Granulicatella elegans infective endocarditis: A case report

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Abstract
Granulicatella elegans is a rare cause of infective endocarditis, accounting for 1–2% of all cases. It is well recognized that this pathogen can present in association with negative blood cultures. There are higher rates of both relapse and mortality compared with endocarditis caused by other bacteria. Microbiological diagnosis can be especially challenging because many conventional blood culture media lack pyridoxal, which can be found in automated blood culture broths like BACTEC™ or BACT/ALERT® and thus they may require ‘helper’ bacteria to culture the organism. This current case report describes a 66-year-old male patient with a 10-year history of post-inflammatory combined aortic valve disease (moderate aortic stenosis and mild aortic regurgitation). He presented with a 3-month history of recurrent fever and general deterioration. Despite targeted, prolonged, combined antibiotic treatment with intravenous penicillin and gentamicin, surgery was eventually required. An aortic prosthetic valve implantation was performed with good results. In case of subacute endocarditis, especially when a causative organism proves difficult to detect, G. elegans should be considered. Identification is greatly enhanced by using polymerase chain reaction methods and this test should be considered in all cases of culture negative endocarditis.

Keywords
Infective endocarditis, echocardiography, aortic valve, Granulicatella elegans, case report

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Introduction
Abiotrophia and Granulicatella, previously grouped as nutritionally variant streptococci (NVS), are responsible for only 5–6% of all cases of infective endocarditis (IE) and therefore represent a relatively rare but clinically important cause of infective endocarditis.1 Granulicatella elegans (originally

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known as *Abiotrophia elegans*) was first described in 1998 as a catalase-negative, oxidase-negative, nonmotile, facultative anaerobic Gram-positive bacterium. However, the bacterium can exhibit variability and pleomorphism on Gram staining; forms range from bacilli in nutrient-depleted media to cocci arranged in short chains in nutrient-rich media. Most predominant pathogens of IE are bacterial species in the oral cavity and being a mouth commensal, the transmission of *G. elegans* from the mouth should be noted as a possible cause of IE. Since this bacterium requires pyridoxal and l-cysteine as growth factors, it may fail to grow on conventional blood culture media (because many of them lack pyridoxal unlike the automated blood culture broths like BACTECTM or BACT/ALERT®) and it requires ‘helper bacteria’ or semi-chemically defined media and is therefore hard to recognize. Some of the critical characteristics of *G. elegans* are the production of bacteriolytic activity and production of large amounts of exopolysaccharide in combination with slow growth requiring a longer course of antimicrobial therapy. These characteristics lead to higher relapse rates, complications that may in turn be associated with higher mortality than endocarditis caused by other viridans streptococci. This current case report describes the first case of *G. elegans* endocarditis in Central and Eastern Europe.

**Case report**

In April 2010, a 66-year-old male patient with a 10-year history of post-inflammatory combined aortic valve disease (moderate aortic stenosis and mild aortic regurgitation) and arterial hypertension presented to the 1st Department of Internal Medicine, L. Pasteur University Hospital and Medical faculty of Pavel Jozef Šafářík University, Košice, Slovakia with a 3-month history of recurrent fevers up to 39°C, with associated chills, profuse sweating, arthralgia and myalgia. On admission, examination revealed pyrexia of 37.6°C, tachycardia and a grade 4–5/6 continuous systolic and diastolic murmur in the second left intercostal space. Blood pressure was normal and there were no clinical signs of heart failure. Laboratory tests showed the following: (i) mild normocytic anaemia; (ii) elevated inflammatory parameters (white cell count: $11.25 \times 10^9/l$ with neutrophilia $7.88 \times 10^9/l$, C-reactive protein 95 mg/l); (iii) fibrinogen 5.47 g/l; (iv) erythrocyte sedimentation rate 85/140. Rheumatoid factor, procalcitonin and antistreptolysin O titres were within normal limits. An electrocardiogram revealed no significant abnormalities. Extensive microbiological and serological investigations did not reveal any positive results.

