



Bicuspid aortic valve endocarditis caused by *Gemella sanguinis*: Case report and literature review

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ARTICLE INFO

Article history:

Received 26 September 2018

Received in revised form

19 December 2018

Accepted 3 January 2019

Keywords:

Gemella sanguinis

Infective endocarditis

Bicuspid aortic valve

Aortic regurgitation

ABSTRACT

Gemella species are catalase-negative, facultative anaerobic, Gram-positive cocci, which are part of the human oral microbiome and may occasionally cause systemic infections. Infective endocarditis (IE) has been reported as the most common infection caused by *Gemella* species. We report the first case of IE due to *Gemella sanguinis* in Greece, in a patient with bicuspid aortic valve and review the available literature. The patient was successfully treated with antibiotics and aortic valve replacement.

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Contents

Introduction	304
Case report	305
Discussion	306
Funding	308
Competing interests	308
Ethical approval	308
References	308

Introduction

Infective endocarditis (IE) remains a severe illness associated with high morbidity and mortality [1]. *Staphylococcus aureus*, viridans streptococci and *Enterococcus* spp. are the most common causative pathogens identified [2].

Gemella species are a newly discovered genus differentiated from viridans group streptococci only by 1960. *G. haemolysans* was the first described species of the genus *Gemella*. Nine species, namely, *G. haemolysans*, *G. morbillorum*, *G. bergeri*, *G. sanguinis*, *G.*

assacharolytica, *G. taiwanensis*, *G. parahaemolysans*, *G. palaticanis*, and *G. cuniculi*, are currently recognized. Only the first 7 species have been associated with human infection [3]. *Gemella* species colonize the oral cavity and are associated with opportunistic infections in immunocompromised patients. IE is the most frequent type of infection caused by *Gemella*. Other infections associated with *Gemella* spp. include septic arthritis, osteomyelitis, spondylodiscitis, empyema, lung abscess, foreign device infections, and meningitis [3]. *G. sanguinis* was first isolated in 1998 from blood cultures of 6 patients with bacteremia, one of whom was diagnosed with IE [4]. Since then, 11 cases of *G. sanguinis* have been published in the medical literature [5–14].

We describe the first case of bicuspid aortic valve endocarditis caused by *G. sanguinis* in Greece and present a concise review of the literature.

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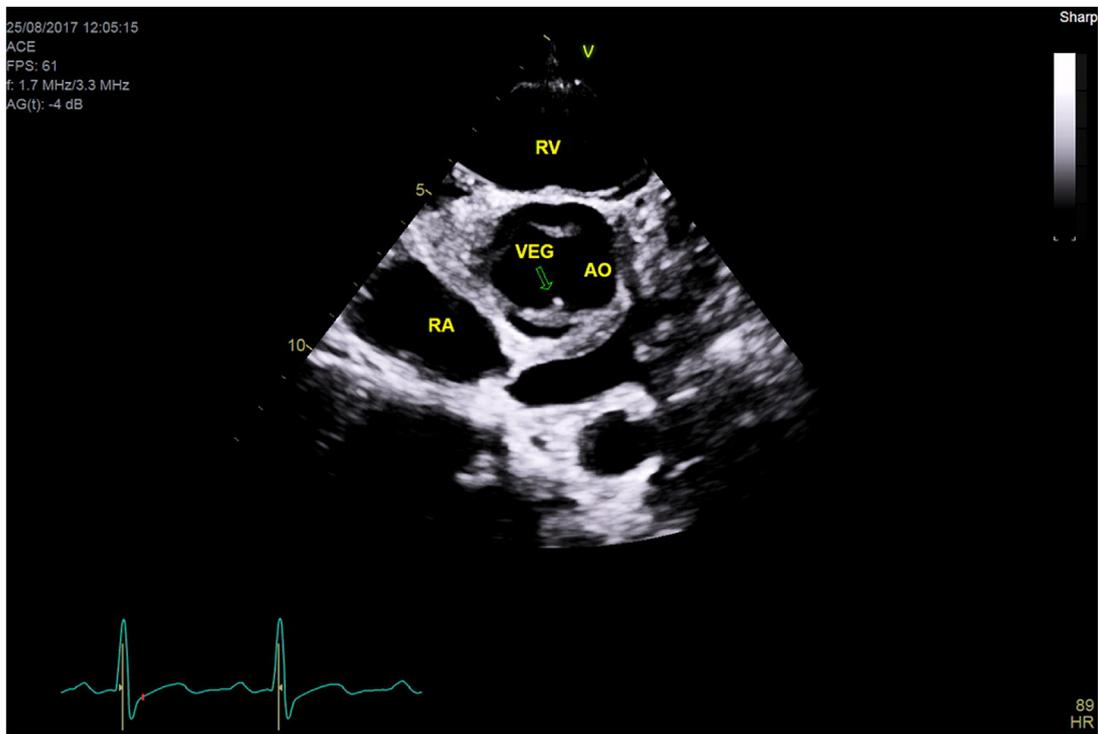


