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Case report

An immunocompetent patient with culture-negative multiple brain abscesses caused by *Fusobacterium nucleatum*

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ABSTRACT

The diagnosis and treatment of brain abscesses have advanced due to the utilization of modern microbiological and neurosurgical methods. Here we present a 49-year-old female patient presented with headache and neurological symptoms. Initial evaluation revealed multiple ring-enhanced brain lesions and a lung cavitary lesion initially suspected to represent a malignant process. Stereotactic aspiration provided the diagnosis of brain abscesses but yielded negative cultures. 16S ribosomal RNA analysis enabled the identification of *Fusobacterium nucleatum*. For ten weeks, the patient was treated with ceftriaxone and metronidazole. A marked clinical and radiological improvement was noted. Brain abscess is a severe intracranial infectious process with significant morbidity and mortality. Microbiological analysis is challenging due to the location of the infection, the broad spectrum of causative agents, and the low yield of cultures. *Fusobacterium nucleatum* is an anaerobic bacteria with a tendency to abscess formation and is isolated from 2% of brain abscesses. The utilization of 16S RNA analysis improves microbiological identification rates in brain abscesses, as in other infectious entities, enabling better pathogen characterization and more suitable treatment.

1. Introduction

Modern imaging-driven stereotactic aspiration methods and molecular pathogen detection revolutionized the diagnosis and treatment of patients with brain abscesses. Here we present a case of an immunocompetent patient who presented with multiple brain abscesses, causing severe neurologic symptoms. Despite negative bacterial cultures and serology, 16S sequencing has enabled the diagnosis of *Fusobacterium nucleatum (F. nucleatum)*, an important anaerobic pathogen with a propensity for abscess formation, as the causative agent.

2. Case presentation

A 49-year-old female patient has presented to our emergency department with progressing weakness of her left upper limb in the preceding week, accompanied by a speech disturbance starting two days before admission and a dull, diffuse headache. She denied fever, photophobia, nausea, vomiting, respiratory or gastrointestinal symptoms, as well as head or face trauma or any recent dental procedure or infection. Medical history was remarkable for heavy smoking (60 pack-years), hyperlipidemia, and fatty liver.

Upon arrival, the patient was alert, with normal vital signs. Neurologic examination was remarkable for dysarthria, right-sided central facial palsy, severe weakness of the left upper limb (strength scoring 2/5), and mild weakness of the left lower limb. Laboratory evaluation upon arrival, including complete blood count, renal function tests, electrolytes, liver function tests, and C-reactive protein, were unremarkable. Due to suspected cerebrovascular accident, a computer tomography (CT) scan with IV contrast was

Abbreviations: CT, computer tomography; PCR, polymerase chain reaction.

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performed. The scan revealed three ring-enhancing lesions measuring 18–19mm in her right parietal lobe, lateral to left ventricle body, and in the left thalamus (Fig. 1A). Edema was noted around the lesions. A whole-body CT scan was performed, showing a left upper lobe lung cavitary lesion with spiculate borders, measuring 3.5cm in the axial plane (Fig. 1B). The patient was hospitalized in the internal medicine ward for further evaluation with suspected brain metastasis from a possible primary lung lesion. Due to brain edema, treatment with dexamethasone was initiated.

On day two of hospitalization, the patient deteriorated, presenting new paresis of the right upper limb. A magnetic resonance imaging was performed, showing the lesions mentioned above with thin nodular rim-enhancement and a hypointense flair signal, representing fluid restriction (Fig. 1A). These findings raised the possibility of multiple brain abscesses. After collecting blood cultures and samples for serology, empiric treatment with vancomycin (1.5g IV bid), ceftriaxone (2g IV bid), and metronidazole (500mg IV tid) was initiated. Blood cultures were sterile, and serologic evaluation for human immunodeficiency virus, *Aspergillus* spp. galactomannan and *Cryptococcal* antigen were negative; however, *Toxoplasma gondii* IgG was positive. An attempt for a CT-guided biopsy of the cavitary lung lesion was canceled after a second chest CT scan showed a significant decrease in lesion size following therapy. The patient underwent stereotactic aspiration of the lesion in the right parietal lobe, which obtained cloudy, pus-like materiel. Samples were sent to pathological evaluation, demonstrating fibrinopurulent exudate with acute inflammatory infiltrates, microgliosis, and partial necrosis, suggestive of cerebritis with abscess formation.