Transthoracic echocardiography followed by transoesophageal echocardiography (TEE) demonstrated further progression of known aortic stenosis and severe progression of aortic regurgitation. There were also features suspicious of an organised vegetation on the right and left coronary cusp with potential left cusp perforation. On the day of the TEE, three blood culture samples were collected at an interval of 30 min from three different sites and were processed. BACTECTM Plus Aerobic/F Culture Vials (Becton, Dickinson and Co., Franklin Lakes, NJ, USA) and BACTECTM Plus Anaerobic/F Culture Vials (Becton, Dickinson and Co.) in a BACTECTM 9050 automatic cultivating system (BioG, Bratislava, Slovakia) were used. If there was no culture observed after 5 days, culture results were reported as negative. The blood was also ‘subcultured’ for recovery of other extracellular fastidious bacteria such as the HACEK group of organisms. At 24 h after receiving a series of blood cultures, there was positivity in all of the culture vials. Subcultures were undertaken on human blood agar, chocolate agar, Sabouraud
agar and MacConkey agar. Gram stains from positive blood cultures exhibited Gram positive cocci arranged predominantly in chains. After overnight incubation at 37°C on enriched blood agar (5% sheep blood), a satellite growth of alpha-haemolytic colonies around *Staphylococcus aureus* CCM 6188 was seen. The colonies were greyish-white and approximately 1–3 mm in diameter after 48 h. On agar with the addition of 0.4 g/l of L-cysteine (VL medium; Imuna Pharm, Sarišské Michalany, Slovakia), the alpha-haemolytic colonies showed no satelitism. An isolate was identified on a VITEK® 2 system (bioMerieux, Durham, NC, USA) as *G. elegans*. Antibiotic susceptibility was tested according to Clinical and Laboratory Standards Institute 2010 recommendations for *Streptococcus* spp. other than *Streptococcus pneumoniae*.4 Isolates were shown to be susceptible to penicillin, azithromycin, cefotaxime, ciprofloxacin, gentamicin, vancomycin, quinupristin/dalfopristin and linezolid by the disc diffusion method. Isolates were resistant to doxycycline.

Immediately after TEE, high suspicion of IE prompted commencement of combined antibiotic therapy with 2.4 g co-amoxiclav intravenously every 4 h and 240 mg gentamicin intravenously daily for 5 weeks. The patient provided informed consent for treatment. Antibiotic therapy led to resolution of fever and some improvement of inflammatory parameters. After more than 5 weeks of antimicrobial therapy and treating potential infection foci (extraction of devital tooth number 24 and tonsillectomy due to chronic tonsillitis), the patient was stable without fever but with laboratory findings of on-going infection. Repeated blood cultures failed to reveal a causative organism. One month after the diagnosis of IE was made, repeat TEE showed severe progression of aortic regurgitation and again identified a possible perforation of the left coronary cusp. Vegetations on the aortic valve were still present and initial left ventricle dilatation was noticed. The patient was referred to the Department of Cardiosurgery, East Slovak Institute of Cardiovascular diseases, Košice, Slovakia and having completed 7 weeks of antibiotic treatment underwent aortic valve replacement using a bioprosthesis. Postoperative assessment and investigations confirmed adequate postoperative valvular function. The reporting of this case report conforms to CARE guidelines.5 All patient details have been de-identified. This study was approved by the Ethics Committee of L. Pasteur University Hospital, Košice, Slovakia (no. 2022/EK/05044). Despite all available means, the patient or his relatives could not be contacted to obtain informed consent for publication.

