Granulicatella spp.

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Granulicatella spp. are non-motile, non-sporulating, facultatively anaerobic Gram-positive cocci. These organisms have been referred to by several names, such as “nutritionally deficient streptococci”, “vitamin-B dependent streptococci” and “pyridoxal-dependent streptococci”, because of their fastidious nutritional requirements, which can often make culture isolation challenging. Known to be a member of the normal microbiota of the human oral cavity and urogenital and intestinal tracts, similar to other streptococci, *Granulicatella* spp. can cause bacteremia, sepsis and infective endocarditis. Considering the difficulty in growing this organism on culture medium, the fact that it is now included among the bacteria known to be responsible for culture-negative infective endocarditis suggests that its pathogenic role could be highly underestimated. Moreover, being considered such a rare causative agent, it is not a target of standard antibiotic empiric treatment.

Keywords: Granulicatella ; nutritionally variant streptococci ; infective endocarditis

1. Introduction

Granulicatella species, formerly referred to as a Nutritionally Variant Streptococci (NVS), known as *Abiotrophia species*, are Gram-positive bacteria, which are part of the normal microbiota of the oral cavity and intestinal and genitourinary tracts [1][2] and have been found to be responsible for severe infections, especially in patients with predisposing factors.

Isolated cases of central nervous system infections [3][4][5][6][7], as well as keratitis [8], endophthalmitis [9], sinusitis, otitis media, prostatitis, cholangitis, arthritis [10][11][12] and osteomyelitis [13][14][15], have been reported, but the most significant clinical syndromes associated with *Granulicatella* spp. are bacteremia and endocarditis, the latter mainly observed in patients with a background of congenital cardiac disease [16][17].

Infective endocarditis (IE) from *G. elegans* is rare in the general population and in children. Furthermore, it represents a diagnostic challenge because of the non-specific symptoms at presentation and difficulties in growing the organism on culture medium.

2. Case Report

A 13-year-old Caucasian male presented to hospital with a 1-month history of low-grade fever (Tc max 37.7 °C) and pharyngodynia, treated at home with macrolide antibiotics without improvement. His past medical history was significant for the presence of a peri-membranous interventricular septal defect and a high-velocity left-to-right shunt without any hemodynamic consequence. In the two months before admission, a mildly symptomatic infection with SARS-CoV-2 was reported.

The initial physical examination was unremarkable, except for a cardiac murmur 2-3/6 on the Levine scale, detected along the left sternal border. Cardiac tones and peripheral pulses were normal. The initial laboratory findings revealed only a slight increase in the C-reactive protein (subsequently reduced) with a normal blood count. Because of the persistent fever, a serological examination for CMV, a urine culture and the Widal-Wright test (to exclude Salmonellosis and Brucellosis) were performed with negative results. A chest X-ray and a subsequent CT scan showed a pronounced thickening of the interstitial fiber network of the lungs and signs of emphysema.

The echocardiography examination revealed the presence of an endocardial vegetation (1 × 0.8 cm).

At the same time, the growth of *G. elegans* was detected from the blood cultures previously carried out. The antibiogram showed resistance to macrolides and vancomycin. Intravenous antibiotic therapy with ceftriaxone and gentamicin was administered for 4 weeks, leading to complete clinical recovery of the patient, a major reduction in the size of the

vegetation and negative follow-up blood cultures. The post-discharge cardiology follow-up led to the decision of performing a surgical procedure to correct the pre-existing interventricular septal defect.

3. A Causative Agent of Infective Endocarditis in Children

The genus *Granulicatella*, which comprises three species (*G. adiacens*, *G. elegans* and *G. balaenopterae*), was recently identified after a taxonomic revision by Collins and Lawson [18]. It was historically classified as a Nutritionally Variant Streptococci (NSV), a group of microorganisms first described by Frenkel and Hirsch in 1961 [19] as being a new type of *Streptococci* exhibiting satellite formation around colonies of other bacteria, with specific growth characteristics, including thiol and pyridoxal nutrient requirements. To date, NSV includes two genera, namely, *Granulicatella* and *Abiotrophia* (which literally means “life nutrition deficiency”) [20], including the spp. *defectiva* and *para adiacens* [21].

