The First Case of Invasive *Bacteroides Dorei* Infection Detected in a Mycotic Aortic Aneurysm Patient-Raising A Rebellion of Major Indigenous Bacteria in Humans: A Case Report and Review

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Case Report

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Abstract

Background: *Bacteroides dorei* is an anaerobic, gram-negative bacterium first described in 2006. Due to the high similarity in mass spectrum patterns between *B. dorei* and *Bacteroides vulgatus*, discriminating these species is arduous in clinical practice. In recent decades, 16S rRNA gene sequencing has been a complementary method for distinguishing taxonomically close bacteria to the genus and species levels, including *B. dorei* and *B. vulgatus.* Accordingly, *B. dorei* has been shown to contribute to some diseases, including type 1 autoimmune diabetes mellitus and atherosclerotic diseases. Nevertheless, there are no reports on invasive infectious disease caused by *B. dorei*. This report describes the first case of *B. dorei* presenting direct invasion and colonisation into human tissue, providing a warning for the previously proposed application of *B. dorei* as live biotherapeutics for atherosclerotic diseases.

Case presentation: A 78-year-old man admitted with suspicion for mycotic thoracic aortic aneurysm was diagnosed by enhanced computed tomography scan, exhibiting the appearance of infection and dissection at the distal aortic arch. Despite strict blood pressure control and empirical antibiotic therapy, the patient's condition worsened. For the prevention of aneurysmal rupture and elimination of infectious foci, the patient underwent surgical treatment, and the resected specimen was subjected to tissue culture and 16S rRNA gene sequencing analysis to identify pathogenic bacteria. A few days after the surgery, culture and sequencing results revealed that the pathogen was *B. dorei/ vulgatus* and *B. dorei*, respectively. The patient was successfully treated by appropriate antibacterial therapy, improved and was transferred to another hospital for rehabilitation at postoperative day 34. There was no recurrence of symptoms after the patient transfer.

Conclusions: This report describes the first case of invasive infectious disease caused by *B. dorei*, casting a shadow over its utilisation as a probiotic for atherosclerotic diseases.

Background

Bacteroides dorei is a gram-negative and anaerobic rod generally isolated from the human and animal gastrointestinal tract [1] and one of the cardinal indigenous bacteria in humans [2]. In clinical settings, matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) analysis has prominently contributed to the identification of pathogenic bacteria and fungi, and its identification accuracy was estimated as high as 84% for species and 92% for genera [3]. However, it is known that this methodology has some limitations for taxonomically close species or anaerobic bacteria. Some researchers have shown the low performance of MALDI-TOF MS for identifying anaerobic bacteria spp., partially due to insufficient commercial mass spectrum reference libraries, resulting in the misidentification of pathogens, e.g., *B. dorei* to *Bacteroides vulgatus* [4–7]. In the last decade, 16S rRNA gene sequencing for bacterial identification has been applicable in many facilities. This polymerase chain reaction (PCR)-based method is highly potent for discriminating phylogenetically close bacteria to the genus and species levels; therefore, it has been relevant as a complementary method for blood culture, MALDI-TOF MS, and conventional phenotypic screening tests to identify bacterial pathogens [8]. Recently,

the role of *B. dorei* as an immunomodulator in autoimmune disease has been uncovered [9]. Other reports also showed that alteration of the abundance of Bacteroides species in the intestinal microbiota was associated with susceptibility to autoimmune disease or atherosclerotic diseases; they are thus assumed to be therapeutic targets for these diseases, especially in the form of probiotics or biotherapy [10]. However, there are almost no reports indicating the direct infectious pathogenesis of *B. dorei*. This report describes the first case of *B. dorei* as a pathogen of invasive infectious disease, suggesting the need for caution in the usage of *B. dorei* as a biotherapeutic material.

