**Case Report**

**Granulicatella adiacens and Abiotrophia defectiva Native Vertebral Osteomyelitis: Three Cases and Literature Review of Clinical Characteristics and Treatment Approach**

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**Granulicatella para-adiacens** and **Abiotrophia defectiva** are an increasingly recognized cause of osteoarticular infections. We describe two cases of **G. adiacens** and one case of **A. defectiva** native vertebral osteomyelitis (NVO) and review all published cases. Nine cases of **G. adiacens** NVO and two cases of **A. defectiva** NVO were previously described. Patients were usually middle-aged men, and classical risk factors for NVO were present in half of the cases. Concomitant bacteremia was reported in 78.6% of cases, and concurrent infective endocarditis occurred in 36.4% of this sub-group of patients. Many different antibiotic schemes were recorded, with median treatment duration of 6 weeks. In the most recent reports, glycopeptides represented the most frequent empirical therapy, possibly due to the increasing emergence of **G. adiacens** and **A. defectiva** penicillin-resistant strains. Stabilization surgery was rarely required (14.3% of cases), and clinical cure was generally achieved. In conclusion, **Granulicatella spp.** and **Abiotrophia spp.** NVO is rare but increasingly described. A total antibiotic course of six weeks seems to be appropriate for noncomplicated cases, and clinical outcome is generally favorable.

1. **Introduction and Inclusion Criteria for Case Definition**

**Granulicatella** species and the related genus **Abiotrophia** are Gram-positive lactic acid bacteria, previously referred to as nutritionally variant streptococci because of their requirement of L-cysteine or pyridoxal into culture media for growth [1]. **Granulicatella** (formerly **Abiotrophia**) **adiacens**, **Abiotrophia defectiva**, and **Granulicatella elegans** are parts of the normal oropharyngeal, gastrointestinal, and urogenital microflora but might also act as opportunistic pathogens [2]. Recently, thanks to 16S rRNA sequence analysis, **Granulicatella para-adiacens** (a species closely related to **G. adiacens**) has also emerged as pathogenic for humans [3].

Usually considered a rare cause of infective endocarditis (IE), **G. adiacens**, **G. elegans**, and **A. defectiva** account for 5–16% of all streptococcal IE cases [4, 5], even if the challenge in identification of these fastidious organisms may lead to underestimate the real incidence. Indeed, the pathogenic role of **G. adiacens** and **A. defectiva** in osteoarticular infections such as native vertebral osteomyelitis or spondylodiscitis [6–15], prosthetic-related infections [16, 17], and septic arthritis [18] is increasingly recognized.

Here, we described two cases of **G. adiacens** and one case of **A. defectiva** native vertebral osteomyelitis occurring in our institution between 1 January 2008 and 1 December 2018. We also reviewed all cases of native vertebral osteomyelitis due to these organisms described in the medical literature.
We searched PubMed articles written in English between 1 January 1990 and 1 December 2018 using a combination of the following key words: “granulicatella,” “abiotrophia,” “nutritionally variant streptococci,” “spondylodiscitis,” and “vertebral osteomyelitis.” Moreover, in the Discussion section, we summarize applicable guidelines and recent data about G. adiacens and A. defectiva antibiotics susceptibility, focusing on molecules of clinical utility in the setting of bone infections.

2. Presentation of Institutional Cases

2.1. Case 1. In April 2017, a 50-year-old man with irrelevant past medical history started to report nocturnal low-grade fever and low back pain. He empirically received a short course of antibiotics but fever occasionally relapsed. During the following weeks, the patient experienced progressive dyspnea that led him to the local emergency department (ED). At the arrival in the ED, the patient was febrile (38.2°C), and his laboratory exams showed marked leukocytosis (WBC = 22.9 G/μL, 77% neutrophils), mild anemia (Hb = 10.6 g/dL), and increased C-reactive protein (CRP = 11.2 mg/dL).

