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Short Communication

Case of *Rickettsia typhi*-induced Brain Abscess Mimicking Brain Tumor

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ABSTRACT

Murine typhus is one of the most prevalent rickettsial infections in the world, caused by the bacterial genus *Rickettsia*. Though the disease manifests a relatively benign clinical course with fever, rash, and headache being the 3 classic symptoms, neurological complications may arise in patients that could become permanent. In this case study, a patient with a brain abscess caused by *R typhi* infection is described. Based upon the recent reemergence of arthropod-borne disease, the findings in this case are significant; *R typhi* can cause a brain abscess that mimics a brain tumor, which delays the diagnosis and appropriate management of the disease. Murine typhus should always be considered when performing the differential diagnosis of brain abscesses in South Korea.

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Introduction

Murine typhus is one of the most prevalent rickettsial infections in the world, caused by *Rickettsia* bacteria [1] and transmitted by the rat flea, *Xenopsylla cheopis*, and causes problems for travelers who visit rural infected areas [2-4]. Though the disease manifests a relatively benign clinical course with the classic triad of fever, rash, and headache, the infection may lead to neurological complications in patients could be permanent [5].

Compared to other rickettsial infections, *R typhi* invasion of the central nervous system is rare, but may result in a wide spectrum of severity, ranging from a mild headache to a life-altering coma [5, 6]. To date, all cases of infection with *R typhi* have been reported as meningitis and/or encephalitis associated with a severe systemic infection [5-7]. In this report, we describe a patient with *R typhi* infection that resulted in a brain abscess.

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Case Report

A 52 year old man was referred to the clinic with an intractable, ongoing (5 months), moderate headache in the vertex area. He was previously a fit and healthy individual who was working as a cook in a local restaurant in Seoul. After a vacation in August where he visited Gangwon-do (rural province of South Korea), he presented with a skin rash that covered his whole body. The rash lasted for 1 month and disappeared spontaneously without any treatment. He did not remember being bitten by an insect during the holidays, and as a precaution, he was denied contact with domestic or wild animals.

In October, stabbing headaches recurred twice a day, accompanied by patient experiencing cold sensations and myalgia. There were no definite upper respiratory tract symptoms or gastrointestinal symptoms during the headache episodes.

Although the patient had received supportive management for 2 months in a local clinic, the headaches persisted so he was referred to the Seoul National University Hospital, the following March.

A physical examination did not reveal any abnormalities; his body temperature was 37.5°C, there was no skin rash, hepatomegaly, splenomegaly, or lymphadenopathy.

The neurological examination was also normal, and laboratory findings were within the normal range showing white blood cell count of 9.93 x 10^3/μL and a C-reactive protein level of 0.32 mg/dL. The chest X-ray was normal. However, magnetic resonance imaging (MRI) of the brain disclosed a 2 cm mass near the right periventricular area (Figure 1 A). With T1-weighted, gadolinium-enhanced imaging, the mass was observed along with the central cystic component. A cerebrospinal fluid (CSF) sample revealed a white cell count of 440/mL; 45% other cells, 42% lymphocytes, 13% polymorphonuclear cells, elevated proteins (107 mg/dL), and normal glucose (65 mg/dL, blood serum 121 mg/dL). In the serum and CSF, all cultures, viral polymerase chain reactions, and serological tests, including herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus, Epstein-Barr virus, cytomegalovirus, influenza, adenovirus, enterovirus, JC virus, measles, human immunodeficiency virus, human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8), *syphilis*, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Chlamydia*, *Borrelia*, *Cryptococcus*, *Aspergillus*, and *Pneumocystis* were all negative. Chest/abdominal computational tomography and echocardiography were also normal, disclosing no systemic infection source.