Fig. 1. Transthoracic echocardiography, parasternal short axis view (level of great vessels) showing small vegetation of the posterior leaflet of the bicuspid aortic valve (arrow). RA, right atrium; RV, right ventricle; AO, aorta; Veg, vegetation.

Case report

A 21-year-old male presented to our hospital with a 10-day history of fever. Recent history in the preceding 2-months was pertinent for poor appetite, weakness, fatigue, marked weight loss (~15 kg in 2 months), and arthralgias. Notably, he had undergone dental cleaning and extraction of the third molar 2 months before admission. The patient had a history of bicuspid aortic valve with moderate regurgitation and he did not receive antibiotic prophylaxis before the dental procedures.

Physical examination revealed pallor, a psoriasis like rash of the scalp and symmetrical tenderness of the proximal joints of the fingers and the left ankle. On admission, he was afebrile. Other vital signs were grossly within normal limits. Oral examination revealed poor dental hygiene with dental caries.

On lung auscultation no pathological findings were detected. Cardiopulmonary auscultation was significant for an early Grade IV diastolic murmur best heard in the left third intercostal space, consistent with an aortic valve regurgitation murmur, and an holosystolic murmur best heard at the apex, consistent with a mitral valve regurgitation murmur.

Abdominal examination was normal, neurological status and remaining systemic examinations were all within normal limits. No immunological phenomena (Roth spots, Osler nodes) and vascular phenomena (Janeway lesions, conjunctival petechiae) were observed.

Laboratory investigations on admission revealed a total white blood cell count 7,500/ μ l (72.8% neutrophils), hemoglobin 11.2 g/dl, platelet count 223,000/ μ l, erythrocyte sedimentation rate of 52 mm/h and C-reactive protein of 9.11 mg/dl (normal range: 0.08–0.8 mg/dl). Electrolytes, blood urea nitrogen, creatinine, glucose and liver enzymes were within normal levels. Urinary analysis was normal.

A chest X-ray on admission had no abnormalities. An abdominal ultrasonography showed mild hepatomegaly and splenomegaly.

Electrocardiography demonstrated normal sinus rhythm at 93 beats/minute. A transthoracic echocardiography (TTE) revealed a bicuspid aortic valve with a 5mm-vegetation on the posterior leaflet, climbing over the leaflet, with moderate to severe aortic regurgitation (Fig. 1, Fig. 2). Transesophageal echocardiography (TEE) confirmed the findings of TTE. Fever up to 38.5°C was recorded during hospitalization and a total of three sets of blood cultures were obtained during the first week. Empiric antibiotic therapy was initiated pending culture results with a combination of intravenous (IV) ceftriaxone (2 g every 24 h), gentamicin (200 mg every 24 h) and daptomycin (500 mg every 24 h).

Following 37 h of incubation, all 3 sets of blood cultures yielded a Gram-positive coccus, catalase-negative, that produced acid from mannitol, sorbitol and sucrose. It also produced alkaline phosphatase, acid phosphatase, ester lipase C8, and alanine-phenylalanine-proline arylamidase. The isolate was identified as *G. sanguinis* by the Vitek 2 automated system (Marcy L' Etoile, France). Molecular confirmation of the isolate identity was achieved through sequencing of 1289 nt from the 16S rRNA gene. Briefly, a PCR product using universal primers was sequenced by the Sanger method (Macrogen) and the derived nucleotide sequence was aligned against the publicly available sequences of the database (www.ncbi.nlm.nih.gov) using the BLAST tool. Our sequence clustered phylogenetically with *G. sanguinis* along with 66 partial sequences of 16S RNA available in the data library (tree not shown) and exhibited 100% identity with *G. sanguinis* isolate NTUH8428.