A transthoracic echocardiography showed a massive aortic insufficiency with evidence of multiple vegetations on the free edge of the aortic cuspids. Two sets of blood cultures were performed in the ED, and G. adiacens grew both from aerobic and anaerobic blood bottles after 17 and 21 hours in the first set and after 17 and 22 hours in the second set, respectively. Blood cultures (BACT/ALERT FA Plus and BACT/ALERT FN Plus) were processed using the BACT/ALERT system (bioMérieux). Agar MHF for fastidious organism plates was incubated in 5% CO₂ at 35–37°C for 48 hours. Identification was carried out by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) using the Vitek MS system (bioMérieux). Antimicrobial susceptibility was performed by E-test method, and MICs were reported according to PK-PD (nonspecies related) breakpoints as stated in March 2017 EUCAST Clinical Breakpoints Tables [19] (Figure 1(a)). Three days after ED admission, reparative aortic surgery was performed in a local cardiac surgery unit. Subsequently, the patient underwent a CT scan of the spine for persistent back pain, and a diagnosis of L3-L4 native vertebral osteomyelitis was made. The patient was transferred in May 2017 to our clinic to continue the antibiotic course. MRI of the spine showed an increased STIR signal at the L5-S1 level suggestive for early spondylodiscitis. To determine if the morphostructural bone changes described in MRI were metabolically active, a total body FDG-PET/CT scan was performed: an intense L5-S1 standardized uptake value (SUV = 7.1) was detected (see Figure 2) and diagnosis of native vertebral osteomyelitis was made; no other metabolically active areas were detected. The patient started empirically iv vancomycin 2 g/daily plus ceftriaxone 2 g/daily for one week, and then switched to ceftriaxone alone for 3 weeks. At discharge, the patient was switched to oral amoxicillin 3 g/daily for 2 weeks. A three-month clinical follow-up was uneventful, with gradual pain reduction. The patient fully recovered; no follow-up MRI was performed.

2.2. Case 2. A 47-year-old man was admitted to our clinic on May 2017 with a 10-day history of fever and severe low back pain after returning from a scuba diving session in Maldives. His past medical history included hypertension and chronic back pain due to L5 disc herniation. On examination, body temperature was 38.5°C and blood pressure was 110/80 mmHg. Laboratory results showed a normal white cell formula (WBC = 10.3 G/μL, 79% neutrophils) and a raise of C-reactive protein (CRP = 16.5 mg/dL). Two sets of blood cultures were performed at admission, and G. adiacens grew both from aerobic and anaerobic blood bottles after 15 and 18 hours in the first set and after 16 hours in both aerobic and anaerobic bottles of the second set. Blood cultures (Bactec Plus Aerobic/F and Bactec Plus Anaerobic/F) were processed using the BACTEC FX system (Becton Dickinson). Identification and antimicrobial susceptibility (Figure 1(b)) were carried out as in Case 1.

A transthoracic echocardiography was negative for IE. MRI of the spine showed an increased STIR signal change at the L5-S1 level suggestive for early spondylodiscitis. To determine if the morphostructural bone changes described in MRI were metabolically active, a total body FDG-PET/CT scan was performed: an intense L5-S1 standardized uptake value (SUV = 7.1) was detected (see Figure 2) and diagnosis of native vertebral osteomyelitis was made; no other metabolically active areas were detected. The patient started empirically iv vancomycin 2 g/daily plus ceftriaxone 2 g/daily for one week, and then switched to ceftriaxone alone for 3 weeks. At discharge, the patient was switched to oral amoxicillin 3 g/daily for 2 weeks. A three-month clinical follow-up was uneventful, with gradual pain reduction. The patient fully recovered; no follow-up MRI was performed.