Case Presentation

A 78-year-old man presented with intermitted chest-back pain and was admitted to our hospital with suspicion of a mycotic thoracic aortic aneurysm. On the day of admission, the patient was afebrile and showed unremarkable manifestations except for dysphoria of his back. A contrast-enhanced computed tomography (eCT) scan confirmed the appearance of a mycotic thoracic aortic aneurysm and dissection at the distal arch with intramural fluid-density collection and periaortic inflammatory changes (Fig. 1). We started empiric intravenous antibiotic therapy with meropenem, vancomycin and micafungin. After three days, we assessed the effectiveness of the treatment by laboratory examination and eCT. Despite strict blood pressure control and broad-spectrum antibiotic therapy, inflammation scores became exacerbated, represented by elevated C-reactive protein (CRP), procalcitonin (Pct), and white blood cell (WBC) count (CRP 11.61 to 28.71 mg/dl, WBC 9.920 to 17,800/μl, and Pct 0.34 to 0.84 ng/ml), and the patient suffered from a high fever up to 39.9 °C. For the prevention of aneurysmal rupture and the elimination of infected foci, the patient underwent ascending aorta and aortic arch resection and subsequent total arch replacement with rifampicin immersed in artificial vessels on day five, and the resected infected tissue was subjected to pathological analysis (Fig. 2), culture examination and 16S rRNA gene sequence analysis (Fig. 3) to identify the pathogen. A few days after surgical treatment, the culture and sequencing results revealed *B. vulgatus/dorei* and *B. dorei* (Fig. 3 and additional file 1–2) as the pathogen, respectively. By the determination of the pathogen and susceptibility tests, the three antibiotic therapies could be de-escalated and stepwise shifted to a single metronidazole p.o. therapy. The patient satisfactorily improved and was transferred to another hospital for rehabilitation at postoperative day 34. There was no recurrence of symptoms after patient transfer.

Discussion And Conclusions

Anaerobic bacteria, including *Bacteroides spp.*, usually reside in the lower intestinal tract as indigenous bacteria. However, they are sometimes detected as pathogens in infectious disease patients. Anaerobe infection can be highly lethal and life threatening, and its mortality rate is estimated to be as high as 40% [11]. Therefore, it is crucial to identify pathogenic bacteria immediately and initiate appropriate antibiotic therapy targeting the identified specific pathogen. In the last decade, in addition to conventional culture tests, MALDI-TOF MS has been widely used for clinical examination. This method is capable of detecting pathogens in a few minutes after applying samples, but this mass spectrum-based bacterial

identification has some limitations among bacteria having similar protein compositions or uncommon bacterial species, partially due to incomplete reference databases. Because of only 5% gene sequence divergence between *B. dorei* and *B. vulgatus* [1], two major MALDI-TOF MS systems commercially available misidentify *B. dorei* as *B. vulgatus* or cannot distinguish them [12, 13]. Our facility also employs the MALDI-TOF MS system for the identification of pathogens and could not discriminate between *B. dorei* and *B. vulgatus*, determining the pathogen as "*B. vulgatus/dorei*" in this case.

16S rRNA gene sequencing is a highly potent molecular biological approach for identifying specific bacteria to the species level, particularly in the case of uncommon, slow-growing or uncultivable bacteria, such as minor anaerobes. Due to the inexpensiveness and easy availability of PCR and DNA sequencing needed for this method, it has been a complementary examination tool for the accurate identification of bacteria and the discovery of novel bacterial species in clinical and laboratory settings [14]. In 2019, J. S. Johnson *et al*. reported the interspecies sequence entropy of the 16S rRNA gene, depicting that the V2, V3, V6, and V9 regions had relatively high sequence variations and noted the validity of sub-regional sequencing for discriminating closely related bacteria from specific taxa [15]. As preliminary experiments, we initially amplified the full, first-half and second-half lengths of the 16S rRNA gene sequence, and thereby, it was shown that the second-half sequence was prone to more effective amplification and that amplicon sequencing could identify specific bacteria satisfactorily (data not shown). In this case, through amplification and sequencing of the V5-V9 segments, we successfully identified *B. dorei* as a pathogen with 100% sequence identity. Altogether, it was corroborated that partial 16S rRNA gene sequencing, which included at least two of the four high variant regions mentioned above, has sufficient detectability and capability of discriminating specific bacteria among allied species.

Under this sequencing-based bacterial identification, the pathophysiology of *B. dorei* has been gradually uncovered. When we searched the PubMed database using the keyword "*Bacteroides dorei*", only 50 articles were published by June 1st, 2020. It is seemingly innocuous in healthy individuals, as *Bacteroidetes* and *Firmicutes* constitute over 90% of healthy gut microbial assemblage [16]. However, it has been demonstrated that the *B. dorei* proportion in the gut microbiota is responsible for a variety of diseases, including autoimmune type 1 diabetes mellitus [9, 17–22], colorectal diseases [23–26], atherosclerotic diseases [27–30], and even Parkinson's disease [31]. On the other hand, there is almost no report regarding *B. dorei* as a cause of infectious diseases or even a part of its contagious process, which consists of tissue invasion, multiplication and colonisation and infliction of host tissue damage by cytotoxic materials or direct interactions. In immunocompromised or dysbiosis states resulting in a permeable gut and impairment of mucosal barriers, pathogens may invade nearby tissues or the systemic circulation, consequently initiating infectious diseases. Despite the assumption of these mechanisms, there is no sufficient evidence for understanding the pathogenesis of *B. dorei*. As a result, this report describes the first case of invasive infectious disease caused by *B. dorei*. Further studies are needed to elucidate its infectious processes.

