Disseminated Multi-Organ Aspergillosis with Acute Cerebral Infarction in A Patient with Myelodysplastic Syndrome. A Case Report.

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Abstract

Background: *Central nervous system invasive aspergillosis (CNS-IA) is a relatively uncommon but frequently fatal infectious disease, especially in immunodeficiency patients. The clinical manifestations of CNS-IA are diverse; however, the cases with blindness and cerebrovascular events as the main clinical manifestations are extremely rare. We present, herein, the case of a patient with myelodysplastic syndrome, who was diagnosed with disseminated aspergillosis involving the CNS, lungs, and eyeballs, followed by a fatal basal ganglia infarction as the major cause of death. This report reveals the diversity of clinical manifestations in the patients with CNS-IA, and essence of a dreadful infectious disease.*

Case presentation: *A 48-year-old male patient with myelodysplastic syndrome was admitted to the hospital with progressive visual extinction in the left eye and recurrent fever. Imaging examination showed multiple intracranial and pulmonary lesions. The metagenomic next-generation sequencing (mNGS) test of the patient's peripheral blood and cerebrospinal fluid both positive for Aspergillus nidulans. Endophthalmitis was diagnosed based on the patient's clinical symptoms and mass-like echogenicity observed in the atrium on ophthalmologic ultrasound. Combined antifungal therapy (voriconazole + caspofungin) was provided to the patient, followed by significant symptom relief and imaging improvement at the time of one week post treatment. However, after the continued antifungal treatment for another four days, the patient suddenly suffered from new-onset acute infarcts in the left basal ganglia, and died five days later.*

Conclusions: *CNS-IA is an infectious disease with diverse clinical manifestations and high mortality. Due to the angioinvasive capacity of Aspergillus, multiple organ involvement, especially more severe cerebrovascular events may occur in patients with CNS-IA, which is worth clinicians to be alert to this complication.*

INTRODUCTION

Invasive aspergillosis (IA) is a rapidly progressing, frequently fatal disease, particularly affecting immunocompromised patients, including thosewith hematological malignancies. Central nervous system invasive aspergillosis (CNS-IA) is an infrequent form of IA, accounting for approximately 10% of cases.[1] The clinical manifestations of CNS-IA are generally nonspecific, and include meningitis, local abscesses, cerebrovascular events, and focal neurological deficits.[2] Although a direct invasion from adjacent infection sites is one possible route of transmission, CNS-IA is primarily caused by the hematogenous dissemination of spores from affected organs, the lungs in particular.[3] We present, herein, the case of a patient with myelodysplastic syndrome, who was diagnosed with disseminated aspergillosis involving the CNS, lungs, and eyeballs, followed by a fatal brainstem infarction with a causative organism of Aspergillus nidulans.

Case History/Examination

A 48-year-old male patient with a known 5-year history of myelodysplastic syndrome (MDS) was

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Financial Disclosures: This work was supported by grants from the General Project of the National Natural Science Foundation of China (81970180), the Science and Technology Project of Tianjin Municipal Health Committee (TJWJ2022QN030).
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admitted to the hospital due to recurrent fever, pain, and progressive visual extinction in the left eye for the past two months. After receiving an initial diagnosis of MDS, the patient has been consistently prescribed Cyclosporine A and Eltrombopag as the main forms of treatment on a daily basis. In the two months prior to admission, the patient had received outpatient treatment for fever and had been taking oral cephalosporin drugs. Upon admission, the physical examination revealed no significant impairments, except for cloudy vitreous in the eyes. The body temperature measured at 38.2℃, while the respiratory rate, heart rate, and pulse were within the normal range. The re-evaluation of patient's hematological disorder revealed a diagnosis of myelodysplastic syndrome with multilineage dysplasia. The karyotype analysis showed a chromosomal abnormality of 46, XY, +1, der(1:12)(q10:q10)[10]. No typical mutations associated with MDS, such as TET2, RUNX1, ASXL1, DNMT3A, and JAK2, were detected in the molecular analysis of the bone marrow. The white blood cell count in the patient's peripheral blood was 6.1 × 109/L (neutrophils = 5.9 × 109/L). The patient underwent antinuclear antibody (ANA) and Extractable Nuclear Antigen (ENA) examinations, both of which showed no abnormalities.