The biopsy specimen was placed in a sterile tube with a large air volume and was transported to the laboratory. An anaerobic transport system was not available in our institute. Basic microbiology workup, including Gram stain, acid-fast and modified acid-fast stains, and calcofluor white stain, were negative for bacteria (including *Mycobacteria* spp. and *Nocardia* spp.) and fungi. Anaerobic cultures were performed using blood agar media in an anaerobic jar with GasPaK system for five days, and thioglycolate broth for 14 days. Aerobic and anaerobic cultures were sterile, presumably due to the prior antimicrobial treatment and the lack of appropriate anaerobic environment during the transport and primary processing of the specimen. Thus, a molecular assay for the presence of bacteria was advised. For 16S Ribosomal RNA analysis, nucleic acids were extracted from the pus sample using the QIAamp DNA Mini Kit (QIAGEN). The sample was tested for 16S rRNA using Kapa SYBR® FAST qPCR Kit (Sigma Aldrich) and V3F(5′-CCAGACTCCTACGGGAGGCAG-3′) and V6R(5′-ACATTTCACAACACGAGCTGACGA-3′) primers mix. Amplification was performed on Rotor-Gene Q (QIAGEN). Sequencing results were analyzed with Geneious bioinformatics software and compared to the National Center for Biotechnology Information world database for bacterial species (International Nucleotide Sequence Database Collaboration). The sequenced fragment yielded full identity to *F. nucleatum*. Vancomycin was discontinued, and the patient remained on IV ceftriaxone and metronidazole. Cervical CT did not show evidence of thrombophlebitis, and an oral examination, including dental radiography, revealed no periodontal source of infection. Gradually, physical strength and dysarthria improved, more markedly on the left upper limb and legs, with the right hand remaining paralyzed until the date of discharge. The patient was discharged home with a peripherally inserted central catheter line for outpatient antibiotic therapy. Ten weeks of antibiotic treatment with IV ceftriaxone and PO metronidazole were completed with significant improvement in the imaging findings (Fig. 1C). Neurologically, the patient improved with the recovery of motor deficits. She continued to suffer from neuropathic pain, which was considered to be focal sensory epileptic seizures and, therefore, was treated with Lamotrigine with improvement.

3. Discussion

Brain abscesses carry significant risk for mortality and neurological sequela. Therefore, a prompt evaluation and treatment process, combining microbiological and neurosurgical techniques, is required. The current implementation of advanced brain imaging, minimally invasive neurosurgery, and microbiological assessment lead to >90% cure rates [1]. Although brain abscesses are an infectious process, the clinical picture is usually dominated by the intracranial mass effect, resulting in headache and neurological symptoms. Fever is frequently absent, and the complete triad of fever, headache, and neurological deficit is found only in 20% of patients [1,2].

Microbiological evaluation of brain abscesses is challenging for several reasons. First, access to the infectious site is challenging and confers potential risks. Second, blood cultures only detect the

