

Endocarditis caused by nutritionally variant streptococci: a case report and literature review

Endocardite da varianti nutrizionali streptococciche: descrizione di un caso e revisione della letteratura

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INTRODUCTION

In the present study we investigated a case of IE caused by a fastidious bacterium, *Granulicatella adiacens*, previously grouped with the nutritionally variant streptococci (NVS). *Abiotrophia* and *Granulicatella* are found as part of the normal flora colonizing oral, genitourinary, and intestinal tracts and can be responsible of infections such as endocarditis, conjunctivitis, endophthalmitis, infectious keratopathy, otitis, pancreatic abscesses and post-partum sepsis [1, 2].

Since we have found relatively few cases of endocarditis caused by NVS described in literature in the past 10 years, this case report and the accompanying review may be of some interest for clinical practice.

CASE REPORT

A 40-year-old man presenting with malaise, worsening dyspnea, palpitation and acute heart failure was admitted to the Emergency Department at University "La Sapienza" of Rome. One month before presentation, patient had suffered an episode of bronchitis treated with antibiotics (ceftriaxone, azithromycin and amoxicillin in sequence) and he had had no dental or surgical procedures.

Physical examination revealed no fever, normal blood pressure, sinus tachycardia, peripheral

oedema and a holosystolic murmur of moderate intensity heard best at the cardiac apex and irradiating to the axilla.

Leukocyte count on admission was 8.360 per μl , the hemoglobin level was 12.0 g/dl. Multiplanar transesophageal echocardiography showed erosion of both cusps of the aortic valve and a 15 mm vegetation on the noncoronary cusp; a periannular abscess with suspect perivalvular pseudoaneurysm was seen; severe aortic regurgitation, left ventricle enlargement with reduced ejection fraction were also observed.

Pending the availability of diagnostic data, the patient was empirically treated with intravenous ampicillin (2 g q4h) plus gentamicin (80 mg q8h) and vancomycin (500 mg q6h). Vancomycin was withdrawn on day 4, after blood culture results.

Two sets of blood cultures yielded a slow growing Gram-positive catalase-negative streptococcus, subsequently identified as *Granulicatella adiacens* by Vitek GPI card (bioMerieux Vitek). Antimicrobial susceptibility was performed using Kirby-Bauer disc diffusion method according to standard guidelines [1, 3]. Isolates were susceptible to penicillin, ampicillin, linezolid and vancomycin and resistant to ceftriaxone. Susceptibility to gentamicin was not assessed.

On day 2 the patient underwent to aortic valve replacement. On day 7 he was discharged from the ICU, fever subsided and general condition improved allowing the patient to be transferred to a cardiac rehabilitation center on day 14.

Combination therapy with ampicillin 12 g/die and gentamicin 80 mg q8h lasted for 4 weeks and then the patient was given an additional two-week treatment regimen with ampicillin alone same dosage as above.

No evidences of relapse were detected after a six month follow-up.

Analysis of the literature

Up until 2001 more than 100 cases of endocarditis caused by NVS were reported in literature [2, 4-6]. These microorganisms have been responsible for 5-6% of all cases of streptococcal endocarditis; preexisting heart disease was documented in up to 90% of patients and prosthetic heart valve involvement was found in 10% of patients [2, 3, 6, 7].

Systemic embolization occurred in one-third of patients, aortic and mitral valves were reported to be affected with similar frequency (13% and 11%, respectively) 7. Morbidity and mortality proved higher than those associated with other forms of viridans streptococcal and enterococcal endocarditis [2, 4]. Although a bactericidal effect was demonstrated *in vitro*, therapy turned out to be unsuccessful in 41% of patients. About 27% of patients required heart valve replacement surgery and mortality was approximately 20%. More than 30% of strains of NVS showed resistance to penicillin concentrations of 0.12 mg/l [2, 5].

After an extensive search in MEDLINE over the past 10 years, we found 22 well documented cases of endocarditis caused by NVS with identification of bacterial species.

We have analyzed patient risk factors, bacterial species involved, penicillin susceptibility, sites of infection, therapy administered and mortality rates (Table 1).

We have examined 6 female patients (26%) and 17 male patients (74%), with a mean age of 47 years (range 12-85).

