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CASE REPORT

Brain abscess from oral microbiota approached by metagenomic next-generation sequencing: A case report and review of literature

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Abstract

BACKGROUND

Brain abscess is a serious and potentially fatal disease caused primarily by microbial infection. Although progress has been made in the diagnosis and treatment of brain abscesses, the diagnostic timeliness of pathogens needs to be improved.

CASE SUMMARY

We report the case of a 54-year-old male with a brain abscess caused by oral bacteria. The patient recovered well after receiving a combination of metagenomic next-generation sequencing (mNGS)-assisted guided medication and surgery.

CONCLUSION

Therefore, mNGS may be widely applied to identify the pathogenic microorganisms of brain abscesses and guide precision medicine.

Key Words: Brain abscess; Metagenomic next-generation sequencing; Periodontitis; Oral bacteria; Precision medicine; Case report

Core Tip: Brain abscesses are mixed infections, and there is difficulty in detecting all pathogens on routine bacterial cultures. We report the case of a 54-year-old male with a brain abscess caused by oral bacteria. The patient recovered well after receiving a combination of metagenomic next-generation sequencing (mNGS)-assisted guided medication and surgery. mNGS may be used for the rapid diagnosis of pathogenic microorganisms and may play an important role in precision medicine.

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INTRODUCTION

Brain abscess is a serious and potentially fatal disease caused primarily by microbial infection[1,2]. Brain abscesses can result from the spread of bacteria from distant sites of primary infection or from direct sequential invasion from adjacent sites[3,4]. Pus evolves from a localized area of encephalitis to an enveloped membrane in the brain parenchyma[5].

Patients with brain abscesses have had high morbidity, disability, and mortality rates in recent decades[6,7]. In recent years, the morbidity and mortality of brain abscesses have only declined with significant advances in imaging techniques, neurosurgical techniques, microbiological detection techniques, and antibiotic therapy[8]. However, the predisposing factors of bacterial brain abscesses and the prevalence of associated bacterial pathogens have different effects on mortality.

Brouwer *et al*[8] found that the common pathogens in blood and abscess fluid cultures from patients with brain abscesses were *Streptococci*, *Diplococci*, and Gram-negative bacteria. Notably, most cases were mixed infections with multiple microorganisms, including rare ones. In recent years, the application of new molecular biotechnologies has expanded the range of microbial pathogens isolated in brain abscesses[9].

Detection and identification of the pathogen are essential to confirm the diagnosis and select the best antibiotic regimen. Microbiological cultures of abscesses remained negative in approximately 20% of patients with bacterial brain abscesses. In recent years, metagenomic next-generation sequencing (mNGS) has been used for its ability to detect all potential pathogens - bacteria, viruses, fungi, and parasites in a sample and to detect host responses simultaneously[10]. Thus, mNGS has great potential utility in the diagnosis of infectious diseases.

Herein, we present a case of a brain abscess due to periodontitis pathogens in a 54-year-old man. The patient recovered well after receiving a combination of mNGS-assisted guided medication and surgery.

CASE PRESENTATION

Chief complaints

A 54-year-old man presented to the neurology department with a headache and fever for 5 d.

History of present illness

The symptoms started 3 mo before the presentation and included headaches while bowing his head, which started 19 d before the presentation with double vision while viewing distant objects, and fevers during the headaches started 5 d before presentation.