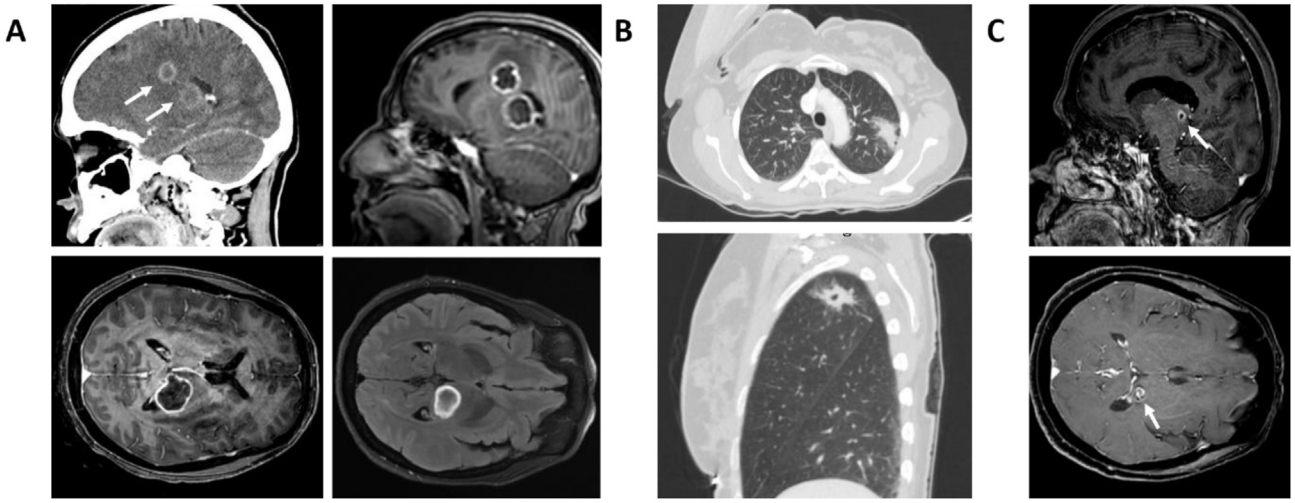

Fig. 1. Imaging findings. (A) Head CT (left upper image) and MRI images obtained during the patient's first hospitalization showing two out of three brain abscesses (located in the left thalamus and left ventricle border). (B) Chest CT scan presenting a cavitary lesion with speculated borders in the left upper lobe. (C) MRI images obtained after ten weeks of antibiotic treatment, revealing a marked improvement in abscesses size. **Abbreviations:** CT, computer tomography; MRI, magnetic resonance imaging.

causative organism in 28% of cases [3]. Third, the scope of possible causative agents is broad and depends on the clinical scenario, geographical distribution, and the immune state of the patient [2,3]. In immunocompetent patients, the pathogenesis is either a direct spread from an adjacent contiguous site or a hematogenic seeding. Consequently, the pathogens involved differ depending upon the location of primary infection. Immunocompromised patients, on the other hand, are prone to brain abscess from various pathogens such as *Toxoplasma gondii*, Mycobacterium spp., *Nocardia* spp., *Aspergillus,* and *Candida* spp. etc [2]. *F. nucleatum* is an uncommon pathogen in immunocompetent adults. Nevertheless, it has a propensity to abscess formation (including in the brain, liver, and gastrointestinal tract) and may be involved in polymicrobial infections [4]. *Fusobacteria* spp. is isolated from 2% of brain abscesses [3]. In a case series of five fusobacterial brain abscesses, *F. nucleatum* was involved in four cases as part of a polymicrobial infection, while *Fusobacterium nacroforum* was the causative agent of one monomicrobial abscess. The authors suggested that the less virulent *F. nucleatum* requires synergy from other organisms [5]. However, our and other reports present cases in which *F. nucleatum* was the only pathogen isolated [6].

The presence of multiple lesions in our case point to a hematogenic source of infection. However, a thorough evaluation including dental examination, a CT scan of the neck soft tissues, transthoracic echocardiography, and a whole-body CT scan did not reveal a common source for both the lung and brain abscesses. Chakvetadze et al. reported a similar case of multiple abscesses due to *F. nucleatum* involving the brain, liver, and pleura in which the diagnosis was obtained by molecular techniques. The exact origin of infection was not identified [6]. The difficulty of identifying the source of the *Fusobacterium* infection is not unusual, amounting to 42% of cases in one study [4]. Potential sources of *F. nucleatum* include malignancies of the oral cavity and the colon. The quantity of *F. nucleatum* is significantly elevated in colorectal tumors compared to that in adjacent healthy tissue, possibly contributing to the neoplastic processes [7]. Also, chronic oral cavity infection with *F. nucleatum* is considered to promote oral mucosa dysplasia [8]. There was no evidence of these malignancies in the oral cavity examination and abdominal CT scan, although colonoscopy was not performed.

PCR-amplified 16S ribosomal gene sequencing plays a vital role in circumventing the limitations of culture-based bacteria detection in brain abscess specimens and therefore has a significant impact on patient management. It is particularly useful when samples are collected after the initiation of effective antibiotic treatment or for identifying fastidious or non-cultivable organisms. Proper transportation and processing of the sample are critical in the evaluation of obligate anaerobes related infections, and insufficient anaerobic environment may affect culture results. In one study, in 6 out of 17 proven bacterial intracranial or spinal collection specimens, the etiological agent was detected only by PCR [9].

In this report, we presented a case of brain abscesses encompassing some of the diagnostic and management challenges of this important, though rare, infectious entity. The possibility of infection should be suspected in any patient presenting with neurological symptoms, let alone when a ring enhanced lesion is apparent on imaging. In our case, initial working diagnosis favored a malignant process due to the smoking history, lung lesion, and family history of our patient. However, the implementation of novel imaging, neurosurgery, and microbiological methods, enabled the diagnosis of an infectious process, though failed to elucidate its source. This case emphasizes the importance of molecular microbiological methods in identifying non-cultivable pathogens or partially treated patients with a clinically suspected brain infection.

Disclosure

The authors declare that they have no conflict of interests to declare.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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