Risk factors: Fourteen patients (61%) showed underlying valvular heart predisposing conditions, such as congenital valvular heart disease (28%) or heart valve prosthesis (9%) and 9 patients (39%) had no risk factors for endocarditis.

Bacterial species: *Abiotrophia* spp. was isolated in 10 (43%) cases of endocarditis, while *Granulicatella* spp. was found in 13 (57%) cases.

Penicillin susceptibility: Eighteen (78%) strains were reported to be susceptible to penicillin, 3 strains (12%) were variably resistant to penicillin; among them, 2 showed a reduced susceptibility to penicillin (1 *Abiotrophia* spp. and 1

Granulicatella spp.) and 1 proved to be resistant (*Abiotrophia* spp.). In two cases the penicillin susceptibility was not reported.

Sites of infection: Endocarditis involved native mitral valve in 10 patients (44%), native aortic valve in 7 (26%), prosthetic valve in 2 (9%), pacemaker lead in 1 (4%). No site of infection was reported in 4 cases.

Therapy: All patients were treated with appropriate antimicrobial combination chemotherapy (antibiotic regimen not reported in 3 cases); heart valve replacement was performed in 11 patients (48%).

Mortality: Overall mortality was 9% meaning 2 patients died out of 23. For both, no data about either antibiotic therapy administered or possible heart valve surgery were reported. One of them had *Abiotrophia defectiva* isolated from blood cultures and the other one *Granulicatella adiacens*. Both isolates were susceptible to penicillin.

■ DISCUSSION

Abiotrophia and *Granulicatella*, previously known as NVS, are considered etiologic agents of 5% of streptococcal endocarditis [6, 8]. These fastidious bacteria have been reported to be a common cause of culture-negative bacterial endocarditis and their role in this infectious disease could be underestimated [6].

Streptococcus adiacens and *Streptococcus defectivus* were first recognized by Woo and Bouvet [9, 10]. As a result of 16S rRNA gene sequence data and other phylogenetic analysis, the names *Abiotrophia adiacens* and *Abiotrophia defectiva* were proposed in 1995 [9, 11]. *Abiotrophia adiacens* was subsequently transferred to *Granulicatella adiacens* by Collins and Lawson in 2000 [9, 12].

The identification, epidemiology and the spectrum of clinical diseases caused by *G. adiacens* and *A. defectiva* have always been dependent upon phenotypic characterization, but unusual phenotypic characteristics that do not correlate with the species descriptions in the literature are not uncommon and the gold standard of identification is considered 16S rRNA gene sequencing [9, 13].

Such organisms may require broth supplemented with pyridoxal hydrochloride or cysteine and may exhibit a laboratory phenomenon of "penicillin tolerance". For tolerant strains, the minimum bactericidal concentra-

Table 1 - Data from case reports of Abiotrophia and Granulicatella spp. endocarditis in the last 10 years.