The MRI scan and CSF sample did not indicate an infectious abscess but, to rule out a brain tumor, a stereotactic biopsy was performed. Aspiration of the lesion revealed a yellow fluid without foul odor that was negative for bacteria

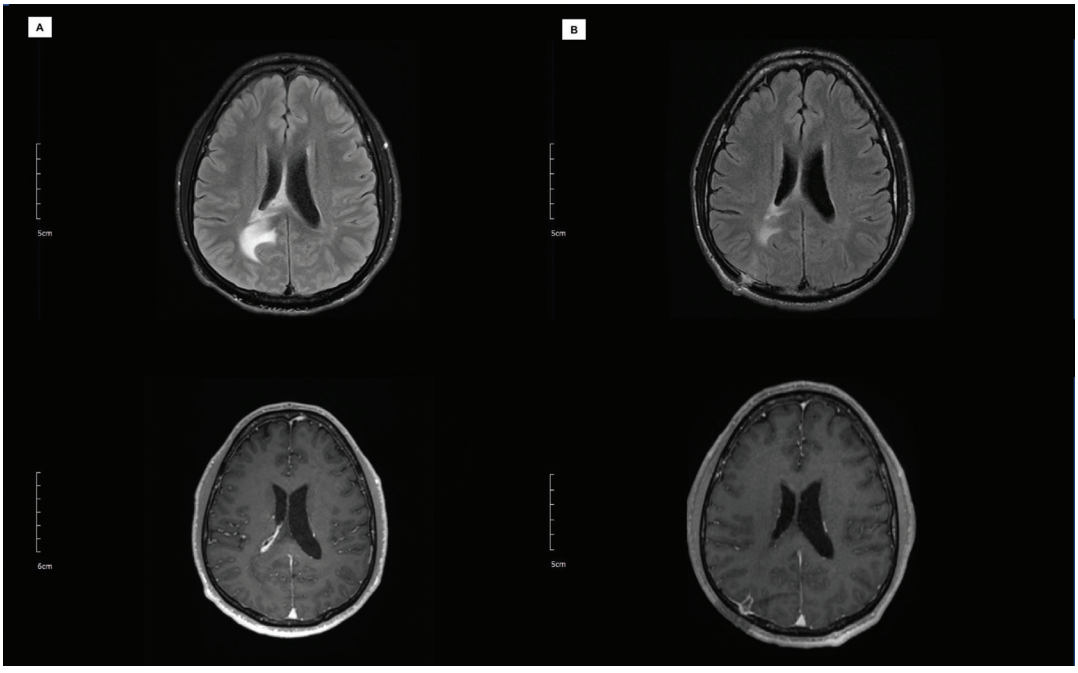

Figure 1. T2-weighted FLAIR and Gadolinium-enhanced T1-weighted axial views.

(A) Periventricular edema along corpus splenium and right lateral ventricle. A 2 cm cystic lesion was prominent near the posterior horn of the right lateral ventricle. (B) After aspirational biopsy and 3 weeks of antibiotics, periventricular edema showed partial decrease.

following culture. Whilst waiting for the pathology results, the patient received antibiotics according to a bacterial infection (ceftazidime 2g (3 times per day) + vancomycin 1g (2 times per day) + ampicillin/sulbactam 750mg (three times per day). After 5 days, pathology revealed a chronic, active inflammation with perivascular lymphoplasma cells and neutrophilic infiltration, without malignancy. Two more weeks of the empirical antibiotics were maintained. The patient's headaches did not subside and a follow-up MRI did not show a full response (Figure 1 B) to antibiotic treatment. Thus, additional serum tests were requested from the Korea Centers for Disease Control and Prevention (KCDC; Cheongju-si, South Korea) to test for atypical bacteria: *Rickettsia spp., Leptospira spp.*, and *Brucella*. Ceftazidime and ampicillin/sulbactam were administered for an additional 2 weeks until the result of a serum immunofluorescence assay was received. Antibodies against *R typhi* to a titer of IgM 1:32 and IgG 1:64 were detected. According to the diagnostic criteria of murine typhus, 1 of the following is required: 1) an IgM titer of ≥ 1:32, 2) a single IgG antibody titer of ≥ 1:128, or 3) a 4-fold increase in sera antibody titers between the acute phase and the convalescent phase [8].

