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Case Report

Chronic mandibular osteomyelitis caused by *Granulicatella adiacens* in an immunocompetent child☆

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We report a pediatric case aged 10 years with *Granulicatella adiacens*-associated chronic mandibular osteomyelitis. The causative pathogen was uncertain because polymicrobial species were detected from the bacterial culture in bone marrow fluid. In contrast, *G. adiacens* was predominantly identified in the clone library analysis of the bacterial 16S rRNA gene sequence. Vancomycin to which *G. adiacens* was reported to be susceptible was not administrated sufficiently to this patient because of its adverse event, whereas linezolid and ciprofloxacin was alternatively effective for the treatment of chronic mandibular osteomyelitis.

1. Introduction

The treatment of chronic mandibular osteomyelitis is often difficult, because the causes of the disease are various [1]. The main causative pathogens of chronic suppurative mandibular osteomyelitis are oral bacteria [2], but the epidemiology is uncertain because the antimicrobial treatment has been already started in most patients when the bone tissue is obtained for the identification of the causative pathogen. Therefore, no initial treatment of the disease is established.

Granulicatella species, facultatively anaerobic, Gram-positive cocci, are known as nutritionally variant streptococci (NVS). *G. adiacens* causes endocarditis in patients with cardiac abnormalities, and rarely causes neonatal sepsis, infection of the central nervous system [3]. There were two reports for vertebral osteomyelitis caused by *G. adiacens* [4,5], whereas no report for madibular osteomyelitis was known.

We herein report a pediatric case with *G. adiacens*-associated chronic mandibular osteomyelitis diagnosed by the analyses of the bacterial 16S rRNA gene.

2. Case report

A previously healthy 10-year-old girl was admitted to our hospital for the evaluation of a 3-month history of pain and swelling in the left cheek. The patient had been treated twice with cefditoren pivoxil for 1 week before admission (2 and 3 months before), but swelling in the left cheek did not disappear. Two days before admission, she had a fever over 38 °C. A facial computed tomography, which was taken in our affiliated hospital one day before admission, showed the thickening of left mandible and the swelling of the surrounding soft tissue.

On admission, her body temperature was 37.4 °C. Her left cheek was markedly swollen with pain and the skin was reddish. There was no injury around the cheek, oral wound, or caries. Peripheral white blood cell (WBC) and neutrophil counts were 11.7×10^9/L and 8.9×10^9/L, respectively. Serum C-reactive protein (CRP) level was 12.4 mg/dL. No bacterium was detected from blood in aerobic or anaerobic cultivation. The gadolinium-enhanced T1-weighted magnetic resonance imaging in the face revealed the discontinuous

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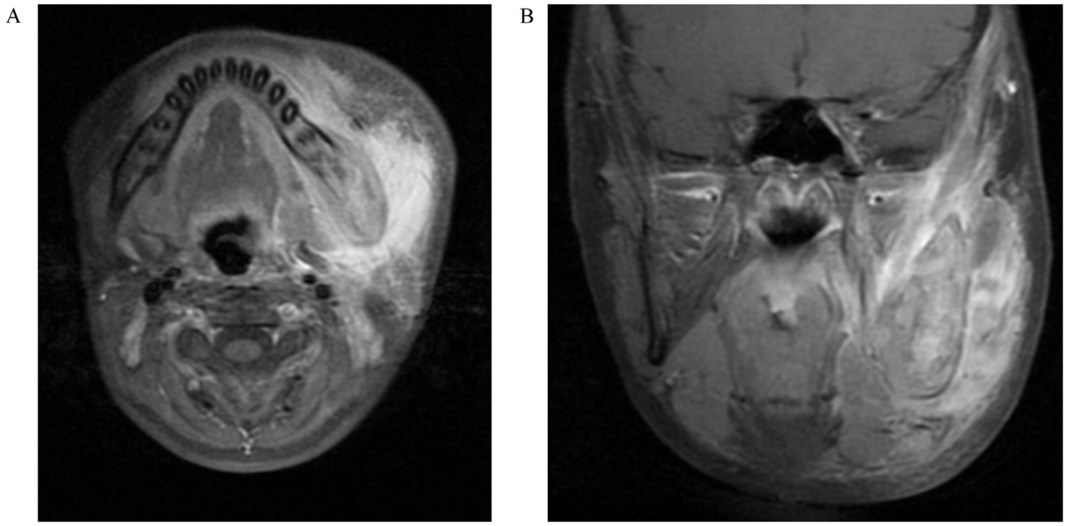

Fig. 1. The gadolinium-enhanced fat-suppressed T1-weighted magnetic resonance imaging in the face (A: axial image, B: coronal image).

high-intensity signals in the bone cortex of left mandible and the swelling and high-intensity signals of surrounding soft tissue and muscles, indicating the findings of chronic osteomyelitis (Fig. 1).