History of past illness

Seven years prior, the patient underwent surgery for appendicitis in a local hospital. Moreover, he was diagnosed with chronic severe periodontitis for 5 years, type 2 diabetes for 2 years, and an allergic reaction to aminotriol keto chromate injection. Ten days prior, the patient was admitted to a local hospital complaining of headaches for three months, and brain magnetic resonance imaging (MRI) revealed multiple signal abnormalities in the left cerebellum and abnormal signal foci in the cavernous sinus region. Laboratory examinations showed that the C-reactive protein (CRP) was 44.91 mg/L (normal 0-10), and the erythrocyte sedimentation rate (ESR) was 45 mm/h (normal 0-15). cyfra21-1 (CF21-1) was 3.5 ng/mL (normal 0-3), neuron-specific enolase (NSE) was 22.8 ng/mL (normal 0.6-5.4), and the levels of immune markers were normal. No abnormalities were found in the electrolyte test, kidney function test, liver renal function test, or routine blood and urine analyses. Therefore, the local hospital's staff considered that the patient could have metastases or inflammatory lesions. Five days prior, the treatment showed no avail, and the patient presented with an aggravated headache and pyrexia. The patient was admitted to our hospital for further diagnosis and treatment.

Personal and family history

The patient denied any family history of genetic disorders.

Imaging examinations

Thyroid and abdominal ultrasound, chest computed tomography (CT), and abdominal CT did not reveal any tumor lesions, and lymph node biopsy showed no significant abnormalities. Brain CT showed abnormal signal foci in the cavernous sinus region. Brain MRI showed irregular patchy long T1 and long T2 signal shadows in the left cerebellar hemisphere, with blurred borders, and patchy low signal shadows within them. Enhancement scanning of the lesion area showed a multiventricular ring-like enhancement (Figure 1A-D).

Laboratory examinations

The serum sodium was 133.6 mmol/L (normal 135-145), the serum chlorine was 92.6 mmol/L (normal 95-100), the blood glucose was 8.68 mmol/L (normal 3.9-6.1), the glycated hemoglobin was 11.3% (normal 4%-6%), the CRP was 11.00 mg/L (normal 0-10), and the ESR was 23 mm/h (normal 0-15). The cytomegalovirus IgG was 92.2 U/mL (normal 0-4), and the rubella virus IgG was 24.5 IU/mL (normal 0 < 10). The antinuclear extract antibody profile (Anti-Sm antibody, anti-Scl-70 antibody, anti-RNP antibody, anti-Jo-1 antibody, anti-SSA antibody and anti-SSB antibody), tumor anti-nervous system antibody profile (anti-hu, anti-Ri, anti-Yo, anti-Amphiphysin), and tumor marker (CA125, CA199, CA72-4, CY21-1, CEA, NSE, SCC, AFP, TPSA, FPSA and ProGRP), all of which were normal. No abnormalities were found in the eight tests for infectious diseases, tuberculosis T-cell test, G test, GM test, kidney function, liver renal function test, or routine blood and urine analyses.

Physical examination

The vital signs were as follows: body temperature, 36.5 °C; blood pressure, 105/70 mmHg; heart rate, 70 beats per min; and respiratory rate, 16 breaths per min. Furthermore, the patient had the following: clear mind, clear language, normal emotions; orientation, understanding, memory, computing power were all normal; stable vitals; gums with residual crowns and roots; reduced tendon reflexes in the extremities; no obvious abnormality in cardiopulmonary and abdominal physical examination; and no edema in the lower limbs. Moreover, nonpersistent horizontal nystagmus was observed in both eyeballs, especially in left eye fixation. The tongue was centered, the right pharyngeal reflex was slightly diminished, the left finger nose test and heel knee tibial test were slightly less accurate, and other physical examinations showed no obvious abnormalities.

Further diagnostic work-up

On day 7 of admission, mNGS was used to detect pathogenic microorganisms in the CSF, and the results showed that the pathogens were two oral bacteria, *Tannerella forsythensis* and *Campylobacter rectus* (Table 1). Moreover, the intracranial lesions were preliminarily considered inflammatory tissue, which may have been secondary to oral bacteria. On day 10 of admission, these lesion tissues were extracted. Intraoperatively, three flexible, light yellow lesion tissues with a normal blood supply were found in the left cerebellum. We used a syringe to puncture the abscess and aspirate it and found yellow, sticky, foul-smelling pus. Histopathological examination of the resected specimen (size, 1 cm × 0.6 cm × 0.3 cm) confirmed that the abscess originated from a bacterial infection (Figure 2A). Immunohistochemical analysis revealed that inflammation was positive for CD3, CD4, CD8, CD20, CD56, CD68, CD138, and MPO and negative for PAS (Figure 2B-I).