2.3. Case 3. In October 2018, a 75-year-old woman with previous mitral valvuloplasty and previous breast cancer was admitted to our clinic for persistent low back pain started three months earlier without fever. An MRI of the spine performed two days before admission showed a L4-L5 infectious process. At the admission, blood tests showed a mild anemia (Hb = 9.5 g/dL) and a mild elevation of CRP (CRP = 2.5 mg/dL). A chest CT scan revealed a right pleural effusion with bilateral parenchymal consolidation; a diagnostic thoracentesis was negative for microbial growth. At day 15, the patient became feverish, and two sets of blood cultures were performed. A. defectiva grew both from aerobic and anaerobic blood bottles after 27 and 28 hours in the first set and after 70 and 34 hours in the second set, respectively. Blood cultures processing, microbiological identification, and antimicrobial susceptibility were carried out as in Case 1. The isolated A. defectiva strain showed a reduced penicillin and ampicillin susceptibility (Figure 1(c)); thus, a glycopeptide-based antibiotic regimen was started. A transthoracic echocardiography showed a severe mitral insufficiency without evidence of vegetations. The patient refused to perform a transesophageal echocardiography. A FDG-PET/CT scan confirmed a localized metabolic uptake at the L4-L5 level (SUV = 3.5); no other metabolically active areas were detected.

The patient received initially iv vancomycin 2 g/daily, and then, she was transferred to a local cardiac surgery unit.
for mitral valve replacement. Because of initial renal failure, after two weeks, the patient was switched to teicoplanin 400 mg/daily according to the local infectious diseases specialist’s consultation. Mitral valve culture was negative for microbial growth. Surgical follow-up was uneventful, and after three weeks, the patient was transferred to a cardiac rehabilitation unit, where she completed a six-week course of iv teicoplanin. At a six-month follow-up visit, the patient reported an initial improvement of low back pain; no follow-up MRI was performed.

3. Clinical Characteristics of Granulicatella adiacens and Abiotrophia defectiva Native Vertebral Osteomyelitis

During a ten-year period, we recorded in our institution two cases of native vertebral osteomyelitis due to G. adiacens and one due to A. defectiva. Other eleven cases of native vertebral osteomyelitis due to these fastidious organisms were identified from PubMed search: nine due to G. adiacens [6–13] and two due to A. defectiva [14, 15]. At the present, no cases of G. elegans or G. para-adiacens spondylodiscitis have been described.

G. adiacens and A. defectiva vertebral osteomyelitis clinical characteristics and therapeutic regimens, including our three cases, are shown in Table 1. Patients were predominantly males (78.5%) with a median age of 50.5 years (IQR = 47.7–63.5). Many patients (8/14, 57.1%) presented identifiable risk factors for native vertebral osteomyelitis such as injecting drug use, infective endocarditis, degenerative spinal disease, and diabetes mellitus.

As expected, all patients reported back pain; fever was recorded in 9/14 cases (64.3%). Most nutritionally, variant streptococci native vertebral osteomyelitis cases were associated with bacteremia (11/14 cases, 78.6%); meanwhile, concurrent IE occurred only in a subgroup of these patients (4/11, 36.4%).

Twelve different therapeutic schemes were recorded; median antibiotic therapy duration was six weeks (IQR = 6–7), ranging from to 4 to 15 weeks. Surgical stabilization was required in 2 out of 14 cases (14.3%). When outcome was described (12 patients), clinical cure was achieved in all cases.
Table 1: Clinical characteristics, antibiotic treatment, and outcome of *Granulicatella adiacens* and *Abiotrophia defectiva* NVO cases.

