





Granulicatella adiacens as an Unusual Cause of Empyema: A Case Report and Review of Literature

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Abstract

Granulicatella adiacens, a nutritionally variant *Streptococcus* (NVS), is part of the normal commensal flora of human mouth, genital, and intestinal tracts and rarely causes disease. It has been mostly reported from bacteremia and endocarditis cases, but rarely can cause vertebral osteomyelitis, pancreatic abscess, otitis media, and endovascular, central nervous system, ocular, oral, bone and joint, and genitourinary infections. Due to requirement of fastidious culture conditions and non-specific colony morphology, serious diagnostic difficulties may arise in cases of NVS infections. Here, we are reporting a rare fatal infection of *G. adiacens* presented with empyema complicated to sepsis and necrotizing fasciitis.

Keywords

- ▶ empyema
- ▶ *Granulicatella adiacens*
- ▶ nutritionally variant *Streptococcus*
- ▶ sepsis

Clinicians should be aware of the pathogenic potential of *Granulicatella adiacens* (a normal commensal flora of human mouth, genital and intestinal tracts). Appropriate supplemented media and a reliable detection system should be used to identify these fastidious organisms. We present this rare case to bring awareness among clinicians regarding such a rare but potentially fatal infection.

Introduction

Granulicatella adiacens is a nutritionally variant *Streptococcus* (NVS). Pyridoxine or other additional agents supplementation into standard media is required for its laboratory isolation.¹ Taxonomically, these bacteria were transferred from *Streptococcus* to a separate genus *Abiotrophia*² and later, on the basis of 16S rRNA gene sequencing this genus was divided into the genera *Abiotrophia* and *Granulicatella* (species *Granulicatella adiacens*, *G. elegans*, and *G. balaenopterae*).³

Granulicatella is part of the normal commensal flora of human mouth, genital and intestinal tracts and rarely causes disease. *Granulicatella adiacens* has been mostly reported to cause bacteremia and endocarditis, but rarely can cause vertebral osteomyelitis, pancreatic abscess, otitis media and endovascular, central nervous system, ocular, oral, bone and joint and genitourinary infections.⁴

Infections due to nutritionally variant *Streptococcus* may have a high mortality rate because of difficulties in robust

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and reliable diagnosis and therapeutic failures. In a recent survey, mortality rate in nutritionally variant *Streptococcus* infections was found to be 9.0%.⁵ For treatment of *Abiotrophia* and *Granulicatella* endocarditis and other serious infections, penicillin or ceftriaxone is the drug of choice as per the American Heart Association (AHA) guidelines.⁶ Through this article, we present a review and our experience of a rare case of empyema caused due to *G. adiacens* complicated to sepsis and necrotizing fasciitis and ultimately death.

Materials and Methods

Case History

A 68-year-old male patient presented with left side chest pain and pain in lower limbs to the emergency department. On examination, the body temperature was 38.5°C, blood pressure 78/50 mm Hg, and pulse rate was 93/min. On chest examination, heart sounds were normal but respiratory rate was 28/min, vesicular breath sound and crepitations were present in the left chest. He was a known case of type 2 diabetes mellitus, hypertension and osteoarthritis of knee joints. He was alcoholic. Chest X-ray showed left-sided encysted pleural effusion. The patient was diagnosed with left-sided empyema with ruptured baker's cyst and septic shock. On ultrasound-guided aspiration, thick pus was aspirated and sent for biochemical analysis, bacteriological culture and sensitivity, Ziehl-Neelsen stain and CBNAAT (Cartridge-based nucleic acid amplification test). Simultaneously, one set of blood (BACT/ALERT FA Plus and BACT/ALERT FN Plus) and urine samples were sent for bacteriological culture. The patient was diagnosed as a case of left-sided empyema with septic shock and transferred to the ICU for management. Intercostal chest tube was placed and fluid was drained. The patient was managed with intravenous saline infusion and empirical antibiotic (inj. cefuroxime) was started. Laboratory findings showed an increased total leukocyte count (18,580/mm³), absolute neutrophil count (17,290/mm³), increased C-reactive protein (CRP 11.2 mg/dL), and hemoglobin level was 11.2 g/dL. Fasting blood sugar was 201 g/dL and serum uric acid was 8.9 mg/dL. Kidney function test was also deranged with serum urea level 102 mg/dL and creatinine 1.2 mg/dL. Pleural pus grew minute colonies on sheep blood agar after 48 hours, which were gram-positive cocci in small chains, catalase-negative, and subsequently identified as *Granulicatella adiacens* using the VITEK2 system (bioMérieux, France) using Gram positive (GP) identification card with 98% probability index. Antimicrobial susceptibility was performed using the E-test method (HiMedia, Mumbai, India) and MICs in µg were reported according to the EUCAST Clinical Breakpoints.⁷ The isolate was sensitive to benzylpenicillin (MIC: 0.002 µg/ml), ampicillin (0.016 µg/ml), ampicillin sulbactam (0.016 µg/ml), ceftriaxone (0.002 µg/ml), teicoplanin (0.016 µg/ml), vancomycin (0.016 µg/ml) and linezolid (0.5 µg/ml) and resistant to gentamicin (MIC >16 µg/ml) and cotrimoxazole (MIC > 40 µg/ml). After 5 days of incubation, blood culture also grew same organism with same sensitivity