METHODS (Differential Diagnosis, Investigations and Treatment)

Upon admission, Magnetic resonance imaging (MRI) of the brain revealed abnormal infiltrates in the bilateral frontal and temporal lobes, lateral ventricles, corpus callosum, and choroid plexus, while computed tomography (CT) of the chest revealed patchy, high-density infiltrates in the upper and lower lobes of the left lung (Figure 1). Additionally, Aspergillus galactomannan antigen was also detected in the patient's peripheral blood at an elevated value of 9.3 pg/mL (normal value range: <0.5 pg/mL), although his β-(1-3)-D-glucan level was normal (59.2 pg/mL; normal value range: <70 pg/mL negative; 70-95 pg/mL: grey zone; >95 pg/mL: positvie). Both the interferon gamma release assay and procalcitonin yielded negative results. An evaluation of the patient's CSF revealed reduced glucose (1.8 mmol/L) and elevated protein (1,199.7 mg/L) levels, as well as on the elevated galactomannan antigen levels and pleocytosis (white blood cell count = 40/mm3). Based abnormal infiltrates observed in the imaging examination; it is indicative of a potential IA infection in the patient.

To identify the possible pathogen, therefore, we performed a metagenomic next-generation sequencing examination of the patient's peripheral blood and CSF, which were both positive for A. nidulans sequences (51 sequences in the peripheral blood and 152 in the CSF). No identifiable pathogenic organisms, however, were found in the patient's CSF or peripheral blood cultures. The diagnosis of pulmonary and CNS-IA were both classified as "probable," based on the fungal disease guidelines provided by the European Organization for Research and Treatment of Cancer/Mycoses Study Group.[4] Endophthalmitis was diagnosed by an ophthalmologist, based on the patient's clinical symptoms and a large amount of mass-like echogenicity observed in the atrium on ophthalmologic ultrasound. The patient was started on combined antifungal therapy with voriconazole (400mg/day) and caspofungin (50mg/day), at a plasma concentration of 2.4 mg/L for voriconazole.

CONCLUSION AND RESULTS (Outcome and Follow-Up)

After receiving anti-fungal treatment, the patient's body temperature quickly returned to normal, followed by the patient experiencing significant relief from the eye pain. Brain MRI and chest CT performed on day 8 after the initiation of the antifungal therapy demonstrated radiographic improvement (Figure 1). The galactomannan antigen levels in the patient's peripheral blood decreased from 9.3 to 6.1 pg/mL, and a repeat lumbar puncture, performed on day 8, also showed that the glucose and leukocyte count in the CSF had returned to normal. After the continued administration of the antifungal treatment for another four days, the patient suddenly developed hemiplegia of the right extremity, with a muscle strength of grade 0. Brain MRI performed at that day revealed multiple new-onset acute infarcts in the left basal ganglia and cerebellum (Figure 2), although no intracranial hemorrhage was observed on the head CT performed at the same day as barin

Figure 1 : Diffusion weighted imaging magnetic resonance imaging (DWI-MRI) of the brain revealed multiple patchy infectious lesions (arrows), while computed tomography (CT) of the chest revealed patchy high-density infiltrates in the left lung (arrows); (A) initial MRI and CT obtained upon admission (day 1); (B) re-evaluation at one-week post-treatment, showing improvement in these lesions (day 8).