| Reference (year of publication) | Patient age, sex | Clinical presentation | Past medical history | Concomitant endocarditis | Bacteremia Vertebral infection site | Positive microbiological specimens | Methods for microbial identification | Microbiological identification | Antibiotic regimen | Total duration of treatment | Spinal surgical intervention | Outcome |
|---------------------------------|------------------|----------------------|----------------------|--------------------------|-----------------------------------|-----------------------------------|----------------------------------|---------------------------------|-------------------|-----------------------------|-------------------------|---------|
| Our first case (2017)           | 50, male         | Cardiogenic shock, fever, back pain | None                 | Yes                      | Yes L3-L4, L5-S1                  | Blood cultures                     | Vitek MS                         | *Granulicatella adiacens*        | Vancomycin + ceftiraxone + gentamicin for 2 weeks, ceftiraxone for 2 weeks, amoxicillin po for 2 weeks | 6 weeks | No | Cured |
| Our second case (2017)          | 47, male         | Fever, back pain     | Hypertension, L5 disc herniation | No                       | Yes L5-S1                         | Blood cultures                     | Vitek MS                         | *Granulicatella adiacens*        | Vancomycin + ceftiraxone for 1 week, ceftiraxone for 3 weeks, amoxicillin po for 2 weeks | 6 weeks | No | Cured |
| Our third case (2018)           | 75, female       | Back pain            | Previous mitral valvuloplasty | No                       | Yes L4-L5                         | Blood cultures + bone biopsy       | Vitek 2 system + 16S rNA sequencing | *Abiotrophia defectiva*      | Vancomycin for 2 weeks, teicoplanin for 6 weeks | 8 weeks | No | NA   |
| [15] (2017)                     | 54, female       | Fever, back pain     | Patent ductus arteriosus (pulmonary artery endarteritis) | Yes                      | Yes L5-S1                         | Blood cultures                     | Vitek 2 system + 16S rNA sequencing | *Abiotrophia defectiva* | Penicillin G + gentamicin | Planned 6 weeks | No | NA   |
| [13] (2017)                     | 48, male         | Back pain            | Intravenous drug abuse, mitral valve prolapse, HCV infection Diabetes, hypertension | No                       | No L3-L4 + L3-L5 epidural phlegmon | Vertebral, disk and paraspinal muscles biopsy | ND                              | *Granulicatella Abbreviation* Abiotrophia spp. | Vancomycin for 6 weeks + cefepime in the first day | 6 weeks | No | Cured |
| [12] (2017)                     | 61, male         | Back pain            | Diabetes, recent dental procedure | No                       | No L3-L4                         | Disk biopsy                        | Vitek 2 system                   | *Granulicatella adiacens* | Ceftriaxone + gentamicin for 6 weeks | 6 weeks | No | Cured |
| [11] (2016)                     | 46, male         | Back pain            | Diabetes, recent dental procedure | No                       | No L2 inferior endplate           | Bone biopsy                        | PCR (not specified)              | *Granulicatella adiacens*        | Vancomycin for 6 weeks | 6 weeks | Yes (L1-L3 fixation and interbody cage position in L2) | Cured |
| [10] (2015)                     | 62, male         | Back pain, fever     | Hypertension          | No                       | Yes T10-T12 with spinal abscess  | Blood cultures                     | ND                              | *Abiotrophia defectiva* | Vancomycin for 6 weeks | 6 weeks | Yes (laminectomy with T9-L2 fusion surgery) | Cured |
| [9] (2013)                      | 48, female       | Back pain, fever     | Parkinson's disease   | No                       | Yes L3-L5                         | Blood cultures + disk biopsy        | 16S rNA sequencing                | *Abiotrophia defectiva*       | Ampicillin for 6 weeks | 6 weeks | No | Cured |
| [8] (2010)                      | 73, male         | Back pain, fever     | Hypertension, hyperlipidemia | No                       | Yes L3-L4                         | Blood cultures                     | Vitek 2 system + 16S rNA sequencing | *Granulicatella adiacens* | Penicillin G + gentamicin for 6 weeks, po amoxicillin for 9 weeks | 15 weeks | No | Cured |
| Reference (year of publication) | Patient age, sex | Clinical presentation | Past medical history | Concomitant infection | Bacteremia site | Positive microbiological specimens | Methods for microbial identification | Microbiological identification | Antibiotic regimen | Total duration of treatment | Spinal surgical intervention | Outcome |
|---------------------------------|------------------|-----------------------|----------------------|----------------------|-----------------|-----------------------------------|---------------------------------|---------------------------------|-----------------|----------------------------|-----------------------------|---------|
| [14] (2005) 51, male            | Back pain        | Mitral valvulopathy, recent dental procedure | No                   | Yes                  | L2-L3, L5-S1, right sacroiliac joint | Blood cultures | 16S rRNA sequencing | *Abiotrophia defectiva* | Amoxicillin + gentamicin (stopped on day 5) + oral rifampicin, po amoxicillin for 11 weeks + po rifampicin for 10 weeks | 14 weeks     | No                       | Cured         |
| [7] (2002) 68, male             | Back pain, fever | Yes (PM lead)         | Yes                  | T10-T11             | Blood cultures | *Granulicatella adiacens* | bioMéneux Rapid ID 32 Strep system | Penicillin + gentamicin + rifampin | ND              | No                        | Cured         |
| [6] (1998) 45, male             | Back pain, fever | ND                    | Yes                  | L2-L4               | Blood cultures | *Abiotrophia adiacens* | ND | Penicillin for 2 weeks, po clindamycin for 2 weeks Penicillin + gentamicin for 2 weeks, ceftriaxone for 2 weeks | 4 weeks | No | Cured |
| [6] (1998) 50, male             | Back pain, fever | ND                    | Yes                  | L3-L5               | Blood cultures | *Abiotrophia adiacens* | ND | Penicillin for 2 weeks, po clindamycin for 2 weeks Penicillin + gentamicin for 2 weeks, ceftriaxone for 2 weeks | 4 weeks | No | Cured |

