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Case Report

Case Series of *Granulicatella* Bacteremia: A Single-centered, Five-year Retrospective Study

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***Granulicatella* species are rare, nutritionally variant streptococci that cause infective endocarditis. Their clinical and microbiological characteristics remain unknown. We reviewed five years of *Granulicatella* cases in our hospital database (Jan 2017-Jun 2022), finding 6 *Granulicatella adiacens* cases and 1 *Granulicatella elegans* case. Clinical backgrounds and bacteremia sources were diverse; 3 cases developed polymicrobial bacteremia. Antimicrobial testing showed non-susceptibility to penicillin G in 4 of 7 cases (57.1%), and high susceptibility to carbapenems and vancomycin in all cases. Determining optimal antibiotic therapy for *Granulicatella* infections is vital in this era of antimicrobial resistance.**

Key words: antimicrobial resistance, bacteremia, *Granulicatella* species, nutritionally variant streptococci

Nutritionally variant streptococci (NVS) are rare Gram-positive organisms that require L-cysteine or pyridoxal-supplemented medium for growth [1]. NVS are comprised of *Abiotrophia* and *Granulicatella* species, known representative pathogens of infective endocarditis (IE) [2]. In addition to IE cases, NVS have the potential to cause various infections, including in bone and soft tissue [3,4], prosthetic joints [5], muscle abscesses secondary to infectious purulent thrombophlebitis [6], and vertebral osteomyelitis [7]. Granulicatella species are reported to be common in NVS strains, accounting for more than 70% of isolates, including *Granulicatella adiacens* (67-71%) and *Granulicatella elegans* (3.3-4.4%) [2,8].

In terms of antimicrobial susceptibility, *Granulicatella* species are generally susceptible to vancomycin, although *G. adiacens* has frequently shown non-susceptibility to penicillin [2,8]. *Granulicatella*-associated IE is clinically common, and a treatment strategy is established in the guidelines [9,10]. However, due to limited case numbers, the clinical and microbiological characteristics of cases of *Granulicatella* non-IE bacteremia remain unclear. In this paper, we describe seven cases of *Granulicatella* bacteremia identified at our institute.

Cases

This retrospective case series study was performed at Okayama University Hospital, an 865-bed tertiary hospital in Japan. We referred to the microbiological database to identify cases of *Granulicatella* species in blood cultures between January 2017 and June 2022. Our institute has an in-house microbiology laboratory equipped with automated blood culture systems (BD BACTEC™ FX system; Becton, Dickinson, and Company, NJ, USA). Two sets of blood culture samples per patient were routinely sent to the laboratory,

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and the incubation period of blood cultures was seven days. We excluded patients aged <16 years because those 15 and younger were usually treated by pediatricians, and most had only one set of blood cultures in our hospital.

The bacteria were identified by mass spectrophotometry (MALDI Biotyper; Bruker Scientific, Billerica, MA), and antimicrobial susceptibility testing was performed using the microdilution method on the dry plate Eiken (Eiken Chemical Co., Tokyo) to determine the minimum inhibitory concentration (MIC). Nosocomial infections were defined as those occurring more than 48 h after hospital admission and were detected in the first positive blood culture [11].

Information on age, sex, underlying diseases, isolated organisms, infectious foci, presence or absence of IE, echocardiographic examinations, course of treatment, and patient outcomes were evaluated from medical records. The sources of bacteremia were determined based on the diagnoses reported in the medical records. The outcome measure was survival or death at 30 days after onset.

During the study period, we identified 7 patients with *Granulicatella* bacteremia: 6 cases (85.7%) of *G. adiacens*, and 1 case (14.3%) of *G. elegans* (Table 1). Patient age ranged from 21-82 years, without predisposition to sex or onset of disease. Nosocomial and community outbreaks were observed in 3 and 4 cases, respectively. Regarding the underlying diseases, 3 cases did not have comorbidities, 3 had malignancy, and 1 had type 2 diabetes mellitus and end-stage renal disease treated with hemodialysis. The causes of bacteremia were varied and included intra-abdominal abscess, central line catheter-induced septicemia, bacterial translocation, intrauterine infection, pneumonia, psoas abscess, osteomyelitis, and decubitus. No cases were diagnosed as IE, although echocardiography was not performed in 4 cases. While no cases had persistent bacteremia or recurrence, polymicrobial bacteremia infection was implicated in 3 cases.