The intravenous administration of ampicillin/sulbactam was started after admission, and the mandibular cortical bone was harvested by an intraoral approach 5th day after admission. The causative pathogen was uncertain because polymicrobial species forming the oral flora, such as *Streptococcus mitis*, *S. parasanguinis* were detected from the culture. The swelling of the cheek did not improve in spite of the antimicrobial therapy. Furthermore, clindamycin and panipenem/betamipron could not be administrated for a sufficient period as the second-line treatment of chronic osteomyelitis because of the appearance of adverse drug events. Two months after admission, the curettage of left mandibular bone was performed by an intraoral approach. As polymicrobial species forming the oral flora, such as *Streptococcus* species, were detected from the culture of aspirated bone marrow fluid, we performed a clone library analysis of the bacterial 16S rRNA gene sequence to identify the causative pathogen as previously described [6]. The 16S rRNA gene was amplified using universal primers after the extraction of DNA from the sample. The PCR products were cloned with a TOPO TA cloning kit (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. A total of 96 colonies were randomly selected from each clone library for sequencing analysis. *G. adiacens* (62%) was predominantly identified in the method. Other main identified bacteria were *Streptococcus oralis* (12%) and *Actinomyces meyeri* (9%). Vancomycin was administrated for the treatment of *G. adiacens*-associated chronic mandibular osteomyelitis based on the results of the antimicrobial susceptibilities of the bacterium in the previous study [7], while we were forced to stop the treatment because of the appearance of adverse drug events. The alternative administration of linezolid for 6 weeks led to rapid improvement of the symptoms and laboratory data. However, as the swelling of the cheek recurred after stopping the treatment, the second curettage of left mandibular bone and the re-administration of linezolid were performed, and the symptoms disappeared. Although the administration of linezolid was planned to continue for 6 months, we were forced to stop the treatment after 3 months because of the appearance of severe anemia. Several weeks after stopping the treatment, the swelling of left cheek was exacerbated. Ciprofloxacin was administrated, in addition to the third curettage of left mandibular bone and hyperbaric oxygen therapy. After the procedure, the swelling of the cheek was improved and serum CRP level became negative. Ciprofloxacin had been continued for 8 months without the adverse drug effects. No symptoms recurred after stopping ciprofloxacin. She did not have any sequelae such as bone defects or functional disabilities.

3. Discussion

In chronic suppurative mandibular osteomyelitis, it is often difficult to differentiate the causative bacteria from the components of oral bacterial flora [2]. Additionally, some of the potential causative bacteria are difficult or impossible to culture [2]. Thus, gene amplification methods may be superior to culturing methods for the diagnosis of the disease. The clone library analysis is useful for predicting the causative pathogen in terms of not only the detection of less culturable bacteria but also the confirmation of the low bacterial diversity in the sample [8]. In addition, the prediction of the causative pathogen using this method is often possible even after beginning the antimicrobial treatment. The aspirated bone marrow fluid collected by intra-oral approach might not be pure because it might be contaminated with oral flora. In our patient, as the bacterial diversity of the sample obtained from the lesion was low and the most predominant bacterium was *G. adiacens*, we considered that *G. adiacens* was a causative pathogen. *Actinomyces meyeri* might be also a causative pathogen. However, it was only slightly detected by clone library analysis and the clinical symptoms of our patient did not improve despite the administration of effective antimicrobial agents to this bacterium. Thus, *A. meyeri* was unlikely to be a causative pathogen. The isolation of *G. adiacens* is often difficult because NVS grows slowly or never without pyridoxal hydrochloride and L-cysteine [3]. We regretted not attempting the cultivation using the medium which was easy to grow NVS. There was no report for *G. adiacens*-associated chronic mandibular osteomyelitis. Although it was possible that the causative bacteria had been killed by antecedent antimicrobial agents, we considered that *G. adiasens* was strongly associated with the development of chronic osteomyelitis in the present case based on the highly frequent detection of the bacterium in the clone library analysis and the persistence of clinical symptoms despite the administration of antimicrobial agents.

The administrations of benzylpenicillin or ampicillin and gentamicin are recommended for the treatment of NVS-associated infective endocarditis [3]. In contrast, the proportion of *G. adiacens* with the resistance to penicillin and cephalosporins was high in a previous study [7]. All isolated *G. adiacens* was susceptible to vancomycin and carbapenems [7]. Furthermore, linezolid and fluoroquinolone may be also effective for *G. adiacens* infection. In our patient, we were forced to change to other antimicrobial agents from vancomycin and carbapenems because of adverse drug events. The disadvantage of the clone library analysis is that the antimicrobial susceptibility cannot be investigated. Although the drug-susceptibility testing could not be performed, linezolid and ciprofloxacin were clinically effective for our patient, indicating that these drugs could be alternatively treatment options for *G. adiacens*-associated chronic madibular osteomyelitis.

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Conflicts of interest

None.

References

[1] Kim SG, Jang HS. Treatment of chronic osteomyelitis in Korea. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:394–8.
[2] Koorbusch GF, Fotos P, Goll KT. Retrospective assessment of osteomyelitis etiology, demographics, risk factors, and management in 35 cases. Oral Surg Oral Med Oral Pathol 1992;74:149–54.
[3] Cargill JS, Scott KS, Gascoyne-Binzi D, Sandoe JA. *Granulicatella* infection: diagnosis and management. J Med Microbiol 2012;61:755–61.
[4] Fukuda R, Oki M, Ueda A, Yanagi H, Komatsu M, Itoh M, et al. Vertebral osteomyelitis associated with *Granulicatella adiacens*. Tokai J Exp Clin Med 2010;35:126–9.
[5] Rosenthal O, Woywodt A, Kirschner P, Haller H. Vertebral osteomyelitis and endocarditis of a pacemaker lead due to *Granulicatella (Abiotrophia) adiacens*. Infection 2002;30:317–9.
[6] Kawanami T, Fukuda K, Yatera K, Kido M, Mukae H, Taniguchi H. A higher significance of anaerobes: the clone library analysis of bacterial pleurisy. Chest 2011;139:600–8.
[7] Alberti MO, Hindler JA, Humphries RM. Antimicrobial susceptibilities of *Abiotrophia defectiva, Granulicatella adiacens*, and *Granulicatella elegans*. Antimicrob Agents Chemother 2015;60:1411–20.
[8] Noguchi S, Mukae H, Kawanami T, Yamasaki K, Fukuda K, Akata K, et al. Bacteriological assessment of healthcare-associated pneumonia using a clone library analysis. PLoS One 2015;10, e0124697.