NA: not assessed; ND: not described; PM: pacemaker; AF: atrial fibrillation; AV: atrioventricular.
4. Discussion and Conclusions

Once known as nutritionally variant streptococci, G. adiacens and A. defectiva are a rare cause of native vertebral osteomyelitis. Discrepancies still exist in terms of correct taxonomic classification, being Granulicatella and Abiotrophia terms used interchangeably even in recent articles [9, 10, 13].

As expected, the clinical presentation of G. adiacens and A. defectiva native vertebral osteomyelitis was back pain, usually associated with fever. Patients with Granulicatella and Abiotrophia spondylodiscitis were usually in their fifth decade or older, and approximately half of cases presented classical risk factors for spondylodiscitis such as endocarditis, intravenous drug use, or immunosuppressive conditions. On the other hand, in a recent analysis, including 38 cases of G. adiacens endocarditis and 38 cases of A. defectiva endocarditis, systemic embolism excluding the central nervous system occurred in 9.4% and 11.8% of patients for each group, respectively [5].

Usually, microbiological diagnosis of G. adiacens and A. defectiva native vertebral osteomyelitis is made through blood culturing and/or bone biopsy. Automatic biochemical test systems, such as Vitek 2, are widely used in clinical practice, but phenotypic characteristics alone may be inaccurate in Granulicatella spp. and Abiotrophia spp. identification [20]. After the advent of 16S rRNA gene sequencing and MALDI-TOF MS, identification within this group of fastidious bacteria have been made more readily and accurately performed both at genus and species levels [21].

At the present, European EUCAST guidelines do not provide specific recommendations on susceptibility testing and MICs interpretation for Granulicatella and Abiotrophia species and suggest the usage of PK-PD (nonspecies related) breakpoints avoiding interpretation on susceptibility [19]. As the vast majority of the European microbiology laboratories, our clinical microbiology laboratory follows EUCAST guidelines, and disk diffusion tests and E-tests are routinely performed for MIC determinations; when indicated and in case of multidrug-resistant organisms, broth microdilution method is used. On the contrary, US CLSI guidelines, through the M45 Document on infrequently isolated or fastidious bacteria [22], give indications on susceptibility testing and suggest interpretative criteria for this class of microorganisms. Indeed, most of the available data for Granulicatella spp. and Abiotrophia spp. are based on CLSI indications. In particular, using broth microdilution for MIC determination as suggested in CLSI guidelines, differences in terms of antimicrobial susceptibilities between the two genera recently emerged [23–26]. In these studies, susceptibility ranged from 34 to 39% for penicillin, from 22 to 47% for ceftriaxone, and from 3 to 83% for cefepime for G. adiacens strains. A. defectiva strains resulted less susceptible to penicillin (range 10.8–24%) but more susceptible to ceftriaxone (range 92–100%). On the contrary, the vast majority of Granulicatella spp. and A. defectiva isolates were fully susceptible to vancomycin, clindamycin, meropenem, and levofloxacin.