Table 2 presents the results of antibiotic susceptibility tests. Four cases showed non-susceptibility to penicillin G (≥0.25 μg/mL), whereas one was non-susceptible to ceftriaxone (>2 μg/mL). Antibiotics in the carbapenem class were almost always sensitive. The MIC of vancomycin was studied in 3 cases, with all strains tested showing susceptibility. As empiric therapy, 3 patients were started on a vancomycin-based

Table 1 Clinical data of seven cases of *Granulicatella* bacteremia

Case No.	Year	Age, sex	Onset	Underlying diseases	Risk for IE	Source of bacteremia	Persistent bacteremia	Echocardiography	IE	Other pathogens	Recurrence
Case 1	2020	60, M	Nosocomial	HCC	None	Intra-abdominal abscess	None	None	N/D	*Streptococcus parasanguinis* *Haemophilus parainfluenza* *Staphylococcus capitis*	None
Case 2	2020	46, F	Nosocomial	ALL	None	CLABSI	None	TTE only	None	None	None
Case 3	2020	42, F	Nosocomial	AML	None	Bacterial translocation	None	TTE only	None	None	None
Case 4	2021	44, F	Community	None	None	Intrauterine infection	N/D	None	N/D	*Fusobacteium* spp *Staphylococcus lugdunensis*	None
Case 5	2022	21, F	Community	None	None	Pneumonia	None	None	N/D	None	None
Case 6	2022	82, M	Community	T2DM, ESRD	None	Psoas abscess, Osteomyelitis	None	TTE and TEE	None	None	None
Case 7	2022	64, M	Community	None	None	Decubitus, pneumonia	N/D	None	N/D	*Staphylococcus hominis*	None

No infective endocarditis (IE) case was diagnosed. Risk for IE includes the presence of prosthetic valve or previous history of IE.
Abbreviations: ALL, acute lymphoblastic leukemia. AML, acute myeloid leukemia. CLABSI, central line associated bloodstream infection. T2DM, type 2 diabetes mellitus. HCC, hepatic cell carcinoma. ESRD, end-stage renal disease. TTE, transthoracic echocardiography. TEE, transesophageal echocardiography. N/D, no data.

regimen, 3 received ceftriaxone monotherapy, and 1 was treated with cefmetazole (Table 3). The definitive antibiotic treatment depended on the individual case; vancomycin and carbapenems were administered in 3 cases. The prognosis was favorable for patients. Although 1 died of a concomitant severe traumatic injury, clinical improvement was observed in the remaining 6 of 7 cases.

In this case series, we summarized the clinical and microbiological characteristics of *Granulicatella* bacteremia diagnosed at our college hospital. The results suggested that: (i) the clinical histories of patients with *Granulicatella* bacteremia vary in terms of onset, underlying disease, and source of bacteremia, which often presents as polymicrobial bacteremia; and (ii) while antimicrobial susceptibility depends on the iso-

Table 2 Antimicrobial susceptibility testing of *Granulicatella* species

	Species	Antibiotics	PCG	ABPC	CTRX (CTX)	CFPM	IPM	MEPM	LVFX	CLDM	VCM
Case 1	*G. adiacens*	MIC (μg/mL)	≤0.06	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	>8	≤0.25	n.t.
		Susceptibility	S	S	S	S	S	S	R	S	–
Case 2	*G. adiacens*	MIC (μg/mL)	0.25	1	0.5	0.5	≤0.25	0.5	1	>8	n.t.
		Susceptibility	I	I	S	S	S	S	S	R	–
Case 3	*G. elegans*	MIC (μg/mL)	2	0.5	1	2	≤0.25	1	>8	>8	n.t.
		Susceptibility	I	I	S	I	S	I	R	R	–
Case 4	*G. adiacens*	MIC (μg/mL)	≤0.06	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	0.5	>8	n.t.
		Susceptibility	S	S	S	S	S	S	S	R	–
Case 5	*G. adiacens*	MIC (μg/mL)	0.25	0.25	0.5	1	≤0.12	0.12	>4	≤0.25	0.5
		Susceptibility	I	S	S	S	S	S	R	S	S
Case 6	*G. adiacens*	MIC (μg/mL)	1	1	>2	>2	≤0.12	0.5	2	>2	1
		Susceptibility	I	I	R	R	S	S	S	R	S
Case 7	*G. adiacens*	MIC (μg/mL)	≤0.06	≤0.12	≤0.25	≤0.25	≤0.12	≤0.06	≤1	≤0.25	0.5
		Susceptibility	S	S	S	S	S	S	S	S	S

Abbreviations: MIC: minimum inhibitory concentration (μg/mL). S, susceptibility. I, intermediate. R, resistant. n.t: note tested. PCG, penicillin G; ABPC, ampicillin; CTRX (CTX), ceftriaxone (cefotaxime); CFPM, cefepime; IPM, imipenem; MEPM, meropenem; LVFX, levofloxacin; MINO, minocycline; CLDM, clindamycin; VCM, vancomycin.
Susceptibility testing was performed using Dry Plate Eiken (Eiken Co. Ltd., Tokyo, Japan), and the results were evaluated on the basis of Clinical and Laboratory Standards Institute M45-A2.