pattern. Urine culture was sterile. There was no significant improvement from the first presentation, except reduced drain fluid from intercostal site. As per the culture report, the empirical antibiotic was changed to inj. ceftriaxone and inj. linezolid. On the fifth day of targeted therapy, pleural pus was still there although minimal, and was sent for bacterial culture was sterile. But on the seventh day of hospitalization, the patient developed right lower limb necrotizing fasciitis with myonecrosis. Fasciotomy was done and it revealed necrotic muscles of lower leg posterior compartment with hematoma in the intra-muscular compartment. Unfortunately, the patient passed away on twelfth day of hospitalization due to acute myocardial infarction.

Discussion

We did the literature search over past 10 years (2011–2020) using search engines PubMed using the MeSH term, "*Granulicatella adiacens*." Case reports with only monomicrobial infection due to *G. adiacens* were included in the review. All articles published in English were included in this analysis.

We reviewed 77 literatures on the subject (*G. adiacens*) over the past 10 years (2011–2020). Using the inclusion and exclusion criteria, 24 literature were found relevant and included in the review.^{8–31} Clinical details of all published literature are compiled in the ►Table 1. As per the review of literature of last 10 years, *G. adiacens* is found to be the cause of various infections such as bacteremia, endocarditis, osteomyelitis, septic arthritis, discitis, prosthetic joint infections, carbuncle, bacterascites (spontaneous bacterial peritonitis), dacryocystitis, and abscess. Out of these, 13 isolated from blood (4 bacteremia, 8 endocarditis, 1 septic arthritis), 10 from synovial fluid/pus (6 prosthetic joint infection, 2 osteomyelitis, 2 discitis), one each from dacryocystitis, bacterascites, and carbuncle. Further extending search in PubMed using MeSH terms such as "empyema" and "*Granulicatella*" found only one case report of empyema (pleural pus) caused by *Granulicatella elegans*.³² None of them were from empyema pus and blood simultaneously except our present report of *G. adiacens*. All cases were reported from abroad, except three from India: one from New Delhi (suprapatellar abscess), one from Odisha (carbuncle), and the present study from Bhubaneswar, Odisha (empyema pus and blood). To the best of our knowledge, the present study is the first case report of thoracic empyema caused by *G. adiacens* complicated to necrotizing fasciitis and sepsis.

Necrotizing fasciitis is a destructive and rapidly progressive soft tissue infection with significant morbidity and mortality. It may necessitate surgical intervention and may progress to systemic involvement, septic shock, and multi-organ failure without intervention. Although the exact cause of necrotizing fasciitis in the present case is not clear, as clinical sample could not be sent for microbiological investigations. But association with *G. adiacens* infection cannot be ruled out as there is one published report of cervical necrotizing fasciitis due to polymicrobial cause including *G. adiacens* following dental extraction and its surgical management.³³

Table 1 Clinicoepidemiological details of infections caused by *Granulicatella adiacens*

| Infections caused by <i>Granulicatella adiacens</i> | Year | Geographical location | Age/sex | Clinical diagnosis | Clinical samples | References |
|-----------------------------------------------------|--------------------------------|-------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------|
| Bacteremia | 2011 | Charlottesville, Virginia | 89 y/F | Multiple trauma victim with bacteremia | Blood | 8 |
| | 2011 | New Haven, Connecticut, USA | 1 d/Mch | Early onset neonatal sepsis | Blood | 9 |
| | 2013 | Rome, Italy | 7 y/F | Shone syndrome (coarctation of aorta, mitral stenosis and subvalvular aortic stenosis) with Bacteremia | Blood | 10 |
| Endocarditis | | | 5 y/M | Infundibular pulmonary stenosis with Bacteremia. | Blood | |
| | 2013 | San Diego, CA, U.S.A. | 50 y/M | Bivalvular (mitral and aortic valves) endocarditis | Blood | 11 |
| | 2013 | Kerala, India | 63 y/M | Infective endocarditis | Blood | 12 |
| | 2015 | Australia | 57 y/M | Subacute Bacterial endocarditis with type II mixed cryoglobulinemia | Blood | 13 |
| | 2016 | Tokyo, Japan | 67 y/F | Infective endocarditis with Sjogren's syndrome with oral complications | Blood | 14 |
| | 2019 | Columbia, USA | 44 y/F | Endocarditis, osteomyelitis, brain abscess | Blood | 15 |
| | 2019 | Switzerland | 32 y/F | Cardiac implantable electronic device related infection and bioprostheses endocarditis | Blood | 16 |
| | 2019 | U.S.A. | 82 y/M | Bilateral lower extremity purpuric rash and complete heart block secondary to infective endocarditis | Blood | 17 |
| | 2020 | Farmington CT, United States | 46 y/M | Infective endocarditis and glomerulonephritis | Blood | 18 |
| | Prosthetic joint infection | 2013 | Paris, France | 55 y/M | Prosthetic joint infection (knee) after dental treatment | Knee fluid aspirate |
| 2016 | | Peterborough, Cambridgeshire, PE3 9GZ, UK | 81 y/M | Prosthetic joint infection (hip) | Pus aspirate from hip | 20 |
| 2017 | | Marseille, France | 75 y/M | Prosthetic joint infection (hip) | Synovial fluid | 21 |
| | | | 65 y/M | Prosthetic joint infection (knee) | Synovial fluid | |
| 2017 | | Eau Claire, WI, USA | 44 y/F | Prosthetic joint infection (hip) | Surgical biopsy sample | |
| 2017 | Swedish Neuroscience Institute | 64 y/M | Prosthetic joint infection (knee) | Synovial fluid | 22 | |
| Osteomyelitis | 2016 | | 46 y/M | Vertebral osteomyelitis | Vertebral body biopsy tissue | 23 |
| | 2018 | Kitakyushu, Japan. | 10 y/F | Mandibular osteomyelitis | Bone marrow fluid | 24 |
| Septic arthritis | 2019 | Iowa City, Iowa | 5 y/M | Ruptured appendicitis and retrocecal abscess presenting as atraumatic knee pain | Blood | 25 |