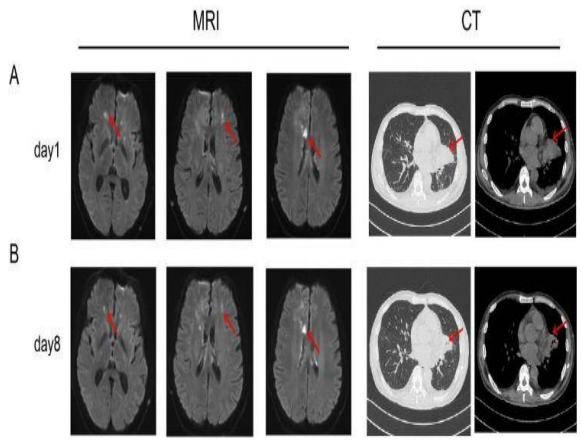
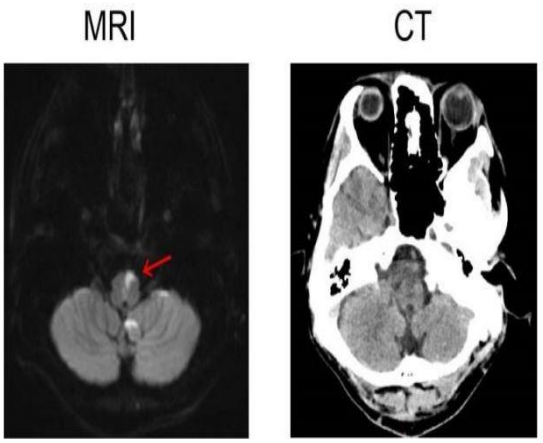


Figure 2 : DWI-MRI showed new-onset infarction at the left basal ganglia and cerebellum (arrows).



MRI. In order to exclude cerebral infarction caused by cardiogenic factors or thrombosis, we performed echocardiography, lower extremity vascular ultrasound, and electrocardiogram. These tests did not reveal any abnormalities. Additionally, we conducted a thorough evaluation of infection-related indicators, including blood and sputum culture, procalcitonin, and C-reactive protein, to eliminate the possibility of concurrent infections. However, no further evidence of other infections was found. The patient's symptoms deteriorated rapidly, including gradually worsening dysarthria and consciousness disorders, and the patient died five days later. The family refused an autopsy.

DISCUSSION

CNS-IA is relatively uncommon, and accounts for only 10% of all IA cases.1 Compared with other sites affected by aspergillosis, CNS involvement significantly increases patient mortality.[5] The symptoms of CNS-IA, however, are nonspecific and can present as headaches, fever, or neurological deficits. Due to its capacity to secrete elastase, Aspergillus can result in angio-invasion by digesting elastic tissue.[6] Disseminated infections, therefore, are more likely to occur in patients with aspergillosis.3 Rhino-orbito-cerebra1 mycosis is another type of invasive mold infection that affects the brain and orbit. This life-threatening infection is primarily caused by the invasion of mucorales originating from the nasal cavity or paranasal sinuses.[7] Extension to deep craniofacial structures through the blood vessels is still the main transmission route of mucormycosis.[8] In the present case, The patient was primarily admitted to the hospital due to progressive vision deterioration,, Based on his clinical symptoms, imaging results, and mNGS testing, we diagnosed the patient with a disseminated Aspergillus infection with concomitant pulmonary, ophthalmic, and CNS involvement, in which hematogenous spreading is one possible route for fungal spores to invade the CNS and the eyes.[9,11] Due to the invasive capacity of Aspergillus, some patients with CNS-IA also present with cerebrovascular accidents, such as aneurysm, hemorrhage, or infarction,[12] and CNS-IA with stroke as the initial clinical manifestation has been reported in a few cases. Tan et al. presented a case study involving a pediatric patient with acute lymphoblastic leukemia who

exhibited hemiparesis and seizures as the primary symptoms. Laboratory investigations revealed the presence of Aspergillus fumigatus.[13] Carla Anciones et al. reported a summary of five CNS-IA patients with stroke as the first manifestation; all of these patients were immunosuppressed, including long-term glucocorticoid therapy or primary hematological malignancies.[14] This result suggests that immunity condition of patients is perhaps an important risk factor for CNS-IA.In the present case, our patient suffered from a sudden basal ganglia and cerebellum infarction during the course of his treatment, despite of the previous combination antifungal therapy has shown signs of improvement in aspergillosis infections.