The association of dysbacteriosis or alteration of the *B. dorei* proportion in the gut microbiota with these diseases might be a target for preventative or therapeutic interventions. Some researchers have proposed

using some indigenous bacteria as pre-/probiotics for modulating gut bacterial composition, including *B. dorei* itself [10, 29, 30, 32–35]. However, as microbiome composition is influenced by daily meals, eating habits and geography and temporally varies even in individuals, the efficacy of probiotic usage may be definite in a specific condition. Furthermore, as the gut microbiota forms complex systems (e.g., metabolic network, interaction with an immune system or inter-microbial interaction), the effect of modification of specific bacterial abundance is not necessarily predictable [36]. Moreover, due to its invasive potential causing infectious diseases, such as in this case report, considerable attention must be paid to the use of *B. dorei* as a probiotic. Additional studies regarding the application of probiotics or modulating strategies of the gut microbiota are needed.

The metabolic profile of *B. dorei* has also been studied and has shown its uniqueness [37–41]. To date, only two bacteria have been identified with cholesterol-reducing capacity in a human microbial community, *Eubacterium coprostanoligenes* and *B. dorei* strain D8 [42, 43], which is proposed to have protective roles for atherosclerosis. However, this report presented a case of an infected aortic aneurysm caused by *B. dorei* detected from a surgically dissected atherosclerotic lesion. This contradictory aspect can be partially explained by the microbial metabolic features described in one report in which *Bacteroides thetaiotaomicron* was shown to selfishly or exclusively metabolise yeast mannan [44]. These results may imply that some bacteria have preferences for a specific tissue site, such as atherosclerotic lesions or microbial community sites. As *B. dorei* strains have the potential to metabolise cholesterol, they may be predisposed to colonise atherosclerotic tissues with plaque deposited by fat, cholesterol and calcium. Therefore, *B. dorei* potentially causes a mycotic aneurysm or infective endocarditis in atherosclerotic patients. This fact also gives us warning regarding the utilisation of *B. dorei* as a biotherapeutic tool, particularly in the form of live bacteria.

In conclusion, we report the first case of invasive infectious disease by *B. dorei* in a mycotic thoracic aneurysm patient, which disagrees with the protective roles of *B. dorei* in atherosclerotic diseases.

Materials And Methods

DNA isolation from infectious tissue and verification of DNA purity

DNA isolation from infectious tissue and purification of the extracted DNA was carried out with the NucleoSpin® Tissue (MACHEREY-NAGEL (MN), #740952) and Monarch® Genomic DNA Purification Kits (NEW ENGLAND BioLabs Inc. (NEB), #T3010) according to the manufacturer's instructions. The DNA concentration was determined by a NanoDrop One spectrophotometer (Thermo Scientific™), as well as its purity. The extracted DNA samples were stored at −20 °C. To prevent interference with the following enzymatic reaction, DNA was eluted from the spin column with DNase/RNase-free water. Throughout the protocol (DNA extraction/purification, primer aliquoting, and 16S rRNA gene amplification), nuclease-free plastics were used unless supplied with the kit: DNA LoBind Tubes (Eppendorf) and OneTouch tips (Sorenson BioScience, Inc.).

Positive control

As a positive control, *Escherichia coli* DH5-alpha (Takara, #9057) was incubated with shaking overnight at 37 °C in LB broth. Before reaching the confluent state, the bacteria were harvested by centrifugation and subjected to lysis following genomic DNA extraction by using a Monarch® Genomic DNA Purification Kit (NEB, #T3010) according to the manufacturer's instructions.

