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Granulicatella adiacens isolated from sterile body fluids: A case series from India

Sushma Krishna, Dinesh Kavitha, Harichandran Deepa, Jayasurya Neeba, Karim Shamsul

ABSTRACT

Introduction: The genera Abiotrophia and Granulicatella spp. (previously known as nutritionally variant Streptococcus) are infrequently isolated from clinical specimens. Literature quotes that they account for about 5–6% of the infective endocarditis and bacteremia, and lesser in central nervous system infections (post instrumentation) and others. The objective of the study was to assess the clinical significance and outcome of the patients with laboratory isolations of Granulicatella adiacens.

Case Series: We reviewed the clinical records from 2011–12 noting down the demographic details, identifiable risk factors, management of patients in whom Granulicatella adiacens was isolated. Seven cases of Granulicatella adiacens were reported in which five were children (<2 years) and two were male adults. Six strains were from blood and one was isolated from cerebrospinal fluid shunt fluid, and were regarded as clinically significant. Pre-existing co-morbidities like nephrotic syndrome, premature birth and dysmorphism were noted in almost all the children. One of the patients had undergone invasive ventriculoperitoneal shunt insertion. All the patients except one (discharged against medical advice) recovered.

Conclusion: The study describes the spectrum of infections by Granulicatella adiacens. G. adiacens can grow on routine sheep blood agar without pyridoxal supplementation in CO2 incubator when sub-cultured from automated blood culture bottles. This is one of the largest study from India.

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Introduction: The genera *Abiotrophia* and *Granulicatella* spp. (previously known as nutritionally variant *Streptococcus*) are infrequently isolated from clinical specimens. Literature quotes that they account for about 5–6% of the infective endocarditis and bacteremia, and lesser in central nervous system infections (post instrumentation) and others. The objective of the study was to assess the clinical significance and outcome of the patients with laboratory isolations of *Granulicatella adiacens*. Case Series: We reviewed the clinical records from 2011–12 noting down the demographic details, identifiable risk factors, management of patients in whom *Granulicatella adiacens* was isolated. Seven cases of *Granulicatella adiacens* were reported in which five were children (<2 years) and two were male adults. Six strains were from blood and one was isolated from cerebrospinal fluid shunt fluid, and were regarded as clinically significant. Pre-existing co-morbidities like nephrotic syndrome, premature birth and dysmorphism were noted in almost all the children. One of the patients had undergone invasive ventriculoperitoneal shunt insertion. All the patients except one (discharged against medical advice) recovered. Conclusion: The study describes the spectrum of infections by *Granulicatella adiacens*. *G. adiacens* can grow on routine sheep blood agar without pyridoxal supplementation in CO2 incubator when sub-cultured from automated blood culture bottles. This is one of the largest study from India.

Keywords: *Abiotrophia*, Blood, India, *Granulicatella adiacens*, Shunt infectious, Streptococcus

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INTRODUCTION

Granulicatella species form a part normal oral, genitourinary and intestinal tract flora. Along with the genus *Abiotrophia*, they were originally known as nutritionally variant streptococci (NVS) because of their requirement for pyridoxal as additional agents to be incorporated into standard media for successful laboratory isolation. Three species of *Granulicatella* have now been described viz, *G. adiacens*, *G. elegans* and *G. balaenopterae* [1]. They are uncommon clinical isolates and are implicated in causing invasive infections such as infective endocarditis, bacteremia, and shunt infections [2–4]. Nutritionally

variant streptococci otherwise called satelliting streptococci (grow around *Staphylococcus aureus* streak on agar plate by extracting nutrients) are regarded as an important cause of culture negative endocarditis and have been estimated to cause between 5–6% of all cases of streptococcal endocarditis. Therapeutic success has been achieved with beta-lactam antibiotics with the addition of gentamicin when the isolates were provisionally identified [5]. The objective of the study was to assess the clinical significance and outcome of the patients with laboratory isolations of *Granulicatella adiacens*.

CASE SERIES

Microbiology records of sterile body fluid cultures done on automated blood culture systems-BACTEC 9240 (BD, Gurgaon, India) and BacT/ALERT (Biomerieux, New Delhi, India) from July 2011 to June 2012 were reviewed to look for isolation of *Granulicatella*. Laboratory work-up included subjecting centrifuged deposit from an aliquot from the bottle which flagged positive to gram stain to reveal gram-positive cocci in chains (Figure 1), then sub-cultured on 5% sheep blood agar (SBA) incubated in CO_2 incubator and MacConkey agar in ambient air. After 48 hours of incubation, small colonies of alpha hemolytic streptococci were seen on SBA (Figure 2). The results of biochemical test done for preliminary identification were—catalase negative, oxidase negative, bile aesculin negative, no growth in 6.5% NaCl, optochin resistant, vancomycin sensitive and bile solubility test were negative [6]. Two of the strains were positive for satellitism around *Staphylococcus aureus*. Identification was by VITEK Compact 2 (Biomerieux clinical diagnostics, France, headquarters: New Delhi, India) with 99% probability. Pyrrolidonyl arylamidase (PYR), leucine amino peptidase (LAP) and ß-glucosidase were positive and both α and ß galactosidase tests were negative. The strains were not sequenced. For susceptibility testing of these isolates, Mueller–Hinton agar supplemented with 5% sheep blood was used for convenience and CLSI guidelines for *Streptococcus* spp. Viridans group were used for interpretation [7].