References	Patient no./age (y)/sex	Related procedures	Risk factors for endocarditis	Identified species	Site of infection/ Surgery	Therapy	Penicillin Susceptibility	MIC	Outcome
Rosenthal O. et al., 2002 [26]	1/68/M	None	Pacemaker	<i>Granulicatella adiacens</i>	Pacemaker lead + vertebral osteomyelitis/ None	Penicillin 30x106U + rifampin 600 mg + gentamicin 260 mg (duration not specified)	Sensitive	NR	healed
Casalta J.P. et al., 2002 [27]	2/29/M	Dental procedures 3M before IE, pneumonia 1M before IE	Bicuspid aortic valve	<i>Granulicatella elegans</i> (negative blood cultures, positive valve cultures)	Aortic valve/ Replacement	amoxicillin 2g q6h + gentamicin 3 mg/Kg q24 x 4W	NR	NR	healed
Perkins A. et al., 2003 [20]	3/57/M	Dental procedures 4 and 5M before IE	Mitral regurgitation caused by myxomatous degeneration	<i>Granulicatella adiacens</i>	Mitral valve/ None	ampicillin 2g q6h x 4W and gentamicin 80 mg q8h x 2W	Sensitive	NR	healed
Woo P.C. et al., 2003 [9]	4/15/M	NR	Congenital heart disease	<i>Abiotrophia defectiva</i>	NR	NR	Sensitive	NR	healed
	5/74/F	NR	Chronic rheumatic heart disease	<i>Abiotrophia defectiva</i>	NR	NR	Sensitive	NR	Dead
	6/85/M	NR	Aortic regurgitation	<i>Granulicatella adiacens</i>	NR	NR	Sensitive	NR	Dead
Lainscak M. et al., 2005 [28]	7/62/M	Dental procedures 4M before IE, pneumonia	Aortic valve prosthesis	<i>Abiotrophia defectiva</i>	Prosthetic valve/ None	penicillin (5x10 ⁶ U q.i.d.) x 6W + gentamicin (120 mg b.i.d.) x 2W*	Sensitive	0.064 µg/ml	healed
	8/26/M	Inflammation of foot toe and tonsillitis 2W before	Marfan syndrome	<i>Abiotrophia defectiva</i>	Aortic valve/ None	penicillin (6x10 ⁶ U q.i.d.) x 6W + gentamicin (240 mg q.d.) x 2W	Sensitive	0.016 µg/ml	healed
Ohara-Nemoto Y. et al., 2005 [29]	9/53/F	Dental procedures 3M before IE	None	<i>Granulicatella elegans</i>	NR/ Surgery	penicillin (30 x10 ⁶ U/kg once a day) + gentamicin (3 mg/kg once a day) + surgery	Sensitive	0.06 µg/ml	healed

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References	Patient no./age (y)/sex	Related procedures	Risk factors for endocarditis	Identified species	Site of infection/ Surgery	Therapy	Penicillin Susceptibility	MIC	Outcome
Jeng A. et al., 2005 [16]	10/18/M	Dental procedures 3-4W before IE	Pulmonary valve prosthesis	<i>Granulicatella adiacens</i>	Prosthetic valve/ None	vancomycin + gentamicin + rifampin x 6W	NR	NR	healed
Senn L. et al., 2006 [30]	11/58/F	None	Rheumatic fever during childhood	<i>Abiotrophia defectiva</i>	Mitral valve/ NR	amoxicillin/ clavulanate + amikacin for 1w, then ceftriaxone for 3W***	Sensitive	NR	healed
	12/55/M	None	None	<i>Abiotrophia defectiva</i>	Aortic valve/NR	ceftriaxone for 6w + amikacin for 4W***	Reduced susceptibility	0.25 µg/ml	healed
Hernando Real S. et al., 2007 [31]	13/77/M	Dental procedures 4M before	None	<i>Granulicatella</i> spp	Aortic valve/ None	ampicillin 2g q4h + gentamicin 80mg q8h x 4W	Reduced susceptibility	NR	healed
Lin C.H., Hsu R.B. 2007 [32]	14/51/M	NR	Mitral valve prolapse	<i>Abiotrophia defectiva</i>	Mitral valve/ Repair	penicillin, gentamicin ^o	Sensitive	NR	healed
	15/12/F	NR	None	<i>Abiotrophia defectiva</i>	Mitral valve/ None	vancomycin, gentamicin, teicoplanin, rifampin, cefotaxime ^o	Sensitive	Ampicillin 0.19 µg/ml	healed
	16/65/M	NR	Mitral regurgitation	<i>Abiotrophia defectiva</i>	Mitral valve/ Repair	penicillin, gentamicin ^o	Resistant	penicillin 0.125 µg/ml	healed
	17/49/M	NR	None	<i>Abiotrophia defectiva</i>	Aortic valve/ Replacement	penicillin, gentamicin, ceftriaxone ^o	Sensitive	penicillin 0.032 µg/ml	healed
	18/18/F	NR	Rheumatic heart disease	<i>Granulicatella adiacens</i>	Mitral valve/ Replacement	penicillin, gentamicin ^o	Sensitive	NR	healed
	19/61/M	NR	None	<i>Granulicatella adiacens</i>	Mitral valve/ Replacement	penicillin, gentamicin ^o	Sensitive	NR	healed
	20/30/M	NR	None	<i>Granulicatella adiacens</i>	Mitral valve/ Repair	penicillin, gentamicin, ceftriaxone ^o	Sensitive	NR	healed
	21/28/F	NR	None	<i>Granulicatella adiacens</i>	Mitral valve/ Replacement	penicillin, gentamicin, vancomycin, teicoplanin ^o	Sensitive	NR	healed