FINAL DIAGNOSIS

The final diagnosis was brain abscess caused by oral bacteria.

TREATMENT

Postoperatively, the antibiotic treatment was changed to linezolid (600 mg, IV, q12h). Meanwhile, the patient received treatment to regulate blood sugar, relieve pain, and protect the gastric mucosa. On day 13 of admission, the patient's body temperature returned to normal, the headaches were gradually relieved, and the mental state gradually improved. On day 25 of admission, the patient recovered well and was discharged.

OUTCOME AND FOLLOW-UP

MRI results showed that the intracranial condition had basically recovered well after 2 wk (Figure 1E-H). The patient was in good condition after 6 months postoperatively.

DISCUSSION

Brain abscesses are usually caused by serious infections such as bacteria, fungi, or parasites and can develop from encephalitis, which can be very disturbing to the quality of life of patients[11]. In most patients, susceptibility factors for brain abscess include immune suppression, chronic systemic disease, disruption of the natural protective barrier around

Table 1 The pathogen of cerebrospinal fluid was isolated in this case

Sample type	Type	Genus name	Species name
Cerebrospinal fluid	G-	Tannerella	*Tannerella forsythensis*
	G-	Campylobacter	*Campylobacter rectus*

G-: Gram-positive bacterica.

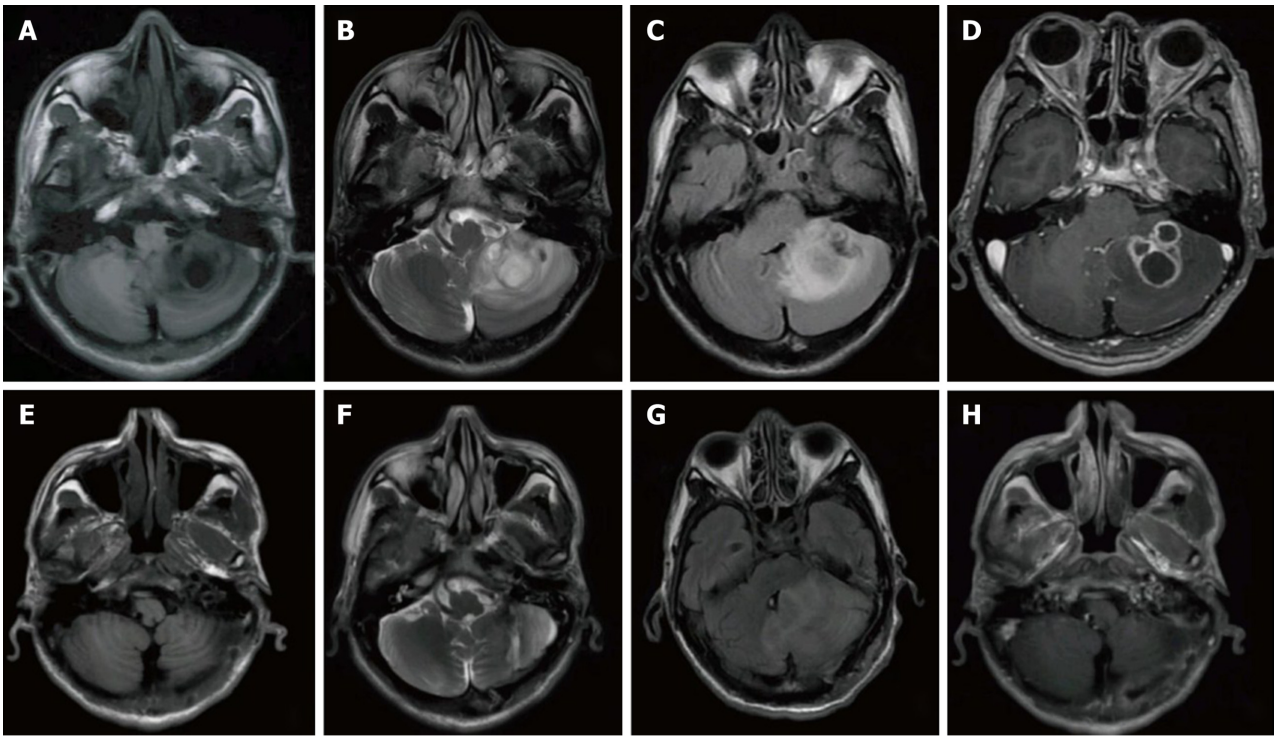

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Figure 1 The patient's brain magnetic resonance imaging results before treatment and follow-up. A and E: Long T1-weighted imaging signal in left cerebellar hemisphere before treatment; B and F: Long T2-weighted imaging signal in left cerebellar hemisphere in follow-up; C: High T2-fluid-attenuated inversion recovery signal in left cerebellar hemisphere before treatment; D: Enhancement showing a multiventricular ring-like enhancement in left cerebellar hemisphere before treatment; G: Slightly high T2-FLAIR signal in left cerebellar hemisphere in follow-up; H: Enhancement showing a ring enhancement in left cerebellar hemisphere in follow-up. MRI: Magnetic resonance imaging; T1WI: T1-weighted imaging; T2WI: T2-weighted imaging; FLAIR: Fluid-attenuated inversion recovery.

