Case Report

Intracranial aspergillus fumigatus infection complicated with cavernous hemangioma: case report and literature review

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Abstract: The aim of this study was to report a rare case of Aspergillus fumigatus infection complicated with cavernous hemangioma in the central nervous system of a patient with normal immune function and to investigate its causes. A 60-year-old male patient was admitted three years ago due to meningioma-induced convulsions. In addition to meningioma, magnetic resonance imaging (MRI) results also suggested the presence of cystic and solid lesions in the left temporal lobe, which was considered to be a brain abscess due to the infection. After antibiotic treatment, the patient underwent meningioma resection, after which no more convulsions occurred. It was recommended that the patient receive treatment on the abscess in the left temporal lobe, but the patient did not consent. He was discharged with follow-up. Recently, the patient returned for treatment due to intermittent headaches with weakness in the right lower extremity for 10 days. MRI results revealed that the lesion in the left temporal lobe had expanded and was associated with abnormality in the midline. Surgical lumpectomy was performed, and the postoperative pathological examination confirmed the brain abscess to be an Aspergillus fumigatus infection complicated with cavernous hemangioma, which indirectly confirmed that the lesion in the temporal lobe three years ago was from the Aspergillus fumigatus infection. On the 7th postoperative day, the patient died due to severe pneumonia. Because the intracranial Aspergillus fumigatus infection in the patient had lasted for three years, with no cavernous hemangioma present at the first assessment but with a lesion evident three years later, the hemangioma is considered to be related to the Aspergillus fumigatus infection.

Keywords: Aspergillus fumigatus, infection, cavernous hemangioma

Introduction

Aspergillus fumigatus exists in soil, plants and corrupted materials and mainly infects people with immune dysfunction, particularly organ transplant recipients and patients who have been receiving immunosuppressive agents for long periods of time and those with hematological malignancies and human immunodeficiency virus (HIV) [1]. In immunocompetent patients, Aspergillus fumigatus infection in the central nervous system is uncommon, and the reported cases are all isolated [2-5]. The mortality of Aspergillus fumigatus infection is extremely high [1, 6]. The infections in the central nervous system are mostly acute, and focal chronic growth in the brain is unusual, while no induced cavernous hemangioma has been reported. This paper reported a case of cavernous hemangioma that occurred in the foci of an immunocompetent patient after Aspergillus fumigatus infection in the left temporal lobe three years prior.

Case report

A 60-year-old male patient was admitted in our hospital due to “intermittent headache with weakness in the right lower limb”. Physical examination: muscle strength was level IV in the right lower limb, without pathological reflection. And no abnormalities were seen in the rest of the nervous system. The patient had no history of rheumatism connective tissue disease, or the application history of glucocorticoids. The patient had a history of tuberculosis which had been cured 10 years ago. But 3 years ago, he appeared apathetic emotion, sudden loss of consciousness and convulsion of the limbs, and went to see a doctor. Head MRI showed that:
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Left temporal lobe showed irregular long T1 and long T2 signal, while fat-suppression and water-suppression phases of low signal. It is about 4.0 cm×4.0 cm. The septum was seen inside. Patchy long T1 and long T2 signals were seen around, with mass reinforcement lesion inside (Figure 1A-D). Abnormal signals of oval equal T1 and equal T2 were seen in longitudinal division next to frontal cerebral falx. It was about 2.8 cm×2.8 cm. The reinforcement was uniformed (Figure 1A and 1D). There were no abnormal signals in nose sinus (Figure 1E).

Chest anteroposterior X film: No irregular funiculuar and calcification density was seen in upper lobe of double lungs, and the diagnosis was obsolete pulmonary tuberculosis (Figure 1F).