16S rRNA gene amplification

For detection of the bacterial 16S rRNA gene, PCR amplification of the V5–V9 region was performed using the following universal primers (forward primer (800F): 5'- GGATTAGATACCCTGGTA -3' and reverse primer (1500R): 5'- TACCTTGTTACGACTT -3'). Amplification was performed with 1.5 µg of DNA per reaction, the primers at a final concentration of 2 µM, and Tks Gflex™ DNA Polymerase (Takara, #R091A). PCR was performed using the following conditions: 60 s of denaturation at 94 °C; 35 cycles of denaturation at 98 °C for 10 s, annealing at 51 °C for 60 s, and elongation at 68 °C for 60 s; and a final extension at 72 °C for 10 min. Negative (nuclease-free and DNA-free water) and positive controls (50 ng of *E. coli* genomic DNA) were also amplified. After completion of the PCR, the amplicons were electrophoresed on a 1.5% agarose gel and purified by gel extraction with a Monarch® DNA Gel Extraction Kit (NEB, #T1020) according to the manufacturer's instructions.

Sequencing and taxonomical identification

The concentration and quality of the PCR amplicons were evaluated before Sanger sequencing. Sequencing was performed by a Sanger sequencing service (GENEWIZ Inc., South Plainfield, NJ, USA) following the sample submission guidelines in which the samples were composed of 10 ng of purified PCR amplicon and 5 µM 800F or 1500R sequencing primer. Sequence contigs were constructed and analysed using bioinformatics software (CLC Main Workbench 20, QIAGEN Digital Insights, Redwood City, USA). Full sequence reads were analysed for initial identification using Nucleotide BLAST (http://www.ncbi.nlm.nih.gov/blast/cg).

Clinical pathogenic bacterial identification

The isolates were initially identified by MALDI-TOF MS using a BRUKER MALDI Biotyper system (Bruker Daltonics, Bremen, Germany). The reference library of spectra was MBT Compass Library version 4.5.1, and a log score of 2.0 was used as the threshold for species identification.

List Of Abbreviations

B. dorei
Bacteroides dorei; *B. vulgatus*:*Bacteroides vulgatus*; CRP:C-reactive protein; eCT:contrast-enhanced computed tomography; LPS:lipopolysaccharide; MALDI-TOF MS:matrix-assisted laser desorption

ionisation time-of-flight mass spectrometry; PCR:polymerase chain reaction; Pct:procalcitonin; rRNA:ribosomal RNA; WBC:white blood cell

Declarations

Ethics approval and consent to participate

Written consent for clinical sample analysis was obtained from the patient. This study was approved by the institutional review boards of the Independent Ethics Committee of Tohoku Medical and Pharmaceutical University Hospital (reference number: 2018-2-105).

Consent for publication

Informed consent for the publication of this case report was obtained from the patient.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TM analysed and interpreted the patient data and was a major contributor in writing the manuscript. TS, TM, WH, and MT contributed to interpreting the patient data. RK advised on the research ideas for this study. SK supervised this study and the patient's therapy. All authors read and approved the final manuscript.