the brain, and systemic infection sources[12]. Diabetic patients have a higher prevalence of microvascular disease, periapical inflammation, and brain abscess than nondiabetic patients[13].

MRI is the radiological method of choice for diagnosis and identification[14]. Clinically, CT must be complemented with MRI. MRI is helpful in differentiating brain abscesses from primary and cystic abscesses and in excluding tumor lesions[15]. CT scanning with contrast enhancement can be used to rapidly detect the size, number, and location of abscesses. The availability of these diagnostic techniques has led to a decrease in brain abscess mortality over the years [16]. The etiology, clinical manifestations, and complications of brain abscesses vary significantly in different populations. Fever, meningitis, elevated ESR, and reduced cyclic enhancement on delayed scans favor the diagnosis of abscesses. However, these are not sufficient to differentiate the pathogens.

Pathogenic bacteria can enter brain tissue through hematogenous spread, closed diffusion, head trauma, and traumatic infection from neurosurgery, which can lead to brain abscess[8]. Brain abscesses are often caused by multiple microorganisms, including staphylococci and streptococci or gram-negative bacilli[17]. Maraki *et al*[18] found that the mortality rate of brain abscesses caused by odontogenic infections was approximately 14%. Lateralized intraoral and intracranial infections help to identify possible routes of transmission. When both sides are consistent, direct venous dissemination should be considered. Otherwise, systemic hematogenous dissemination is considered[19]. The most closely related and abundant pathogen in the oral cavity associated with brain abscesses is anaerobic bacteria. Anaerobic bacteria are present in almost all dental infections, including periodontal and endodontic diseases. Aerobic bacteria are the initiators of infection, while anaerobic bacteria contribute to severe infection[20]. Infections in maxillary teeth can spread to the maxillary sinus, sphenoid sinus, septal sinus, and orbital cavity. Some blood vessels may spread oral infections to the cavernous sinus. Therefore, maxillary teeth are more likely to cause brain abscesses than mandibular teeth[21]. Most odontogenic infections penetrate the bony and fascial spaces and form infected ducts of brain abscesses through the