Therefore, the patient's lesion was diagnosed as a brain abscess caused by *R typhi* Ceftazidime and ampicillin/sulbactam were maintained for an additional 2 weeks without changing to doxycycline dosing, because the patient responded to the combination during the 4th week of treatment. His headaches disappeared completely after a total of 6 weeks of antibiotic treatment.

Discussion

Rickettsial infection evokes a pathogenic process of endothelial cell invasion with destruction of integrity and increased permeability of the endothelium, leading to the term 'Rickettsial vasculitis' [9]. Rickettsial vasculitis of the vascular endothelium can lead to various clinical symptoms: maculopapular rash, interstitial pneumonia, acute renal failure, and meningoencephalitis [5, 10, 11].

Theoretically, the choroid plexus can be a target of rickettsial vasculitis because it consists of a network of capillary endothelial cells. However, the abscess formation via the choroid plexus caused by *Rickettsia spp*. is extremely rare, and this report is thought to be the first to describe an *R typhi* infection that caused a brain abscess in a human patient. The MRI revealed the T1-enhanced mass along the right lateral ventricle, confirmed as a pyogenic abscess by aspirational biopsy. The lesion was potentially the origin of the patient's mild, recurrent headache that was accompanied by a sensation of cold and myalgia . This finding is supported by the result of the immunofluorescence assay, which showed a high IgM titer, even though the test was performed 5 months after the onset of symptoms.

Rickettsial infection was not suspected initially, not only due to its rarity but also because the patient showed a relatively mild, chronic course of clinical manifestations. Unlike a typical bacterial infection of the central nervous system, the lesion did not induce a high fever or altered mental state. Thorough work-up with laboratory tests, whole-body computational tomography, and echocardiography confirmed that there was no other systemic involvement. Moreover, the bacterial culture studies were all negative. Therefore, a brain tumor was considered a more likely diagnosis than a brain abscess.

The current study has limitations; the diagnostic criteria for antibody titers were incomplete because 2 consecutive samples were not tested so even if the IgM antibody titer of the patient's serum was greater than 1:32 and the IgG antibody titer was as low as 1:64 this result was not validated with a comparative results from additional samples. However, the low IgG antibody titer could be confirmed because 3 weeks earlier empirical antibiotics were administered for cryptogenic brain abscess. Another consideration is that the immunofluorescence assay uses an indirect method of detecting host responses, so despite this method being the gold standard of murine typhus diagnosis (sensitivity 53-85%, specificity 99%) this introduces a limitation to the study [12]. Therefore, the fact that diagnosis of *R typhi* was supported by the other comprehensive tests rules out other etiologies, and the clinical course of the patient showed the classic triad of murine typhus. Doxycyclin, which is the treatment of choice for *Rickettsia* infection [4], may have alleviated the patient's symptoms more quickly had the diagnosis not been delayed. However, it is meaningful that the combination of ceftazidime and ampicillin/sulbactam, which is the alternative treatment for cryptogenic brain abscess [13], resolved the patient's symptoms.

Since the first report of a patient with murine typhus in 1959 in South Korea, the annual number of patients with murine typhus increased to 87 in 2008. The incidence of the disease seemed to be on the decline, but in 2014, 20 cases were reported and an increased trend has been reported by KCDC [14]. Based upon the recent reemergence of arthropod-borne disease, this case is remarkable; *R typhi* can cause a brain abscess to mimic a brain tumor. This delays the diagnosis and appropriate management of the disease. It is difficult to differentiate between a brain abscess and a brain tumor because both appear similarly on an MRI and both commonly cause seizures in the patient. Thus, murine typhus should always be considered in the diagnosis of brain abscess in South Korea.

Conflicts of Interest

The authors declare no competing financial interests.

Ethical Publication Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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