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References	Patient no./age (y)/sex	Related procedures	Risk factors for endocarditis	Identified species	Site of infection/Surgery	Therapy	Penicillin Susceptibility	MIC	Outcome
Al Tawfiq J.A. et al., 2007 [33]	22/45/M	Dental procedures 3M before	Mitral valve prolapse	<i>Granulicatella elegans</i>	Mitral valve/Repair	non specified 6W antibiotic treatment	Sensitive	Penicillin 0.06 µg/ml	healed
PR	23/40/M	None	None	<i>Granulicatella adiacens</i>	Aortic valve/Replacement	ampicillin 2g q4h for 6W + gentamicin 80mg q8h for 2W	Sensitive	NR	Healed

Legend: AE = acute endocarditis; W = week; M = month; NR = not reported; PR = present case-report.
 *After 25 days of therapy with penicillin the patient developed macular rash and leucopenia; penicillin was substituted by ceftriaxone (2 g q.d.). **The duration of treatment was not reported. ***Doses were not reported. °Penicillin G 2 to 5 million Units q4h (up to 4-8 weeks) + Gentamicin (2 weeks). Ceftriaxone and vancomycin or teicoplanin administration if persistence of fever or high-level penicillin resistant streptococcus isolation.

tion (MBC) of penicillin greatly exceeds the minimum inhibitory concentration (MIC) (usually by 32-fold). These strains are killed more slowly by penicillin in animal models of endocarditis [14, 15].

Some authors found a high fibronectin binding ability of *A. defectiva* strains associated with endocarditis than the *Granulicatella* spp. isolated from patients with primary bacteremia and this may be an important factor involved in the pathogenesis of *A. defectiva* endovascular infections. *Granulicatella* spp. bacteremias were observed only when predisposing conditions such as mucositis and neutropenia were present, suggesting a low pathogenicity of the isolated strains.

Their poor ability to bind to extracellular matrix components could be correlated with a lower propensity to induce endocarditis [8]. On the contrary, other studies have demonstrated that *G. adiacens* bound fibronectin very avidly in adherence assays and readily caused endocarditis on damaged heart tissue in catheterized rats. *A. defectiva* also infected damaged heart tissue significantly, but had moderate levels of binding to fibronectin and other extracellular matrix proteins. Most of the *G. para-adiacens* and *G. elegans* strains exhibited low binding capacities to any extracellular matrix proteins and poorly infected heart tissue [16, 17].

Despite of old series showing a very high prevalence (90%) of preexisting heart disease, our case report and review of past 10 year literature seem to show an increased involvement

of normal heart valves [2, 7]. On the other hand, we have confirmed old data regarding prosthetic valve involvement (9%) [2, 7]. Unlike streptococci belonging to the *S. bovis* group, no association has been documented between NVS infective endocarditis and gastrointestinal diseases [18].

Treatment failure have been reported in about 41% of cases of IE caused by NVS, and almost 27% of cases required prosthetic valve replacement, especially due to congestive heart failure or major systemic emboli [3, 19, 20]. Treatment failure has been ascribed to the delay in beginning antimicrobial therapy attributable to the length of time required for isolation and identification of these bacteria and for antibiotic susceptibility testing.

The slower generation time for NVS (2-3 h) than that for viridans streptococci (40-50 min), may attenuate the activity of the beta-lactam antibiotics [16, 21]. In addition, NVS has shown increased resistance to penicillin, the mainstay of therapy for treatment of streptococcal endocarditis, with a recent survey finding that only 55% of *G. adiacens* isolates showed penicillin sensitivity, and 8% of *A. defectiva* isolates exhibited sensitivity [16, 22]. Of further concern is that NVS have demonstrated significant tolerance to penicillin, as defined by an MBC/MIC ratio greater than 32 [16]. Therefore, NVS show a similar antimicrobial susceptibility profile to enterococcal species such as *Enterococcus faecalis* and unusual enterococci including *Enterococcus raffinosus* [23].