Table 3 Treatment and outcome of seven *Granulicatella* bacteremia cases

	Antibiotic treatment		30-day Outcome
	Empiric	Definitive	
Case 1	Vancomycin + Meropenem	Vancomycin + Ceftriaxone	Survived
Case 2	Vancomycin	Meropenem + Penicillin G + Gentamicin	Survived
Case 3	Vancomycin + Meropenem	Imipenem/Cilastatin	Survived
Case 4	Cefmetazole	Piperacillin/Tazobactam	Survived
Case 5	Ceftriaxone	Ceftriaxone	Death
Case 6	Ceftriaxone	Vancomycin + Imipenem/Cilastatin	Survived
Case 7	Ceftriaxone	Vancomycin	Survived

lates, the patient prognosis is generally favorable.

Discussion

Granulicatella bacteremia can affect a wide range of patients, from previously healthy individuals with community-onset disease to hospitalized patients with severe underlying illness. The sites of infection also vary among cases, and we should note that *Granulicatella* bacteremia is ubiquitous in any clinical setting, although relatively rare. *Granulicatella* species are among the organisms in the oral cavity, and patients with malignant neoplasms and mucosal disorders should be considered at higher risk of infection [12]. A recent study reported that the maternal vaginal microbiome is often composed of *Granulicatella* species, which can cause perinatal infection [13]. Furthermore, the development of polymicrobial infection is common for *Granulicatella* species [5], as seen in our case series.

Importantly, NVS are high-risk microorganisms that cause IE, with *Granulicatella* species predominating [2]. Based on a study that examined the prevalence of IE in streptococci, the odds ratio of *G. adiacens* compared to *Streptococcus pneumoniae* for potential IE was 28.1 [14]. Of the 7 cases in this study, echocardiography was not performed in 4, and repeat blood cultures were not obtained in 2, indicating the insidious complication of IE in our cases. Despite the insufficient examinations, no patient was diagnosed with endocarditis, perhaps due to the absence of risk factors for IE among patients. However, echocardiography should have been performed for all patients because NVS were detected in the blood cultures. We emphasize the importance of a complete investigation of the IE findings in every case of NVS bacteremia.

Antimicrobial susceptibility testing is critical for determining a therapeutic strategy for NVS infection, because susceptibility varies from strain to strain. Unlike other streptococcal species, NVS strains often show resistance to penicillin antibiotics [2,8,15]; in the literature, penicillin susceptibility in *G. adiacens* has been shown to be 34-83% [2,3,15]. In our cases, only about half of the *Granulicatella* strains were susceptible to penicillin G and ampicillin. Clinical strains of NVS remain susceptible to vancomycin without high resistance to aminoglycosides [2]. The treatment protocol for NVS-associated IE was established by the European Society of Cardiology, which recommends 6 weeks of penicillin G, ceftriaxone, and vancomycin, along with at least 2 weeks of gentamicin [10]. The American Heart Association guidelines also recommend treatment for patients infected with streptococci or other *Abiotrophia* and *Granulicatella* species that have elevated MICs (>0.5 μg/mL) for penicillin; the guidelines recommend penicillin G or ampicillin in combination with gentamicin in such cases, with further treatment to be determined in consultation with infectious disease specialists [9]. None of our patients developed IE; most were treated with vancomycin or carbapenem and had a good outcome. However, considering the antimicrobial susceptibility tests, antibiotics with a narrower spectrum might have been the first choice.

Conclusions

We described a case series of *Granulicatella* bacteremia treated at our medical facility. The clinical background, infectious conditions, and antimicrobial susceptibility varied among cases. While the prognosis of patients was favorable, most were treated with broad-spectrum antibiotics. In an era of antimicrobial resistance, the importance of antimicrobial stewardship is increasingly emphasized. *Granulicatella* species tend to show resistance to various antibiotics, and proper use of antibiotics is required for such infections.

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