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Figures

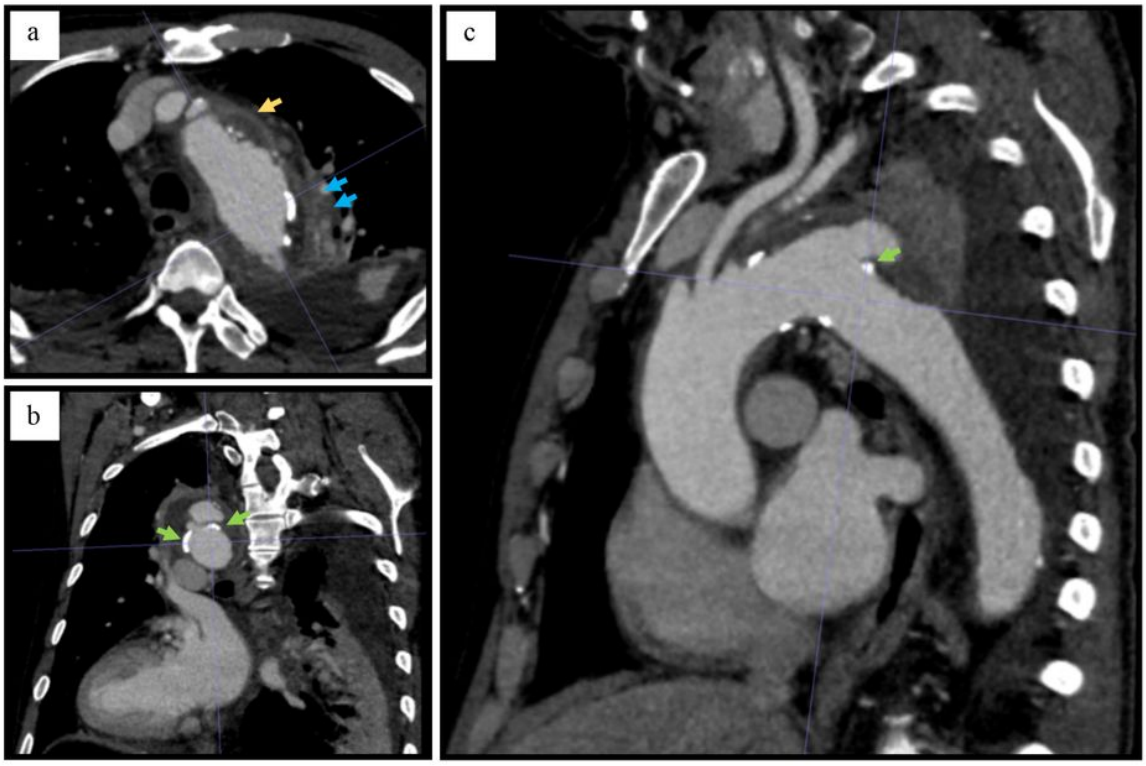

Figure 1

Contrast-enhanced computed tomography scan on admission of the patient. (a) An axial view shows the distal aortic arch aneurysm with perianeurysmal fluid-density collection (yellow arrow) and periaortic inflammatory changes (blue arrows). Coronal (b) and sagittal (c) views show the dislocation of intimal calcification (green arrows) and the appearance of aortic dissection.