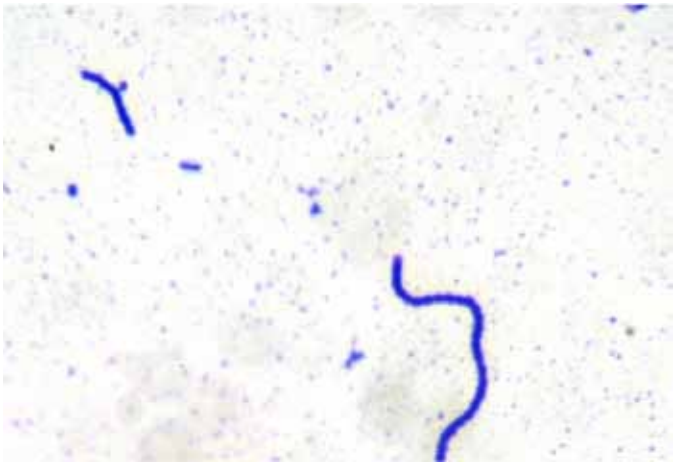

Figure 1: Gram stain picture of *G. adiacens* showing gram-positive cocci in chains.

Figure 2: Translucent alpha-hemolytic colonies of *G. adiacens* on sheep blood agar with vancomycin sensitivity.

Table 1: Antibiotic susceptibility profile of *G. adiacens* by disk diffusion method

	Penicillin	Erythromycin	Cefotaxime	Ofloxacin	Ceftriaxone	Azithromycin
Patient 1	S	S	S	S	S	R
Patient 2	S	S	S	S	S	R
Patient 3	S	S	S	S	S	S
Patient 4	S	R	S	S	S	R
Patient 5	S	R	S	S	S	R
Patient 6	S	R	S	S	S	R
Patient 7	R	R	S	S	S	R

S, Sensitive; R, Resistant

Patient 1: A one-year-old premature baby with duodenal atresia and pelvic pseudocyst was admitted with posthemorrhagic hydrocephalus with ventriculoperitoneal shunt. Shunt infection was suspected and cerebrospinal fluid sent for culture. *G. adiacens*, sensitive to penicillin, erythromycin, cefotaxime, ofloxacin, and resistant to azithromycin (Table 1) was grown in culture and the child was started on vancomycin for one week and rifampicin (one/sixth of 300 mg) for two weeks. Clinical condition improved and shunt was removed later.

Patient 2: A two-year-old girl with nephrotic syndrome on steroids, was admitted with spiking temperatures. Two consecutive blood cultures isolated *G. adiacens*, sensitive to penicillin, erythromycin, cefotaxime, ofloxacin, and resistant to azithromycin. Bacteremia was confirmed and the patient was started on ceftriaxone for 10 days and repeat culture was sterile.

Patient 3: A two-month-old dysmorphic male neonate with global developmental delay, a case of DPT vaccine induced encephalopathy, aspiration pneumonia, failure to thrive, presented with fever of seven days duration. Blood culture set grew pan sensitive *G. adiacens,* Piperacillin-tazobactam was started and on request, child was discharged against medical advice.

Patient 4: A one-year-old female child was admitted with convulsions and fever. Seizure workup was not contributory and a diagnosis of simple febrile seizures was made. While on antiepileptic, blood cultures grew erythromycin and azithromycin resistant *G. adiacens,* she was treated with cefixime for seven days and improved.

Patient 5: A 58-year-old male, a known case of chronic renal failure and multiple myeloma (on thalidomide) with joint effusion and leucopenia was admitted for pyrexia of unknown origin. Two out of six blood cultures received grew *G. adiacens,* erythromycin and azithromycin resistant. With the characteristic mitral valve vegetation on echo, a diagnosis of infective endocarditis was made. He was treated with IV penicillin for forty days and gentamicin for two weeks. Repeat blood cultures on follow-up were negative.

Patient 6: A 43-year-old male presented with severe joint pains and fever. He was a known case of type 2 diabetes mellitus, hypertension and dyslipidemia. Dengue serology (IgM) was positive. Blood cultures grew *G. adiacens,* which was erythromycin and azithromycin resistant. The patient was started on ceftriaxone for seven days with platelet transfusion after which he improved. Repeat blood cultures were negative.