(Continued)

Table 1 (Continued)

| Infections caused by <i>Granulicatella adiacens</i> | Year | Geographical location | Age/sex | Clinical diagnosis | Clinical samples | References |
|-----------------------------------------------------|------|--------------------------------|---------|-----------------------------------------------------------------------|----------------------------------------|---------------|
| Discitis | 2013 | Tokyo, Japan | 48 y/F | Pyogenic discitis | Blood and disk biopsy sample | 26 |
| | 2020 | Rome, Italy | 51 y/M | Spondylodiscitis (L1-L2 and L5-S1 discs) | disk biopsy sample | 27 |
| Dacryocystitis | 2015 | Morgantown, WV 26505, USA | 46 y/F | Dacryocystitis | Purulent material from lacrimal sac | 28 |
| Bacterascites | 2015 | Charlottesville, VA 22908, USA | 50 y/M | Large distended abdomen (ascites) | Ascitic fluid | 29 |
| Abscess | 2018 | New Delhi, India | 30 y/M | Suprapatellar abscess | Aspirated pus from knee joint swelling | 30 |
| | | | 18 y/M | Elbow abscess | Pus swab | |
| Carbuncle | 2012 | Odisha, India | 56 y/M | Carbuncle, multiple discharging sinus over right scapular region | Pus | 31 |
| Empyema | 2016 | South Africa | 30 y/F | Empyema underlying TB and HIV Caused by <i>Granulicatella elegans</i> | Pleural pus | 32 |
| Empyema | 2020 | Odisha, India | 68 y/M | Empyema underlying diabetes mellitus and alcoholism | Pleural pus and Blood | Present study |

Due to requirement of fastidious culture conditions and non-specific colony morphology, serious diagnostic difficulties may arise in cases of NVS infections. Commercial blood culture media contain pyridoxal and support the growth of NVS. However, in the present case, the bacteria isolated from pleural pus and blood samples grew on commercial 5% sheep blood agar (without any additional supplement) as cited in other reports.³¹

With evolvement of the newer advanced laboratory systems, that is, the MALDI-TOF (VITEK MS, Bruker MS) system and the VITEK 2 system, NVS can be identified up to the species level. In our case also, the isolate was identified using the VITEK 2 system.

As NVS are parts of normal commensal flora of human mouth, genital and intestinal tracts, their exact pathogenic role is unclear. Proteins secreted by these species may act as virulence determinants for interaction with the host. The secretome of *G. adiacens* is well documented in infective endocarditis and oral infections. More importantly, *G. adiacens* secretome comprised several putative virulence proteins, which enhance bacterial colonization and virulence through their multifunctional roles.^{34,35} *Granulicatella* and *Abiotrophia* spp. have the ability to bind to fibronectin and other extracellular matrix proteins and this binding ability appears to correlate with their degree of infectivity.³⁶

Thus, clinicians should be aware of the pathogenic potential of these organisms. They can be easily overlooked because of their poor growth or no-growth on conventional solid media. NVS should be suspected when Gram stain shows microbial cells but cultures are negative. Due to the difficulties in identification of these bacteria, it is crucial for microbiology staff to be vigilant to prevent misidentification. For culture-negative cases, molecular test or Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOFMS) would be a faster and reliable method for identification. The difficulty in identifying these organisms leads to delays in diagnosis. In addition, the results of susceptibility testing may not be accurate or reliable. Therefore, appropriate supplemented media and a reliable detection system should be used to identify these fastidious organisms.

Conflict of Interest

None declared.

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