIMEN SOURCE	BLOOD
ORGANISM	GRANULICATELLA ADIACENS
CEFEPIME	4 R
CEFTRIAZONE	1 S
CHLORAMPHENICOL	8 R
CLINDAMYCIN	>1 R
ERYTHROMYCIN	>2 R
LEVOFLOXACIN	<=0.500 S
MEROPENEM	<=0.250 S
PENICILLIN	0.250 I
VANCOMYCIN	1 S

Fig. 4. Showing the susceptibility for *G. adiacens*. Shows penicillin has intermediate susceptibility.

be described in infective endocarditis. However, if we extrapolate from that data, it represents a very rare cause of endocarditis. NVS has been estimated to account for about 3–8% of the total cases of infective endocarditis [7,10].

Granulicatella genus is known to be part of normal flora of the mouth, gastrointestinal and urogenital tract [9,11]. These are nutritionally deficient bacteria which require a supplemented media in order to grow (Figs. 5 and 6) [5,9]. In particular, the addition of cysteine to the agar allows the NVS to convert to more streptococcus-like appearance and gram positivity, this is observed on blood agar as well as it contains cysteine [13]. Another characteristic is the appearance of “satellitism”, which can be observed in Fig. 6 [13]. On the Gram stain, they may appear with different morphologies: cocci, coccobacilli or rod-shaped cells, or even gram negative depending on growth conditions [5]. Also, the organism is able to produce the L-form, which partially or completely lacks the cell wall when exposed to suboptimal conditions [11]. Because of pleomorphic nature, slow growth and ability to produce L-form type there is difficulty interpreting sensitivities.

Nutritional variant streptococci may cause significant destruction of the heart valves, which is concerning, given that they are slow-growing bacteria and therefore may take a longer time to be identified [9,10]. The structural valve destruction is thought to be secondary to secretion of exopolysaccharide and the ability to adhere to fibronectin [9]. A major risk factor that has been described in this type of infection is prior valvular disease, either prosthetic or acquired [9–11]. A frequent source of infection that is recognized is dental manipulation, especially in patients with dental caries [9,10].

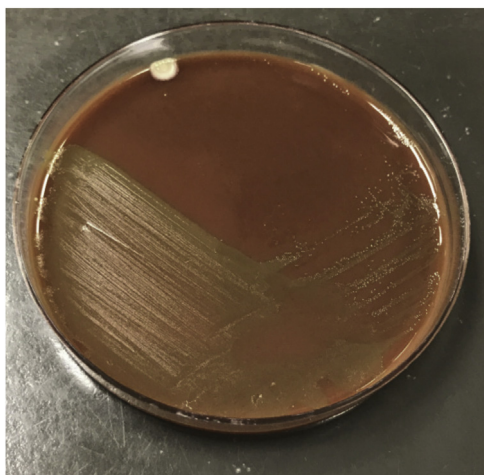


Fig. 5. Chocolate agar media with colonies of *Granulicatella adiacens*.

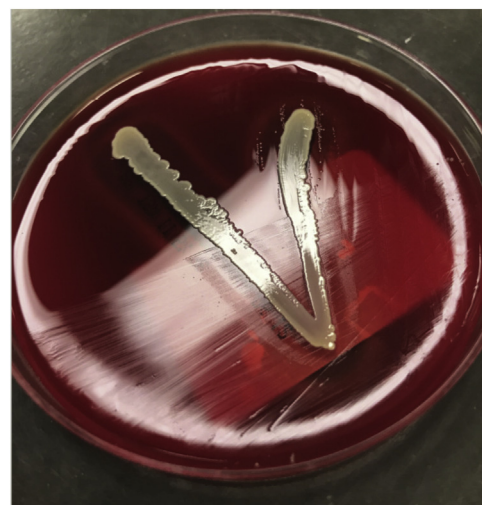


Fig. 6. Blood agar media with *Staphylococcus aureus* streak growing satellite colonies of *Granulicatella adiacens* around the “V”, similar growth as on chocolate agar, proving that cysteine is needed for growth.

Our patient did have poor dentition and very poor oral hygiene, along with a history of intravenous illicit drug use.

For *Granulicatella* endocarditis, the treatment failure rate has been reported as close to 40%, with a relapse rate of 17% [9–12]. American Heart Association, British Society for Antimicrobial Chemotherapy, and ISDA have recommended that these bacteria be treated similar to Enterococcus [9,11,12,14]. Therapy consists of penicillin, for 4–6 weeks with or without gentamicin [9,11,12,14]. However, based on more recent in vitro data, it seems that only around 40% of *Granulicatella adiacens* isolates are truly susceptible to penicillin, with over 50% of them being in the intermediate range [12]. Vancomycin was the only antimicrobial to which no resistance was identified [12]. Susceptibility testing that was done in our patient, showed that *G. adiacens* was intermediate to penicillin.

The majority of the patients with *Granulicatella* species or *Peptostreptococcus* species that have been reported in the literature so far have either aortic or mitral valve involvement, very few implicate both valves. Our patient not only had vegetations on both his aortic and mitral valve, but the involvement of the tricuspid valve as well. In the setting of concern for a high burden of infection, our patient was treated with penicillin and vancomycin for a total of 6 weeks, for double coverage, plus gentamicin for the first 2 weeks of the course. Infective endocarditis caused by these organisms has not been necessarily associated with intravenous illicit drug use, however, we believe that this is a risk factor that

cannot be overlooked in this patient. Consideration has to be given to the practices that some drug addicts have reported, such as using saliva to clean skin prior to injecting the drugs or licking the needle prior to insertion. The tricuspid valve infection has been found to be involved in cases of intravenous drug users [3].

Conclusion

This case is unique as it represents a patient with native heart valves, in which three valves (aortic, mitral and tricuspid) were affected by infection with two different anaerobic bacteria. A similar case has not been reported in the literature so far, to our knowledge. Infective endocarditis caused by anaerobes and NVS represents a challenging infection often leading to extensive organ damage, with many cases requiring surgical intervention. It can result in severe damage of the heart valves, given that signs and symptoms are often insidious, leading to a delay in presentation. The process of identifying these pathogens can be difficult, given their slow growth. As a consequence, there is often a delay in treatment which results in additional valvular destruction. As technology continues to advance, identifying these infections at an earlier stage will facilitate tailoring of antibiotic treatment and hopefully lower the morbidity associated with these anaerobic bacteria.

Submission declaration and verification

I, Jorge Verdecia MD, corresponding author, state that submission of this article has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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