

Aortic Valve Endocarditis Caused by *Abiotrophia defectiva*: Case Report and Literature Overview

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Abstract. *Abiotrophia defectiva* or nutritionally variant *Streptococcus* (NVS) are a rare but important cause of infectious endocarditis, with high rates of bacteriological failure and mortality. We report the case of a 74-year-old man admitted for fever, fatigue and general malaise in the absence of any underlying cardiac, immunosuppressive illness and previous dental manipulations. Transthoracic and transesophageal echocardiogram revealed bacterial vegetation and significant aortic stenosis and regurgitation. Initial blood culture reported gram-positive cocci in chains, subsequently identified as *A. defectiva*. The patient completed 6 weeks of antibiotic therapy with ampicillin, with a significant decrease of serum inflammatory markers. He refused cardiac surgery and had relapsing endocarditis with positive blood culture for the same pathogen. The patient was then submitted to double-valve cardiac surgery, obtaining a prompt resolution of clinical signs and symptoms, without other relapse or any complications. Conclusion: Infectious diseases caused by *A. defectiva* are extremely rare illnesses. Due to the difficult isolation of the pathogen and the slow clinical progression, clinicians should be aware of this bacterium when dealing with blood culture-negative infective endocarditis.

Abiotrophia defectiva or nutritionally variant streptococci (NVS) were first identified by Frenkle and Hirsh in 1961 in a case of sub-acute infectious endocarditis (1). The nomenclature of these bacteria changed repeatedly in the subsequent years. In 1989, Bouvet *et al.* proposed the names *Streptococcus defectivus* and *Streptococcus adjacens*,

following the use of DNA-DNA hybridization studies which revealed that NVS were taxonomically distinct from the other viridans group of organisms to which they were originally related (2). In 1995, Kawamura and associates used 16S rRNA (rRNA) sequence analysis on these two species. Analysis showed that the species were not related to the *Streptococcus* genus. They proposed placing these organisms in a new genus, *Abiotrophia*, to be named as *A. adjacens* and *A. defectiva*, respectively (3). Later several other species such as *A. balaenopterae* and *A. paraadjacens* were identified (4-6). In 2000, Collins and Lawson proposed the re-classification of all *Abiotrophia* species except *A. defectiva* into the new genus *Granulicatella*, based on the 16S rRNA heterogeneity and phenotypic differences observed (7). *A. defectiva* is usually isolated from immunocompetent hosts and *Granulicatella* species from immunocompromised hosts (8).

Accurate identification of NVS can be difficult due to the pleomorphic nature and variable Gram-staining characteristics, including the ability to develop well on Columbia blood agar and Todd-Hewitt broth, whereas they do not grow well on typical culture media. They are often seen as a satellite lesion around other bacteria that secrete pyridoxal such as *Staphylococcus*. Extended incubation may be required for NVS growth. For sub-culture, solid media must be supplemented with vitamin B6 and L-cysteine to sustain growth (9, 10). Generally *A. defectiva* grows more slowly than other streptococci (11). NVS are often seen as white-grey, non-hemolytic colonies. Useful phenotypic characteristics that can be used to differentiate between species within the *Abiotrophia* and *Granulicatella* genera are the production of alpha- and beta-galactosidase (*A. defectiva*), beta-glucuronidase (*G. adiacens*), and hydrolysis of hippurate (*G. elegans*) (12).

Molecular techniques such as 16S rRNA gene sequencing using polymerase chain reaction-restriction fragment length polymorphism analysis may be necessary to identify *A. defectiva* as the causative organism when blood cultures are

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negative (11). While the use of molecular techniques in the diagnosis of culture-negative endocarditis is extremely helpful, the sensitivity of the technique is much greater in resected valves than in blood (13).