**Discussion**

The bacteraemia associated with IE is usually low grade and continuous. Therefore, blood cultures, which usually provides the identification of the aetiologic agent, is considered the most important of the available laboratory diagnostic tests. Negative culture results in the classification of such cases into culture-negative endocarditis, which comprises various conditions. More than 29 cases of *Granulicatella* endocarditis (rather than nutritionally variant streptococcal endocarditis) have been described in the literature up to 2015.6 Endocarditis caused by *G. adiacens* is more common than that caused by *Abiotrophia* species, with *G. elegans* being comparatively rare.7 *G. elegans* is primarily isolated from the oral cavity but can also be found in the intestinal and genitourinary tracts. Rates of oral colonization of *G. elegans* in dental plaque in healthy individuals have been reported at a level of 10%.3 Through these portals, entry is gained to the bloodstream. *G. elegans* has also been implicated...
as etiologic agents of postpartum or postabortal sepsis, pancreatic abscess, wound infection, vertebral osteomyelitis or discitis, conjunctivitis, cirrhosis, endophthalmitis, infectious crystalline keratopathy, and otitis media.\textsuperscript{8–12} This current patient had not received dental procedures but did have dental caries, which are thought to be associated with the onset of infective endocarditis caused by the \textit{G. elegans}.\textsuperscript{3} Moreover, he had another oral infection focus presenting as chronic tonsillitis, although cultures from his tonsils did not confirm this pathogen. Endocarditis caused by \textit{G. elegans} predominantly occurs in the setting of pre-existing heart disease (90%); and prosthetic heart valves are involved in 13% of patients.\textsuperscript{6} This was also the situation for the current patient as he had a 10-year history of post-inflammatory combined aortic valve disease (moderate aortic stenosis and mild aortic regurgitation) that was involved in IE.

Clinical manifestations of IE depend on the infecting genera and the species of the pathogens. In \textit{G. elegans} IE despite forming relatively small vegetations, embolization occurs in up to one-third of patients.\textsuperscript{13} Congestive cardiac failure and the need for surgical intervention are higher with endocarditis due to NVS versus other streptococci.\textsuperscript{14} The aortic and mitral valves are affected with similar frequency, 13% and 11%, respectively.\textsuperscript{14} Mortality data are based on the former nomenclature of NVS and denote that mortality is indeed higher (20%) when compared with endocarditis caused by viridans streptococci (0–12%) or by enterococci (9%).\textsuperscript{14} Most deaths are due to refractory congestive cardiac failure or major systemic emboli.\textsuperscript{15} Approximately 27% of patients require prosthetic valve replacement.\textsuperscript{15} The antibiotic regimen of \textit{G. elegans} endocarditis should include penicillin or ampicillin plus an aminoglycoside or vancomycin in case of antimicrobial resistance for 4–6 weeks.\textsuperscript{16} \textit{In vitro} antibiotic susceptibility does not reflect clinical outcome.\textsuperscript{15} Prevalence of resistance to beta-lactams is about 50% and to macrolide antibiotics is about 93% in NVS.\textsuperscript{17} However, resistance to aminoglycoside is not so high hence penicillin and gentamicin combination is better than penicillin alone.\textsuperscript{18} Despite following the recommended antibiotic regimen in this current patient and the correct length of a treatment, he developed serious complications and surgical valve replacement was thought to be the only possible cure.

In conclusion, as \textit{G. elegans} does not grow on regular blood agar a few cases undoubtedly remain unknown or unidentified.\textsuperscript{14} Therefore, the actual frequency of endocarditis caused by \textit{G. elegans} is difficult to ascertain and the prevalence of the pathogen among patients with endocarditis may well be underestimated. Thus, if a clinician suspects a bacteraemia or IE, sera samples should be cultured in various specific media to identify the pathogen. Identification is greatly enhanced by using polymerase chain reaction methods and this test should be considered in all cases of culture negative endocarditis.

**Author contributions**

J.D. and M.F. drafted the manuscript; L.G. revised the manuscript; E.S. was responsible for microbiological identification of the pathogen and helped to draft the manuscript. All authors have approved the final version of the manuscript and agreed with publication.

**Declaration of conflicting interests**

The authors declare that there are no conflicts of interest.

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