Our patient fulfilled modified Duke's criteria for IE diagnosis according to the American Heart Association (AHA) guidelines [15]. Specifically, two major criteria were present in our case, including (i) evidence of a 0.5 cm oscillating mass on the posterior leaflet of the bicuspid aortic valve observed in TTE and TEE, and (ii) three positive blood cultures obtained >12 h apart from the patient with growth of an organism (*Gemella* spp.) consistent with the diagnosis of IE.

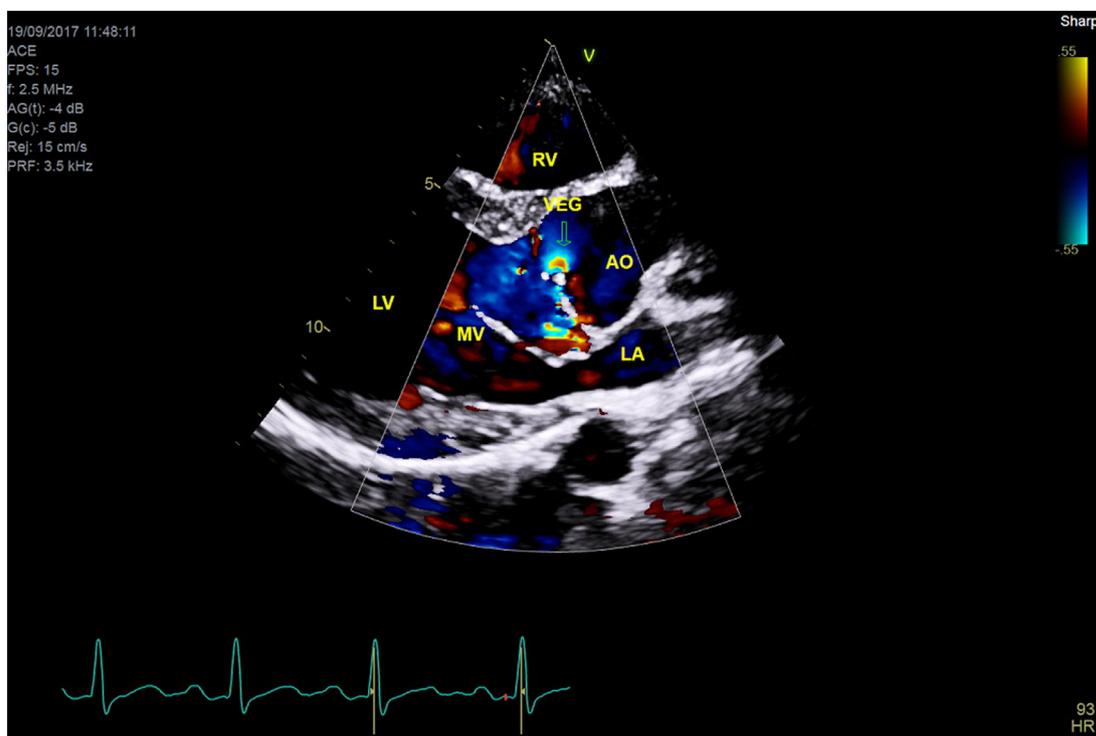


Fig. 2. Transthoracic echocardiography, parasternal long axis view showing eccentric regurgitation jet of the bicuspid aortic valve with direction to the anterior mitral valve leaflet. LA, left atrium; RV, right ventricle; LV, left ventricle; MV, mitral valve; AO, aorta; Veg, vegetation.

Table 1
E-test MICs for the *Gemella sanguinis* isolate

Antibiotic	MIC ($\mu\text{g/ml}$)	Interpretation
Penicillin	0.008	S
Cefotaxime	0.004	S
Ceftriaxone	0.006	S
Meropenem	0.003	S
Vancomycin	0.75	S
Erythromycin	0.023	S
Clindamycin	0.023	S
Levofloxacin	0.125	S

MIC, minimum inhibitory concentration; S, susceptible.