Laboratory examination: routine blood: the white blood cells for 6.96×10^9/L (normal: 4-10×10^9/L), neutrophil percentage for 0.59 (normal: 0.4-0.6), lymphocyte percentage for 0.3 (normal: 0.2-0.4), monocyte percentage for 0.05 (normal: 0.03-0.08×10^9/L), eosinophil percentage for 0.06 (normal: 0.005-0.05), basophil percentage for 0.00 (normal: 0.00-0.01), neutrophils for 4.08×10^9/L (2-7×10^9/L), lymphocyte for 2.1×10^9/L (0.8-4.0×10^9/L), monocytes for 0.34×10^9/L (0.12-0.8×10^9/L), eosinophils for 0.42×10^9/L (0.02-0.50×10^9/L), basophils for 0.02×10^9/L (0.00-0.10×10^9/L), HIV (-) and HBSag (-). The admission diagnosis was frontal meningioma and left temporal brain abscesses. EEG was used for epilepsy positioning: displaying the epilepsy lesion was located in the forehead. The patient was given antibiotics treatment, and then given resection of meningioma. No seizure was seen in postoperative period. MRI was reviewed. The lesion did not disappear in left temporal lobe. Selective surgical treatment was informed to the patient. But the patient was not agreed; he was discharged from the hospital and followed up.

Ten days before admission, the patient experienced intermittent headaches and right leg
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Weakness. A magnetic resonance imaging (MRI) study of the head showed that the abscess in the left temporal lobe had expanded and that the left ventricle was compressed and narrowed, with the midline slightly shifted to the right. The lesion consisted of both front and rear portions. The size of the front lesion was approximately 3.5 cm×2.5 cm×4.0 cm, and the size of the rear lesion was approximately 1.7 cm×1.5 cm×0.8 cm. An enhanced scan showed heterogeneous enhancement in the front lesion (Figure 2A) and peripheral enhancement in the rear lesion (Figure 2B). A brain abscess of the left temporal lobe was diagnosed, and surgical treatment was provided.

The surgery was conducted using a left temporal approach. The front lesion was observed at approximately 3 cm subcortical and was reddish-brown, with a slightly soft texture and a rich blood supply. The lesion was partially adhered to the brain tissue. The lesion was completely removed, the rear lesion was soft and did not have a rich blood supply. Postoperative

![Figure 3. Pathology of the cavernous hemangioma and Aspergillus fumigatus infection. A. The cavernous hemangioma by hematoxylin and eosin (HE) staining, ×200: cavernous sinuses of different sizes were present, and the structure lacked the muscular layer and elastic fibers (white arrows), with a little connective tissue between the vessels. B. The Aspergillus fumigatus infection by CD34 staining, ×400, and C. The Aspergillus fumigatus infection by HE staining ×200: fungal spores were observed, with the hyphal heads of Aspergillus fumigatus bifurcated at acute angles (black arrow). D. PAS staining (+), ×200, of the hyphal heads of Aspergillus fumigatus (black arrows); E. VEGF staining (-), ×400, of the Aspergillus fumigatus and the surrounding brain tissue.](image-url)
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computed tomography (CT) showed mixed signals with high density in the surgical area, which was considered to be hemorrhage. Not much evidence of hemorrhage was found in the surgical area, and conservative treatment was provided. The pathological diagnosis was as follows: the front lesion was a cavernous hemangioma with hemorrhage, infarction and organization, while the dissection surface was mostly red-brown, solid and soft, reminiscent of blood clotting. The rear lesion was an abscess of an Aspergillus fumigatus infection; the dissection surface was light brown, solid and soft. The cavernous hemangioma consisted of different sizes of cavernous sinus and lacked the muscular layer and elastic fibers, with a little connective tissue between the vessels (Figure 3A) and the focal hematoma; fungal spores were observed in the abscess of Aspergillus fumigatus infection, with the hyphal heads bifurcated at acute angles (Figure 3B, 3C). Periodic acid-Schiff staining (PAS) for the indicative hyphae of Aspergillus fumigatus infection was positive (Figure 3D). The postoperative situation of the patient was poor, and treatment consisting of voriconazole 200 mg, twice a day, was provided to the patient. Additionally, broad-spectrum antibiotics with Ceftezole Sodium was administered to the patient as a symptomatic and supportive treatment to prevent infection, but the patient died due to severe pneumonia on the 7th day after surgery.