Bouvet has observed that morbidity and mor-

tality of IE caused by *Abiotrophia* and *Granulicatella* spp. exceeded those of the other forms of viridans streptococcal and enterococcal endocarditis, and patients with endocarditis caused by *A. defectiva* and *Granulicatella* species should be treated with a regimen that is recommended for enterococcal endocarditis (4, 14). Daptomycin is a new drug potentially effective against *Abiotrophia* spp. and *Granulicatella* spp. [24]. However further studies are required to evaluate the possible role of this molecule in the treatment of endocarditis caused by NVS. Our literature review disclosed a higher penicillin sensitivity (78%) compared with old studies [2, 7]. This higher *in vitro* penicillin susceptibility seems to be concordant with a satisfactory rate of clinical successes. Overall, we have found a very low (9%) mortality rate, with heart valve surgery carried out in 48% of patients.

CONCLUSION

IE caused by NVS exhibits higher relapse, treatment failure and mortality rates than those caused by other oral streptococci. Based on our literature review, antimicrobial therapy with penicillin and gentamicin is considered a valuable option for the management of patients with this infection. However, early surgical intervention is often needed in the event of hemodynamic compromise due to extensive valve destruction. This is consistent with previous evidences highlighting the role of surgical interventions in reducing overall mortality compared with medical treatment alone [25].

Keywords: Infective Endocarditis (IE), Nutritionally Variant Streptococci (NVS), *Abiotrophia* spp., *Granulicatella* spp.

SUMMARY

Infective endocarditis (IE) due to *Abiotrophia* and *Granulicatella* species, previously referred to as nutritionally variant streptococci (NVS), occurs rarely and is often associated with negative blood cultures. Rates of treatment failure, infection relapse and mortality are higher than those of endocarditis caused by other viridans streptococci.

We report a case of endocarditis caused by *Granulicatella adiacens* in a young man with no risk factors, who was successfully treated with surgery and combination antimicrobial chemotherapy, and provide a literature review of endocarditis attributable to these rare species of fastidious gram-positive cocci which have proven exceedingly difficult to treat,

with high rates of relapse and therapeutic failure despite *in vitro* effective antibiotic treatment regimens. Analysis of literature revealed a high prevalence (61%) of valvular heart predisposing conditions associated with endocarditis caused by NVS, such as congenital valvular heart disease or heart valve prosthesis. On the other hand, 39% of cases showed no evidence of risk factors. Combination antimicrobial chemotherapy with penicillin and gentamicin represents the antimicrobial treatment of choice in the management of patients with IE attributable to NVS. Heart valve replacement surgery should be considered in cases of hemodynamic derangement due to significant valve destruction.

RIASSUNTO

L'endocardite infettiva dovuta a batteri appartenenti ai generi *Abiotrophia* e *Granulicatella*, precedentemente noti come varianti streptococciche di tipo nutrizionale (VSN), è un evento raro e spesso associato ad emocolture negative. I tassi di fallimento terapeutico, recidiva di infezione e mortalità sono più elevati rispetto a quelli che si riscontrano nelle endocarditi causate da streptococchi viridanti.

Riportiamo un caso di endocardite causata da *Granulicatella adiacens* in un giovane paziente con anamnesi patologica negativa per fattori di rischio di endocardite, trattato con successo mediante l'associazione di un intervento di sostituzione valvolare e di chemioterapia antimicrobica di combinazione. Forniamo, inoltre, una revisione della letteratura relativa ai casi di endocardite

dovuta a queste rare specie di cocchi Gram-positivi di difficile isolamento in laboratorio, il cui isolamento clinico risulta associato ad elevata prevalenza di recidive e fallimenti terapeutici, nonostante l'impiego di antibiotici attivi *in vitro*. L'analisi della letteratura ha rivelato un'elevata frequenza (61%) di condizioni predisponenti associate all'insorgenza di endocardite da VSN, come per esempio valvulopatie congenite o valvole protesiche. D'altra parte il 39% dei pazienti affetti non ha mostrato evidenza di condizioni predisponenti. Il trattamento di scelta nel trattamento dei pazienti affetti da endocardite causata da VSN è rappresentata dalla combinazione di penicillina e gentamicina. L'intervento di sostituzione valvolare dovrebbe essere considerato in caso di compromissione emodinamica dovuta ad esteso danno valvolare.

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