The antimicrobial susceptibility testing was performed by the E-test method and the results were interpreted according to the Clinical and Laboratory Standards Institute guidelines [16]. The organism was susceptible to all antibiotics tested, including penicillin, cefotaxime, ceftriaxone, meropenem, vancomycin, erythromycin, clindamycin, and levofloxacin (Table 1). Once antimicrobial susceptibilities were available, daptomycin was discontinued. Treatment was continued with intravenous ceftriaxone for 6 weeks and gentamicin for 2 weeks. The patient responded well to this antibiotic treatment. Fever, weakness, fatigue and arthralgias resolved, C-reactive protein declined (0.31 mg/dl) and multiple blood cultures were all negative. The dental caries were treated as a likely cause of bacteremia and IE. A new TEE showed a reduction in the size of the vegetation and moderate to severe aortic regurgitation. After his 6-week course of antibiotic treatment, the patient underwent surgery with a successful aortic valve replacement. His postoperative course was uneventful. He has been followed-up clinically and has been doing well at 1-year after the surgery.

Discussion

Infective endocarditis (IE) is an evolving disease and this is reflected in the changing risk factors associated with the disease.

Over the past three decades the clinical and microbiologic profile of IE has been changed. *S. aureus* and enterococcal endocarditis increased with concurrent decrease in viridans group streptococci. These changes have been attributed to increases in elderly population, higher levels of healthcare-related exposure, increasing use of intracardiac and vascular devices, increasing rates of intravenous drug use, and decrease in rheumatic heart disease [17,18]. A recent study from our institution evaluating IE's epidemiology and microbiology over the last two decades found *S. aureus* to be the leading causative pathogen. *Gemella* species have been rarely isolated [19].

IE caused by *Gemella* species are rare with the species *G. morbillorum* and *G. haemolysans* being the most frequent. *G. sanguinis* can be differentiated from other *Gemella* species by conventional microbiological tests. The automated system Vitek 2 provide reliable identification of Gram-positive cocci, including *G. sanguinis*, due to the improvement and the extension of its database [20]. However, confirmation of the identification to the species level should be performed using 16S rRNA gene sequence analysis [4].

G. sanguinis is seldom associated with infections other than rare cases of infective endocarditis, one case of bacteremia with thrombophlebitis of the superior mesenteric vein and one case of prosthetic joint infection [4–14,21,22]. A review of the medical literature since 1998 showed only 11 previously reported cases of *G. sanguinis* endocarditis, with the majority (81.8%) affecting native valves [4–14] (Table 2). Nine (75%) of the 12 patients (including the present case) were males. The patient ages ranged from 4 to 73 years (mean, 48 years).

Predisposing factors included poor dental hygiene, dental procedures, diabetes mellitus and end-stage renal disease. Underlying cardiac pathologies included rheumatic heart disease, surgically repaired intracardiac lesions, and congenitally bicuspid aortic valve. In three cases, neither the source of infection nor underlying intracardiac lesions were found. In our patient, both recent dental surgery with residual poor dental hygiene and the structural abnormality of the aortic valve, were present.

Table 2
Characteristics of patients with *Gemella sanguinis* endocarditis.

Year of report	Ref. no.	Age (yrs)/ Gender	Risk factors for infective endocarditis	Comorbidities	Valve lesion	Antimicrobial therapy/ Valve replacement	Outcome
1998	4	69/M	NR	NR	NR	NR/NR	NR
2002	5	69/M	Periodontal disease Dental abscess Prednisone use Dental caries	COPD	MR (V)	Vancomycin + gentamicin/Yes	Recovery
2009	6	73/M	Diabetes mellitus End-stage renal disease Repaired ventricular septal defect	Hypertension	MR (V)	Ampicillin- sulbactam + gentamicin/No	Death
2009	7	23/M	Aortic valve regurgitation Oral ulcers Rheumatic heart disease	Behcet's dis- ease	AR (V)	Ceftriaxone + gentamicin/No	Death
2011	8	26/F	Mechanical aortic and mitral valve replacement Dental caries Recent root canal treatment Rheumatic heart disease	None	AV	Ceftriaxone + gentamicin/Yes	Recovery
2012	9	27/F	Mechanical aortic and mitral valve replacement Extensive tooth decay	None	AV	Ceftriaxone + gentamicin/Yes	Recovery
2013	10	73/M	None	Hypertension	AR (V), MR	Daptomycin + gentamicin/Yes	Recovery
2013	11	67/M	Dental caries	None	MR (V), AR, TR	Penicillin G + gentamicin/Yes	Recovery
2014	12	67/M	Bicuspid aortic valve	None	AR	Penicillin/Yes	Recovery
2015	13	57/F	None	None	AV	Penicillin G + gentamicin/Yes	Recovery
2016	14	4/M	None	None	TR (V)	Vancomycin + gentamicin/Yes	Recovery
2017	Present case	21/M	Bicuspid aortic valve Dental caries/procedures	None	AR (V)	Ceftriaxone + gentamicin/Yes	Recovery

NR, not reported; COPD, chronic obstructive pulmonary disease; MR, mitral regurgitation; V, vegetation. AR, aortic regurgitation; TR, tricuspid regurgitation.