Patient 7: A one-year-old boy with nephrotic syndrome (on steroids), presented with high-grade fever and wheeze from three days. Two blood cultures grew *G. adiacens,* resistant to penicillin, erythromycin and azithromycin resistant. A diagnosis of lower respiratory tract infection was made, was treated with cefotaxime for seven days and the boy improved.

DISCUSSION

Identification of nutritionally variant streptococci is difficult at the laboratory bench. Gram stain may show pleomorphism and morphology depends upon the conditions of growth. They appear in chains including cocci, coccobacilli in chains and occasionally rod-shaped cells when it is grown in cysteine- or pyridoxal-supplemented broth. Some tendency towards rod formation may be observed in the stationary phase which may lead to a misidentification of gram-positive bacilli group (like *Lactobacillus*, Diptheroids, etc.). Small ovoid cocci occur singly, in pairs or in chains of variable length in CDMT semi-synthetic medium. On culture, they are generally fail to grow on routine culture media. However, the recent automated culture bottles have pyridoxal supplementation in the required concentration (0.001%) which is specifically required for the growth of nutritionally variant streptococci. All the isolates in our study grew well on SBA with alpha-hemolysis in CO_2 incubator without further additional pyridoxal supplementation by 48 hours. The colonies of *G. adiacens* are alpha-hemolytic or non-hemolytic (gamma hemolytic) on SBA [6] and needs to be differentiated from other phenotypically related look alike catalase-negative gram-positive cocci such as Enterococci, Lactococci, Leuconostoc, Vagococcus, Weissella, etc. by biochemical tests, some of which are not routinely available and needs commercial kit systems (like API Rapid Step or Vitek) to identify them. All isolates turned out to be clinically significant and patients were treated with culture sensitive antibiotics and recovered, except one (discharged against medical advice). Five of the study patients with primary diagnosis of other diseases had episodes of bacteraemia and striking pre-disposing factors and recovered with the prompt antibiotic therapy.

About 5–15% of patients with endocarditis have negative blood cultures; in one-third to half of these cases, cultures are negative because of prior antibiotic exposure. The remainder of these is due to fastidious organisms, such as nutritionally variant organisms, HACEK organisms, and *Bartonella* species. *Granulicatella* spp. is known to cause sepsis, bacteremia and infective endocarditis in 5% of cases. The NVS endocarditis has been considered to have a high relapse rate and relapses following treatment have been reported for *Granulicatella* endocarditis and have to be treated in the same way as enterococcal endocarditis. The patient five of infective endocarditis with typical vegetations had no episodes of relapse and was believed to be cured with penicillin and gentamicin for a six-week duration. The need for routine antimicrobial susceptibility testing is not clear as majority of the isolates remain sensitive to penicillin. However, occasional reports of beta-lactam (as in patient seven in the series) and macrolide resistance (most of the isolates in the series were) have been reported where they pose a challenge to treat invasive

infections limiting the available choice [8] and hence, testing should be done even if it is by non-standardized disk diffusion method.

G. adiacens also has been documented to cause central nervous system infections like meningitis, epidural abscess in association with prior neurosurgical procedures including craniotomy, ventriculoperitoneal shunt placement, CT-guided myelography and tumor resection [9]. Patient 1 had a prior shunt placement antecedent to the cerebrospinal fluid isolation. Besides the above, isolation of NVS as likely pathogens has been reported in a diverse list of infections that can be caused by other streptococci, including peritonitis, prosthetic joint infections, breast implant infections and osteomyelitis [10, 11]. In this series, *G. adiacens* was not isolated from any samples other than blood and cerebrospinal fluid. Reporting of more such cases throws light on the clinical spectrum and provides insight about the pathogenesis of these rare listed organisms as definite pathogens, which in turn will allow better and adequate antibiotic therapy for the treatment of invasive infections. Awareness of NVS and willingness to look for them, more so in apparently negative cultures, may unveil them as potential pathogens in other infections too. The report highlights the large series of *G. adiacens* isolations from India conveying that the isolate cannot be disregarded as insignificant commensal and is worth alerting the physician to rule out possible bacteremia, infective endocarditis and shunt infections.

CONCLUSION

Study adds on to the spectrum of infections by *Granulicatella adiacens* from India. *G. adiacens* can grow on sheep blood agar without pyridoxal supplementation in a CO_2 incubator when sub-cultured from automated blood culture bottles containing pyridoxal HCl. We suggest that *Granulicatella* (and *Abiotrophia*) species should be considered in patients where slow-growing α-hemolytic or non-hemolytic streptococci are isolated from blood cultures or other sterile sites in device-associated, in immunocompromised and in the infective endocarditis patients.

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Author Contributions

Sushma Krishna – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published
Kavitha Dinesh – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Deepa Harichandran – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Neeba Jayasurya – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Shamsul Karim – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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