Granulicatella and *Abiotrophia species* are natural inhabitants of the oral, intestinal and urogenital microbiota of humans [1][2]. Although rarely implicated in disease, they have been found to be responsible for isolated cases of central nervous system infections [3][4][5][6][7], keratitis [8], endophthalmitis [9], sinusitis, otitis, prostatitis, cholangitis, arthritis [10][11][12], osteomyelitis and lumbar spine infection [13][14][15][22], but the most frequently reported syndromes due to *Abiotrophia* and *Granulicatella species* are known to be bacteremia, septicemia and endocarditis [16][17].

As for endocarditis, NSV appear to be responsible for approximately 5% of all cases of streptococcal endocarditis in the general population, carrying a worse prognosis than infections with other streptococci [1][23].

The AHA published a scientific statement in 2015 that included and discussed newly available evidence about IE in children [24]. According to this statement, the frequency of endocarditis among pediatric patients appears to have increased over the past two decades, especially in those with congenital heart disease (to date, the predominant underlying condition for IE in children > 2 years of age in the developed world) but also in those without any identifiable risk factor. Such a trend is likely attributable to the improved survival of patients with structural heart defects (where even the corrective surgical procedure can become a long-term risk factor for postoperative IE [25]), as well as to the growing complexity of patient management in neonatal and pediatric intensive care (which has led to the increased incidence of neonatal IE, even in those with structurally normal hearts) [26]. Furthermore, children with no known risk factors can suffer from IE due to invasive procedures, such as dental procedures, bronchoscopy and tonsillectomy [27]. The IE clinical presentation in children is generally indolent with prolonged low-grade fever coupled with non-specific symptoms, such as fatigue, weakness, myalgia, arthralgia, headache, weight loss and diaphoresis. Moreover, the classical signs of extracardiac IE (e.g., petechiae, hemorrhages, Roth’s spots, Janeway lesions, Osler nodes, and splenomegaly) are extremely rare [28].

Both the cardiac examination and the echocardiography findings can be highly variable, depending on the type of presenting heart disease and the particular site of infection. The AHA, therefore, strongly recommends that blood cultures be carried out in young patients with fever of unexplained origin and a pathological heart murmur, a history of heart disease or a history of previous endocarditis [24]

The mortality rate of endocarditis ranges from 4% to 18%, and its complications include congestive heart failure; new or progressive valvular dysfunction; prosthetic valve dysfunction, including dehiscence; sinus of Valsalva rupture; myocardial dysfunction; the obstruction of conduits or shunts; pericardial effusion; and embolization [27][28].

The majority of organisms causing IE in children are known to be Gram-positive cocci, including the Viridans Group Streptococci (e.g., *Streptococcus sanguinis*, *S. mitis* group and *S. mutans*), staphylococci (both *S. aureus* and coagulase-negative staphylococci), β-hemolytic streptococci and enterococci. Less frequently, other organisms, such as the HACEK group (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens* and *Kingella* species), are implicated [26].

When a patient has clinical or echocardiographic evidence of IE but persistently negative blood cultures, a diagnosis of culture-negative endocarditis (CNE) is made. Because studies have revealed that CNE can account for 2.5% to 70% of all endocarditis cases among the general population varying by country [22][29], the inclusion of molecular diagnostics methods on surgical specimens (e.g., polymerase chain reaction (PCR)) in the modified Duke diagnostic criteria has been proposed [30].

Further, the treatment of *Abiotrophia* and *Granulicatella* infections is complicated by a variable susceptibility to commonly used antistreptococcal antibiotics, such as penicillin and ceftriaxone, as well as by significant resistance to macrolides [31][32][33]. According to the AHA’s guidelines, “patients with IE caused by Abiotrophia, Granulicatella species, or streptococci

with an MIC of >0.5 µg of penicillin per milliliter should be treated with the antibiotic regimen listed for enterococci", which would be a 4 week treatment regimen of penicillin, ampicillin or ceftriaxone, combined with gentamicin for the first 2 weeks. Vancomycin is considered an effective substitute for children who are unable to tolerate β-lactam antibiotic drugs, in combination with a 4-week course of gentamicin. Blood concentration tests of vancomycin and gentamicin, as well as renal function tests, should be performed on a weekly basis because of the use of multiple nephrotoxic antibiotic drugs [24].

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