Aortic valve was more frequently affected than mitral valve, while tricuspid valve was rarely involved. The incidence of IE in the bicuspid aortic valve (BAV) population is reported to be between 10 and 30%, predominantly in children and young adults, as in our case [23]. A recent European study analyzing over 3000 IE cases of which 54 occurred in patients with BAV, found higher incidence of viridans group streptococci IE and increased IE of dental origin in patients with BAV than in other IE patients. Of the 54 IE cases only one was caused by *Gemella* species [24].

Patients with bicuspid aortic valve are considered of intermediate risk for IE and do not require antimicrobial prophylaxis for dental procedures according to the current guidelines of both the AHA and the European Society of Cardiology (ESC) [15,25]. Additionally, dental cleaning and dental extraction are not included among dental procedures at high risk for endocarditis. Therefore, our patient did not receive antimicrobial prophylaxis, in accordance with the guidelines. However, the clinical course of IE in patients with BAV and mitral valve prolapse (considered of moderate risk of IE) found to be similar to that of high-risk patients, suggests the need to reconsider IE prophylaxis indication for this group of patients [24].

Disease presentation and progression appear to be variable. In our case, IE was presented as a subacute disease starting insidiously with subtle symptoms, such as intermittent spiking fever, fatigue, weight loss and arthralgias, two months before diagnosis. Similar presentation of the disease has been described in eight other cases [6–11,13,14].

Empirical antimicrobial therapy should be started after blood cultures have been taken. The selection of an optimal empiric regimen is usually broad and is based on factors that relate to patient characteristics, prior antimicrobial exposures, and epidemiological features [15]. In our case, ceftriaxone combined with gentamicin and daptomycin were administered after consultation with infectious diseases specialist.

Once the pathogen is identified as *Gemella* species, the choice of antimicrobial treatment regimens depends on penicillin minimal inhibitory concentration (MIC) data. For highly susceptible

organisms (penicillin MIC ≤ 0.12 $\mu\text{g/ml}$), as in our case, AHA recommends the following parenteral treatment schedules: (i) 4 weeks of monotherapy with either penicillin G or ceftriaxone; (ii) 2 weeks of combination therapy with penicillin or ceftriaxone and gentamicin in patients with uncomplicated IE and no renal disease; and (iii) 4 weeks of monotherapy with vancomycin in patients who cannot tolerate penicillin or ceftriaxone therapy [15]. Our patient received ceftriaxone for 6 weeks combined with gentamicin for 2 weeks. Prolonged therapy with ceftriaxone was given to ensure complete eradication of microorganisms within vegetation because of their high bacterial densities and the relatively slow bactericidal activity of the antimicrobial agent. The majority of the reported cases of IE by *G. sanguinis* were bacteriologically cured with a combination of a beta-lactam, penicillin or ceftriaxone and gentamicin. For penicillin-resistant or penicillin-allergic patients, vancomycin or daptomycin in combination with gentamicin have been effective.

Of the twelve patients, 9 (75%) survived and underwent surgical valve replacement. The 2017 AHA/ACC Valvular Heart Disease Guidelines update recommends early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) for cases with (a) large vegetations with embolic complications or severe valvular stenosis; (b) very large vegetations (>10 mm); (c) significant valve dysfunction or fistula resulting in symptoms of heart failure; (d) left-sided IE caused by fungi or other multidrug-resistant organisms; (e) IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions; (f) evidence of persistent infection 5 to 7 days after initiation of appropriate antimicrobial therapy [26]. In our patient surgery was done because of the severe valvular dysfunction, after completion of the antibiotic course. The decision on the indication and timing of surgical intervention was determined by a multispecialty team with expertise in cardiology, cardiothoracic surgery, and infectious diseases.

In conclusion, *G. sanguinis* should be considered as a cause of IE, particularly in patients with predisposing conditions and subacute clinical presentation. Prolonged antibiotic treatment combined with early surgical valve replacement in complicated cases are necessary to achieve a favorable clinical outcome.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

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