A. defectiva is included in the normal human microbiota colonizing the oral, genitourinary, and intestinal tract. Bacteremia and endocarditis are the most frequently reported infections due to *A. defectiva* worldwide (2). It has been estimated to cause approximately 5-6% of microbiologically-proven cases of endocarditis, and been implicated in the pathogenesis of culture-negative endocarditis (8). Among NVS, *A. defectiva* is especially able to cause endovascular infection because of its ability to adhere to fibronectin in the extracellular matrix (14). Accurate and quick identification of organisms is very important because endocarditis caused by NVS carries greater morbidity and mortality than endocarditis caused by other streptococci. *A. defectiva* affects diseased valves in 90% of cases and is notorious for embolic complications, such as pancreatic abscess, brain abscess, osteomyelitis, septic arthritis, crystalline keratopathy and valvular destruction, despite being sensitive to antibiotics (8). Studies have shown a relapse rate of as high as 17%, despite antibiotic use (15).

Case Report

A previously healthy 74-year-old man was admitted to the Fifth Unit of Infectious Diseases of the D. Cotugno Hospital of Naples on October 2014 for the investigation of recurrent fever, fatigue and general malaise. Fever began 3 months prior to admission, treated with anti-pyretics and different antibiotics at home. He denied underlying disease, alcoholic drinking, intravenous drug use and cigarette smoking. He had not recently undergone any surgery or dental procedures. Physical examination revealed pallor, body temperature of 38.5°C, heart rate sinus of 65 beats for minute, normal blood pressure (110/70 mmHg) and room-air oxygen saturation of 98%. On cardiac auscultation, he presented regular rate and rhythm with a 3/6 pansystolic murmur heard at the apex, fine crepitation in both lungs and nontender hepatomegaly. No Janeway's lesions, Osler's nodes or Roth's spot on the eye examination were observed. Laboratory studies revealed a serum creatinine of 1.9 mg/dl, normocytic anemia (Hb 11.2 g/dl), white blood cells (WBC) of 8,750/mm³ (neutrophil 80%, lymphocyte 13%, monocyte 6%), platelets of 113,000/mm³, erythrocyte sedimentation rate of 30 mm in the first hour, protein chain reaction of 5.6 mg/dl, and ferritin of 1,072 ng/ml. He had normal liver function.

The patient was initially treated with 4 g piperacillin/500 mg tazobactam three times a day and 400 mg ciprofloxacin twice a day *i.v.* as empiric antibiotic therapy. Multiplanar transthoracic and transesophageal echocardiogram showed left atrial enlargement with volume overload, global and

segmental ventricular systolic function preserved, severe aortic stenosis, mild-severe aortic regurgitation and a small structure resembling a vegetation on the coronary cusp of the aortic valve, measuring 12 mm. The modified Duke criteria were considered for the diagnosis of infectious endocarditis (echocardiography, history, and physical examination information).

Four sets of aerobic and anaerobic blood culture were obtained. Blood cultures were processed in the Bacter blood culture system (16, 17). All the blood culture sets showed pleomorphic gram-positive coccobacilli microscopically. Colonies developed well on chocolate agar but poorly on 5% blood agar after 48 h of incubation. The bacterium was identified as *A. defectiva*.

Anti-microbial susceptibility was determined by E-test for penicillin and the disc diffusion method on Mueller-Hinton agar with 5% sheep blood for the other antibiotics. Results were interpreted according to Clinical Laboratory Standard Institute, and European Committee on Antimicrobial Susceptibility Testing (17). The bacterium was found to be susceptible to ampicillin, penicillin, cefotaxime, ceftriaxone, clindamicina, erythromycin and vancomycin. The minimum inhibitory concentration (MIC) for penicillin was 0.06 mg/l. High-level resistance to gentamicin was not seen in this isolate. MIC for vancomycin was <1 mg/l. Therefore, the therapy was switched to 12 g ampicillin a day *i.v.*. No gentamicin was added due to acute kidney injury.

The patient's fever fell in 3 days on the antibiotics administered. He continued antibiotic therapy for 6 weeks, obtaining a marked improvement of clinical signs and symptoms, with a fall in serum inflammatory markers. The patient was also recommended aortic bio-prosthetic valve, but he refused to undergo cardiac surgery, and left the hospital against physicians' advice. After 4 weeks, he again presented fever and relapsing endocarditis with mitral valve involvement, with positive blood culture for the same pathogen. He was then subjected to aortic and mitral prosthetic surgery with mechanical valve, with complete disease resolution. The rest of the course was uncomplicated and the patient is now in follow-up without any relevant complication.