Discussion

Aspergillus fumigatus is widely present in air, soil and organic matter [7]. Many spores might be inhaled into our lungs every day, but these spores will be cleared by the immune system [8]. Aspergillus fumigatus infection is rare in the immunocompetent population [4, 9-14]. The literature has reported three cases of infection that have occurred in patients with pulmonary tuberculosis [9-11] and one case of ulcerated lesions in the gastric wall [12]. Cases occurring in the nervous system are uncommon, with one reported case of hematogenous infection from the lung to the brain [15]. Other cases of central nervous system infections were mostly caused by the direct invasion of iatrogenic infections and adjacent infected tissue. The infections of Aspergillus fumigatus are usually asymptomatic and can be hidden in the lungs [6, 16]. The intracranial lesion of Aspergillus fumigatus infection present in the patient in this study had been identified by MRI in the surgery performed three years ago, and the patient had a history of pulmonary tuberculosis. These findings suggested that the tuberculosis caused damage to the lung defensive barrier; thus, Aspergillus fumigatus had a high chance to cause a pulmonary hematogenous infection in the central nervous system.

The early manifestation of disease after Aspergillus fumigatus infection is inflammatory changes in the brain. An edema with ill-defined boundaries is generated in the brain tissue. Whether this edema is converted to a brain abscess depends on the immune status of the host [17]. For people with normal immune functions, a small amount of Aspergillus fumigatus can be killed in the brain. If the afflicted individual’s immune system functions poorly, the central nervous system can be infected with an acute onset infection. While growth in the brain for three years is rare, the findings of this study suggest that the body’s immunity and the Aspergillus fumigatus infection reached a state of equilibrium. Aspergillus fumigatus can release substances that are highly toxic to astrocytes, microglia and neurons that can cause irreversible damage to these cell types at low concentrations and over a short period of time, thereby reducing the killing and defense effects of the brain tissue against Aspergillus fumigatus [18]. Aspergillus fumigatus has exhibited an obvious tendency to invade the arteries and veins, causing necrotizing vasculitis, secondary thrombosis and hemorrhage [2]. Masses of Aspergillus fumigatus are surrounded by many blood vessels, and the resulting erosion of the blood vessels might cause injury to the peripheral brain tissue and thus reduce its killing effect on Aspergillus fumigatus. Therefore, the long-term survival of Aspergillus fumigatus in the brain of the patient of this study was the co-result of the weakened killing effect of the damaged brain tissue and the toxicity of Aspergillus fumigatus. However, with the growth of the fungus, its toxic secretions increased, causing huge amounts of damage in the surrounding astrocytes in the brain. Ultimately, the patient’s immune system could not contain the Aspergillus fumigatus, leading to the significant symptoms and disease indicative of brain damage.