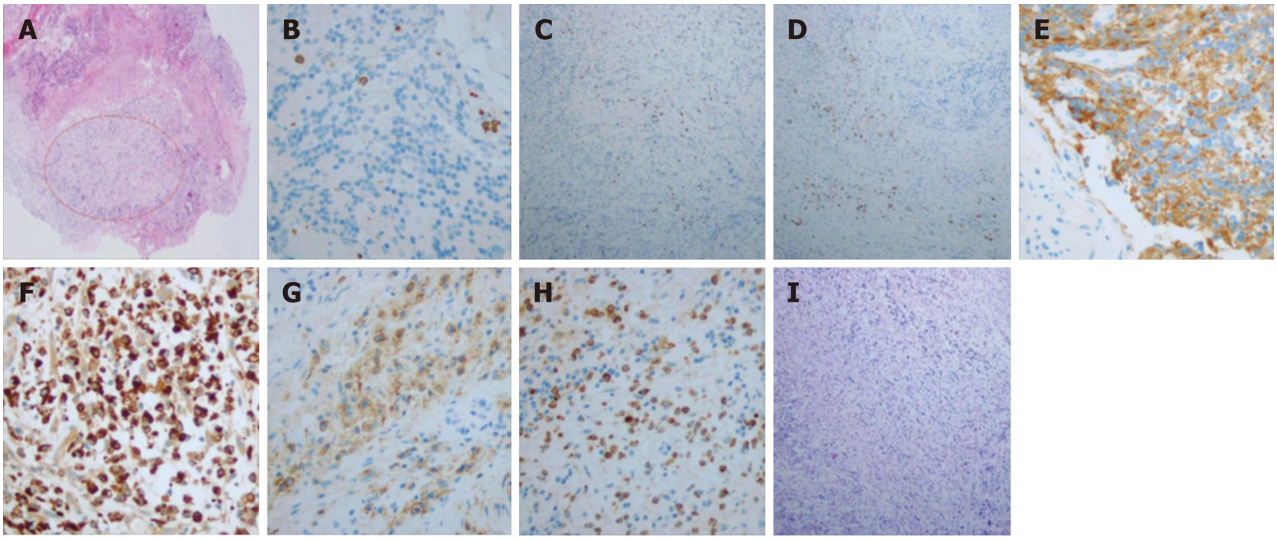

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Figure 2 Histopathological analysis and immunohistochemical examination of the extracted specimen. A: Hematoxylin and eosin staining (× 40); B: Immunohistochemical staining for showing CD3 positive staining (× 200); C: CD4 positive staining (× 100); D: CD20 positive staining (× 100); E: CD56 positive staining (× 400); F: CD68 positive staining (× 400); G: CD138 positive staining (× 400); H: MPO positive staining (× 400); I: PAS negative staining (× 100).

bloodstream, lymphatic vessels, or direct venous drainage[22]. If the infectious process is not treated early, the clinical situation can deteriorate to the point where it becomes life-threatening for patients. The patient was definitively diagnosed with periodontitis, and the bacteria detected in the cerebrospinal fluid were all common in periodontal disease. The skull base CT showed no signs of trauma, such as a fracture. Combined with the abnormal signal in his cavernous sinus area, the brain abscess was thought to be caused by the venous return route or direct diffusion.