Discussion

A. defectiva is primarily isolated from the oral cavity but can also be found in the intestinal and genitourinary tracts (2). The rate of oral colonization of *A. defectiva* in healthy individuals has been reported at a level of 11.8% (18) and entry is usually gained to the bloodstream through these portals. NVS cause approximately 3% to 5% of cases of streptococcal-associated infectious endocarditis. *A. defectiva* is a rare but very important cause of blood culture-negative infectious endocarditis (19). The secretion of exopolysaccharide and the

ability to adhere to fibronectin justify the particular affinity of *A. defectiva* for endovascular tissue (14), even if the organism has also been implicated in causing osteomyelitis, cerebral abscess, septic arthritis, and meningitis (20).

More than 100 cases of *A. defectiva* endocarditis (2, 15, 20, 21) are described in the literature. It predominantly occurs in the setting of pre-existing heart disease (90%); prosthetic heart valves are involved in 10% of patients (19, 20). The aortic and mitral valves are affected with similar frequency (22). Endocarditis caused by NVS carries greater morbidity and mortality than endocarditis caused by streptococci. In the majority of cases, the clinical course is slow. Often there is a history of dental manipulation in the preceding months or a history of dental caries, as this is the predominant route of entry of the organism into the bloodstream (18). *A. defectiva* endocarditis is difficult to treat and has a bacteriological failure rate of 41% despite therapy with antibiotics that are effective *in vitro*. Therefore close monitoring is required. Despite forming relatively small vegetations, embolization occurs in up to one-third of patients (15). Congestive cardiac failure and the need for surgical intervention is higher with endocarditis due to NVS *versus* other streptococci. Mortality data are based on the former nomenclature of NVS and denote in detail that mortality is higher (17%) when compared to endocarditis caused by *viridans streptococci* (0-12%) or by enterococci (9%) (22). The majority of deaths are due to refractory congestive cardiac failure or major systemic emboli. Approximately 27% of patients require prosthetic valve replacement and 50% of the patients require surgery (20, 23).

It has also been shown that the relapse rate can be up to 17% in certain cases (15). Prevalence of resistance to beta-lactams is about 50% and to macrolide antibiotics is about 93% for this organism, however, resistance to aminoglycoside is not as high and penicillin and gentamicin combination is better than penicillin alone (24, 25). Vancomycin represents a good therapeutic choice in patients who have shown a poor response to penicillin-aminoglycoside combination therapy (15). The American Heart Association guidelines recommend treatment of *A. defectiva* should follow the guidelines for the treatment of enterococcal endocarditis. The regimen is 18-30 million units of penicillin per 24 hours divided into six doses or 12 g of ampicillin per 24 hours *i.v.* divided into six doses with *i.v.* gentamicin at 3 mg/kg/24 hours divided into three doses for 4-6 weeks (26).

The reasons for high antibiotic treatment failure rates are multiple in nature. First of all, a longer time period is required for the identification and isolation of these bacteria due to their slow and difficult growth characteristics, with blood cultures requiring at least 2-3 days to become positive, with the consequent frequent need to establish sub-culture with L-cysteine-supplemented media. NVS produce large

amounts of exopolysaccharide *in vivo*, further adding to their virulence. Of course the general increased resistance and tolerance to penicillin have also contributed to the difficulties in treatment of *A. defectiva* endocarditis.

In conclusion, we report on a case of infectious endocarditis caused by *A. defectiva*, in the absence of any underlying cardiac, immunosuppressive illness and previous dental manipulations. The portal of entry of bacteria into the endovascular system in this case remains obscure. In our case, not only ampicillin but also cardiac surgery was necessary to obtain a clinical resolution.

Our case highlights the relevance of a correct diagnosis with a prompt identification of the pathogen, which can facilitate adequate antibiotic therapy and eventually surgical treatment, modifying the prognosis. Because NVS are very slow-growing organisms, it is likely that most cases are misdiagnosed as culture-negative endocarditis and their role in endocarditis may be underestimated.

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