Thus, in the setting of A. defectiva native vertebral osteomyelitis, a third-generation cephalosporin is still an appropriate empiric therapy; meanwhile in case of G. adiacens native vertebral osteomyelitis, an alternative parental agent such as a glycopeptide should be used while antimicrobial susceptibility testing is pending. Agents with high oral availability such as levofloxacin and clindamycin may represent a good option for oral switch. Few data on rifampin, daptomycin, and linezolid are available, and there are no CLSI or EUCAST interpretive breakpoints for these molecules. Elevated MICs and linezolid were found in two different studies including overall more than four hundred G. adiacens and more than one hundred fifty A. defectiva isolates [23, 26]; therefore, these two molecules should not currently be considered an option.

Given the limited microbiological and clinical data and a potential higher risk of complications, the American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines recommend a 4- to 6-week course of antibiotics for the treatment of endocarditis due to G. adiacens and A. defectiva [27, 28]. The suggested regimen combines penicillin G, ampicillin, or ceftriaxone plus an aminoglycoside for at least the first two weeks or vancomycin alone in case of beta-lactam allergy as for enterococci infection. The “2015 Native Vertebral Osteomyelitis IDSA Guidelines” do not expressly focus on nutritionally variant streptococci, but antibiotic treatment can be similarly inferred from enterococci and streptococcal infections, which in turn do not substantially differ from AHA and ESC recommendations [29]. Of note, in the first case reports, initial antibiotic therapy was penicillin based; in the last years, we observed a greater tendency to prescribe a glycopeptide-based antibiotic regimen as empirical or definitive therapy. This may reflect the increasing reporting of penicillin-resistant G. adiacens strains. In our two cases, G. adiacens strains were susceptible to penicillins; thus, after an initial empirical parenteral therapy with vancomycin and ceftriaxone (plus gentamicin in the case with IE), oral therapy with amoxicillin was prescribed at discharge to conclude the antimicrobial course.

Radiological work-up of NVS native vertebral osteomyelitis generally included MRI imaging. In our patient 1, MRI demonstrated a second infectious spine focus not detected from a previous CT scan. However, in early stages of native vertebral osteomyelitis, bone and surrounding tissue changes seen in MRI may be aspecific: in these cases, FDG-PET/CT scan may be helpful to discriminate between a chronic degenerative bone alteration and an early infectious process [30], as well as in our patient two. In this latter case, a negative transthoracic echocardiography along with the absence of FDG-PET/CT uptakes in other sites, gave us a low clinical suspicion of IE, and a transesophageal echocardiography was not performed. Considering cases reported in the literature, treatment duration ranged from 4 to 15 weeks. In our cases as well as in the most recent articles, G. adiacens native vertebral osteomyelitis treatment duration has been set to six weeks, presumably influenced both by the previous cited 2015 native vertebral osteomyelitis IDSA guidelines, and Bernard et al. randomized clinical trial on pyogenic
native vertebral osteomyelitis treatment duration [31]. This seems not to have affected the general favorable clinical outcome observed in all cases, especially because complications as paravertebral abscesses or vertebral instability requiring surgery occurred in two cases only.

In conclusions, Granulicatella and Abiotrophia species are a rare but increasingly more recognized cause of osteo-articular infections, including native vertebral osteomyelitis. Blood isolation of the causative organism is frequent in this setting, and native vertebral osteomyelitis may occur in the absence of infective endocarditis. Considering data about Granulicatella spp. and Abiotrophia spp. reduced susceptibility to penicillins and cephalosporins, a glycopeptide-based regimen may represent a therapeutic option while antimicrobial susceptibility testing is pending. Clinical outcome is generally favorable, and noncomplicated cases of Granulicatella adiacens and Abiotrophia defectiva spondylodiscitis can be effectively treated with a standard six-week course of antibiotic therapy.

Abbreviations

FDG-PET/CT: F18-fluorodeoxyglucose-positron emission tomography/computed tomography
IE: Infective endocarditis
iv: Intravenous
NVO: Native vertebral osteomyelitis
po: Per os
IQR: Interquartile range

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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