Microorganism testing in the patient's mouth, blood, and brain abscesses can be a great diagnostic aid in establishing the relationship between the mouth and the brain[21]. Performing microbiological testing to determine pathogens is key to making an accurate diagnosis[23]. The detection of pathogenic microorganisms in intracranial infections is limited, with low sensitivity and specificity. In approximately 25% of patients, the causative pathogens are identified in blood and cerebrospinal fluid cultures[8]. The researchers identified 80 different bacterial taxa, 44 of which have not been previously described in brain abscesses, and 37 of which have not been reported in culture[17]. Classical identification techniques include bacterial culture combined with Sanger sequencing of 16S rDNA. Bacterial culture usually does not accommodate both anaerobic and aerobic bacteria, so anaerobic cultures are generally negative. In the cases with positive bacterial culture, the results of bacterial culture could not be returned until 3-4 d after the examination. Sanger sequencing is only applicable to single microbial samples and is not applicable to multiple microbial infections[24]. Polymerase chain reaction (PCR) is a tool with good specificity and sensitivity for detecting Mycobacterium tuberculosis that needs to be detected quickly[25]. However, PCR results can sometimes have false-positives and false-negatives. The application of 16S rDNA-based mNGS enables the detection of as many microorganisms as possible in the sample compared to these technologies[26]. mNGS is performed for unbiased sequencing and untargeted diagnostics of microorganisms in a sample (viruses, fungi, bacteria) to obtain the entire sequence of the microorganism. mNGS can quickly and accurately identify the species and source of pathogenic bacteria in brain abscess[27], which guide the clinical use of antibiotics more targeted. In this situation, mNGS avoid the abuse of antibiotics, and reduce the cost of antibiotics. It is an effective method to detect the pathogenic bacteria of brain abscess. The patient's CSF smear, as well as culture, were negative; mNGS detected *Tannerella forsythensis* and *Campylobacter rectus* and postoperative pus culture-confirmed bacterial infections, both of which are oral resident bacteria, especially in the mouth of patients with periodontal disease, but not necessarily with acute periodontal infections. Both bacteria are opportunistic pathogens and parthenogenic anaerobes, which are more difficult to detect and culture clinically. Brain abscesses caused by odontogenic pathogenic bacteria are mostly reported as case reports and are mostly mixed bacterial infections[28].

The cure rate for patients with bacterial brain abscesses treated with a combination of surgical approaches and antimicrobial drugs exceeds 90%. The success of bacterial brain abscess treatment depends on the identification of the pathogen and the targeting of the treatment. Broad-spectrum antibiotics are used preferentially in initial therapy until the results of pathogenic microbial testing are available[29]. Once the pathogen is clearly diagnosed, the antimicrobial agents can be modified to achieve the most effective treatment. In addition, these drugs should have the ability to cross the blood-brain barrier. Drug therapy is preferred for deep infections, small abscesses, or multiple abscesses. When the abscess is larger than 2.5 cm in diameter, surgical excisional treatment can be used to completely remove the purulent material to shorten the hospital stay and the need for reoperation[30]. The patient was treated with anti-infection therapy in the early stage, the symptoms were mild and severe, there was no obvious acute severe inflammatory process clinically, and pathologically, there was also both acute inflammatory reaction and chronic granuloma formation, which was related to the type, virulence, site, and organism immunity of the pathogen. After admission to our hospital, the disease progressed faster, the envelope formed quickly, and the edema increased. Finally, good results were achieved through timely surgical treatment. However, we did not perform mNGS on the surgically removed abscesses.

Hence, we need to consider the possibility of odontogenic infection in common brain abscesses when the patient has poor oral hygiene. Then, the aerobic and anaerobic nature of the potentially pathogenic bacteria must be taken into account when sending samples for laboratory tests. mNGS performed as soon as possible in brain abscesses has a certain value for the determination of clinical medicines. Finally, appropriate surgical treatment can improve the prognosis of patients.

CONCLUSION

Brain abscesses are mixed infections, and there is difficulty in detecting all pathogens on routine bacterial cultures. mNGS may be used for the rapid diagnosis of pathogenic microorganisms and may play an important role in precision medicine.

FOOTNOTES

Co-first authors: Xue-Min Zhu and Chun-Xia Dong.

Author contributions: Zhu XM and Dong CX analyzed and interpreted patient data and wrote the manuscript; Xie L and Liu HX interpreted the data and reread the manuscript to ensure it was intellectually sound; Hu HQ revised the manuscript for content, including content writing; Zhu XM and Dong CX contributed equally to this work as co-first authors; All authors have read and approve the final manuscript.

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