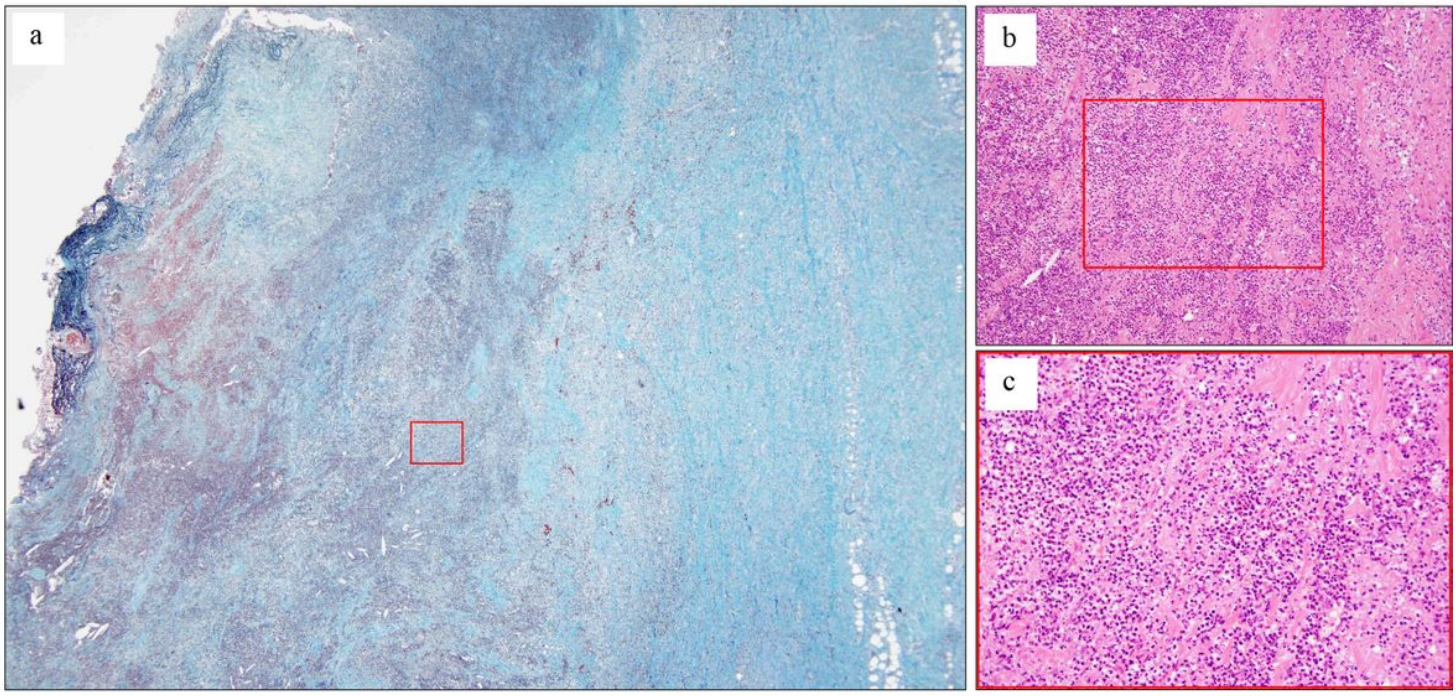

Figure 2

Pathological examination of the resected aorta. Microscopic examination of the resected specimen was achieved with Elastica-Masson staining (a) and Hematoxylin and eosin staining (b, c). (a) Significant immunocyte infiltration is seen in the sub-adventitial layer, depicting purulent inflammation. (b, c) Abundant neutrophils infiltrate into the intramural area of the infected arterial wall, forming an abscess.

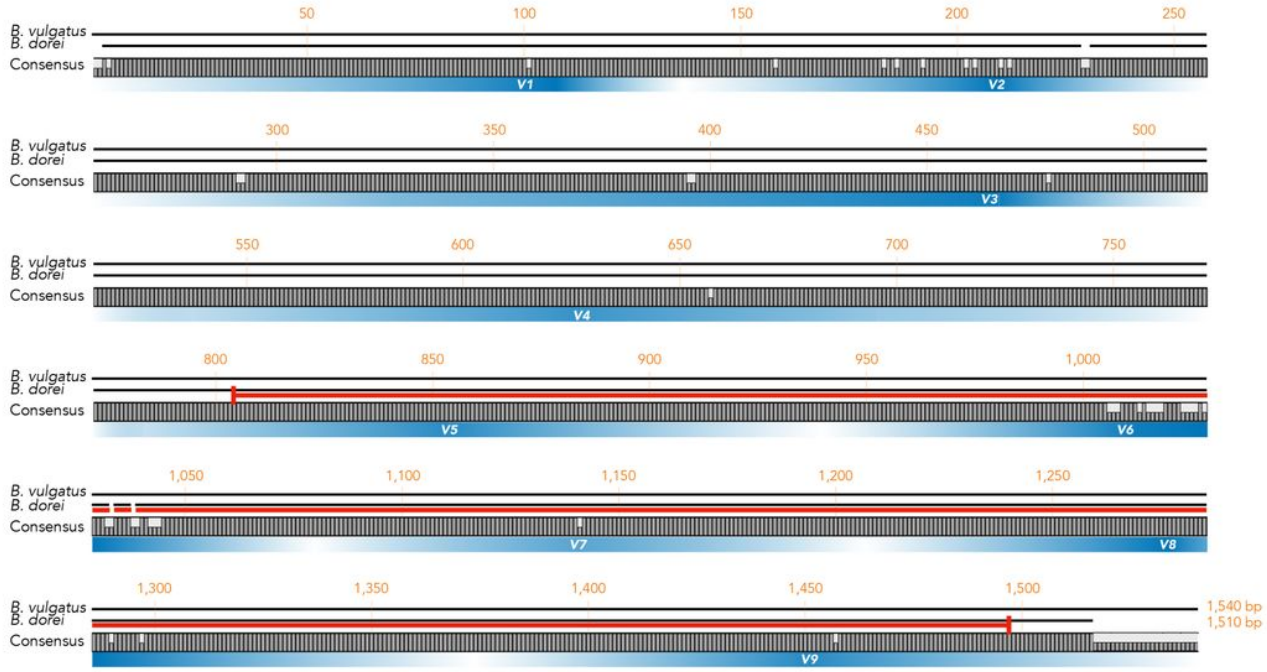

Figure 3

16S rRNA gene sequence analysis for the identification of pathogenic bacteria. Bacteroides dorei (DSM 17855) and Bacteroides vulgatus (ATCC8482(T)) 16S rRNA gene sequences are aligned with the consensus, with a concordance rate as high as 97%. V1-V9 represent an inter-species variant region in its gene sequence, and a red bar indicates the sequencing range for identifying pathogens in this study. B. dorei was identified as a pathogen in this patient, with 100% sequence identity.

Supplementary Files

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- Additionalfile.docx
- Additionalfile2.pdf
- Additionalfile1.xlsx