The patient progressed from hemiplegia to choking and aphasia within a few days, and died in one week after the cerebrovascular event. Since we did not obtain pathological evidence of brainstem lesions in our reported case, we conducted additional tests to eliminate the potential influence of cardiogenic, thrombotic, and other infectious factors. Carrie et al. [15] described a 55-year-old patient with and initial clinical manifestation of headache and gradual vision loss, who was only diagnosed with CNS-IA based on the autopsy results. During treatment, the patient they described developed acute right limb weakness and dysarthria, and a brain MRI demonstrated a left pontine infarction. The clinical course of the patient they described was very similar to that of the patient presented herein, as both experienced a rapid deterioration of their condition after the stroke, and both displayed a new-onset infarct focus on their brain MRI. It is, therefore, possible that systemic fungal infections are not found or known at the time of the stroke; however, during the subsequent course of the disease, patients often develop symptoms involving other sites, such as the pulmonary system. [14] The distribution of fungi in patients with blood malignancies may vary significantly from that in patients with other tumors.[16] A. fumigatus is still the most common pathogenic strain in Chinese patients.[17] The Aspergillus strain involved in the present case was identified as A. nidulans by the mNGS testing. Although it is currently limited to research use only, mNGS has been rapidly developing in recent years as a method for detecting pathogens, with the benefits of short turnaround times and high sensitivity.[18] This unbiased diagnostic approach theoretically makes it possible to detect all microbial pathogens simultaneously in a single sample. In the present case, due to the patient's multiple intracranial lesions and poor disease condition, neurosurgery was not an option for pathogen detection. The mNGS test of the patient's peripheral blood and CSF returned results 48 hours after specimen submission, providing an important basis for the diagnosis of IA. Interestingly, the sequences of A. nidulans detected by mNGS in sterile CSF are significantly higher than those in peripheral blood, which further supports the diagnosis of CNS-IA. In the previous study reported by Pfaller et al, a favorable susceptibility profile of A. nidulans to azoles was observed through the in vitro minimum inhibitory concentration assay. [19] Although clinical data on voriconazole in combination with echinocandins for the treatment of CNS-IA are still limited, some studies have indicated that this combination can improve the survival outcomes of patients with pulmonary-IA infections.[20] Considering that the patient in the present had a disseminated Aspergillus infection involving multiple organs, we adopted a treatment regimen of voriconazole in conjunction with caspofungin. Although the patient presented herein eventually died, his clinical symptoms and imaging examinations after one week of this combined treatment indicated that this treatment regimen might be effective against the A. nidulans strain.

In conclusion, disseminated aspergillosis is an infectious disease characterized by a high mortality rate, particularly when the central nervous system is affected. Fatal complications, such as severe cerebrovascular events, demand careful attention. Additionally, our case indicates the significant role of mNGS, a novel detection method, in diagnosing rare pathogens.

DECLARATIONS

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the

article. Further clinical data are available on request from the corresponding author. [Corresponding author: Minfeng Zhao; e - mail:mingfengzhao@sina.com].

Ethics Approval and Consent to Participate' Legal Representative

Written informed consents for general research and collection of clinical data and publication of the case were obtained from the patient's legal representative.

Authorship List

Zhao Wang: drafted the manuscript and contributed to the literature search.
Xiaofang Wang and Huan Zhang worked on the manuscript and made suggestions to the content.
Xia Xiao and Hairong Lv made suggestions to improve the content and designed the figures.
Mingfeng Zhao supervised the work, and contributes to the manuscript.
All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

Not applicable

Conflict of Interest Statement

The authors declare that there are no competing interests.

Key clinical message

Central nervous system (CNS) invasive aspergillosis is a rapidly progressing, frequently fatal disease that occurs in patients with hematological malignancies. We present the case of a patient with myelodysplastic syndrome, who was diagnosed with disseminated aspergillosis involving the CNS, lungs, and eyeballs, followed by a fatal brainstem infarction. Our case shows that CNS-IA remains a highly aggressive infectious disease, and cerebrovascular events may occur in these patients.

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