The patient in this report was not only infected with Aspergillus fumigatus but also had a com-
Complicated cavernous hemangioma in the infection region whose causes are unknown and that not been previously reported. Cavernous hemangiomas are divided into two categories: familial and sporadic. The familial hemangiomas follow the rules of autosomal dominant inheritance and exhibit the common mutations CCM1, CCM2, and CCM3; however, sporadic hemangiomas do not possess these mutations [19]. Thus, the occurrence of a cavernous hemangioma might be related to the undetected mutations or might be caused by external factors that are not yet well understood. Recent studies have found that radiotherapy can cause the occurrence of cavernous hemangiomas [20-24]. Radiotherapy can up-regulate vascular endothelial growth factor (VEGF) expression in astrocytes [25], and increased VEGF expression can cause endothelial cell proliferation, which results in the formation of the lumen of a cavernous hemangioma [21, 26]. The patient described in this report presented with intracranial Aspergillus fumigatus infection. Aspergillus fumigatus hyphae and culture medium extract have significant serine protease activity [27]. Serine proteases can release a variety of growth factors and can increase the expression of adhesion molecules; thus, these proteases can play a significant role in angiogenesis [28]. The MRI of the patient three years ago revealed that the masses of Aspergillus fumigatus were surrounded by many blood vessels. Aspergillus fumigatus shows an obvious tendency to invade the arteries and veins, causing necrotizing vasculitis, secondary thrombosis and hemorrhage [2] and providing the conditions for Aspergillus fumigatus-mediated vascular invasion and damaged vascular proliferation. Studies have also shown that VEGF expression in cavernous hemangiomas is significantly increased [26, 29]. The VEGF staining for Aspergillus fumigatus and its surrounding brain tissue showed no VEGF expression, indicating the death of a large number of glial cells (Figure 3E). These findings might be related to the toxic effects of Aspergillus fumigatus causing the destruction of the surrounding tissue: necrotic brain tissue surrounding the lesion might be the reason for the failure to detect VEGF expression in this case. However, we still could not rule out the possibility that the occurrence of Aspergillus fumigatus infection complicated with cavernous hemangioma in this patient was due to the release of substances with serine protease activity by Aspergillus fumigatus, which would result in increased VEGF expression and endothelial cell proliferation. The long presence and repeated stimulation of Aspergillus fumigatus led to the formation of a cavernous hemangioma.

The MRI findings of the cavernous hemangioma in this patient were not typical, with rich blood vessels and MRI contrast enhancement, which were different from the signs of a common cavernous hemangioma. Common intracranial cavernous hemangiomas are usually not enhanced, instead possessing a typical peripheral hemosiderin belt. The atypical findings of the cavernous hemangioma in this case might be related to its accompanying hemorrhage, infarction and organization. It has been reported that the MRI findings of a cavernous hemangioma outside of the brain can be enhanced [30, 31], though cavernous hemangiomas in the central nervous system after radiotherapy have exhibited different manifestations. MRI enhancement can appear, and both uneven enhancement and no enhancement have been observed [20, 21, 32]. Considering the possible atypical MRI manifestations of a cavernous hemangioma, the result of enhancement could be related to the completeness of the blood-brain barrier. The patient in this report was associated with Aspergillus fumigatus infection, and increased VEGF expression could stimulate angiogenesis, leading to a rich blood supply for the cavernous hemangioma. At the same time, the Aspergillus fumigatus was vascular invasive, causing damage to the blood-brain barrier and resulting in atypical manifestations of cavernous hemangioma with contrast enhancement. For the treatment of Aspergillus fumigatus, voriconazole is effective in treating aspergillosis, and its efficacy is superior to that of amphotericin [33]. For patients with severe immune dysfunction, voriconazole could improve the cure rate of Aspergillus fumigatus infections [34]. The mortality of intracranial Aspergillus infection undergoing surgical treatment is much lower than that of drug treatment only, confirming the important role of surgery in the treatment of Aspergillus fumigatus infection [1]. The patient in this report underwent surgery followed by voriconazole therapy and died on the seventh postoperative day due to severe pneumonia, which might be related to the impairment of the mechanical defensive barrier in the lung and surgical stress in the patient.
Conclusions

Aspergillus fumigatus is an opportunistic pathogen. The impairment of the mechanical defensive barrier could increase the chance of Aspergillus fumigatus infection. When an individual's immune function is depressed, Aspergillus fumigatus can spread to the central nervous system through the blood and grow. The long-term colonization of Aspergillus fumigatus in the brain can then stimulate angiogenesis to form a cavernous hemangioma. For immunocompetent patients with Aspergillus fumigatus infection in the central nervous system, surgery combined with drug therapy has good efficacy and should be provided at an early disease stage. Postoperative complications should be prevented for patients with impaired mechanical defense barriers.

Disclosure of conflict of interest

None.

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