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CASE REPORT

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Central nervous system *Aspergillus fumigatus* infection with subarachnoid haemorrhage secondary to hemophagocytic lymphohistiocytosis: a rare case report

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Abstract

Background Secondary central nervous system (CNS) *Aspergillus fumigatus* infection leading to subarachnoid hemorrhage following the onset of hemophagocytic lymphohistiocytosis (HLH) represents an extremely rare case. We provide a detailed account of the disease course, including laboratory results and brain imaging.

Case presentation A 23-year-old male patient presented with fever and was subsequently diagnosed with HLH after comprehensive examinations. His symptoms were significantly alleviated following treatment with liposomal doxorubicin, etoposide, and methylprednisolone. Three months later, the patient returned with headaches. After completing brain MRI and cerebrospinal fluid next generation sequencing (NGS), he was diagnosed with CNS *Aspergillus fumigatus* infection. Antifungal treatments including caspofungin, voriconazole, and amphotericin B were administered sequentially. Various indicators were dynamically monitored throughout the course, including cerebrospinal fluid NGS. Four months after the diagnosis of CNS *Aspergillus fumigatus* infection, the patient suddenly developed subarachnoid hemorrhage, and deceased one month later.

Conclusions Patients with HLH on immunosuppressive therapy may be at increased risk of invasive fungal infections, including CNS *Aspergillus fumigatus*, and close follow-up is necessary. Early completion of cerebrospinal fluid NGS in patients suspected of having concurrent CNS *Aspergillus fumigatus* infection has positive significance for diagnosis and treatment. Aggressive treatment also plays a significant role in prolonging life expectancy.

Keywords Hemophagocytic lymphohistiocytosis, *Aspergillus fumigatus*, Next generation sequencing, Subarachnoid hemorrhage, Case report

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Background

Hemophagocytic lymphohistiocytosis (HLH) is a rapidly progressive inflammatory disorder. HLH can be classified as primary or secondary. Primary HLH is mostly caused by genetic mutations that affect the cytotoxicity of T lymphocytes and NK cells, and is most common in children. Secondary HLH can occur in infections, malignancies, autoimmune or metabolic diseases [1]. Occasionally, idiopathic HLH may occur for unknown reasons. HLH is frequently misdiagnosed or overlooked in clinical practice, posing significant challenges in its early diagnosis and effective treatment [2]. *Aspergillus* species, a kind of filamentous fungi ubiquitous in nature, found immunocompromised groups the most vulnerable, functioning both as opportunistic pathogens and potentially lethal infectious agents. While pulmonary infections are the most common sites of *Aspergillus* infection, central nervous system (CNS) *Aspergillus* remains uncommon, constituting only 1% of all cases [3]. CNS *Aspergillus fumigatus* infections are characterized by atypical symptoms, rapid progression, diagnostic difficulties, and poor outcomes. Moreover, CNS *Aspergillus fumigatus* infections may be complicated by cerebrovascular accidents during the course [4–5]. We presents a case from Hainan Hospital of Chinese PLA General Hospital, where a patient diagnosed with HLH subsequently developed CNS *Aspergillus fumigatus* infections, culminating in subarachnoid hemorrhage and death from brain herniation.

Table 1 Main laboratory indicators during the patient's hospitalisation

Main laboratory indicators	2023.07	2023.08	2023.11	2024.03
White blood cells (WBC)	1.49×10^9 /L	7.69×10^9 /L	8.34×10^9 /L	8.08×10^9 /L
Neutrophils	0.46	0.8	0.88	0.768
Platelets	26×10^9 /L	253×10^9 /L	143×10^9 /L	253×10^9 /L
Hemoglobin	89 g/L	67 g/L	81 g/L	98 g/L
D-dimer	20,243 ng/ml	1836 ng/ml	1467 ng/ml	1686 ng/ml
Plasma fibrinogen	1.28 g/L	3.83 g/L	1.27 g/L	3.29 g/L
Aspartate aminotransferase (AST)	199.9 U/L	59.3 U/L	17.2 U/L	28.9 U/L
Total bilirubin	162 umol/L	17.8 umol/L	13.9 umol/L	7.8 umol/L
Blood urea nitrogen (BUN)	45.4 mmol/L	11.8 mmol/L	5.5 mmol/L	2 mmol/L
Creatinine	510 umol/L	144 umol/L	126 umol/L	130 umol/L
Lactate dehydrogenase (LDH)	1203 U/L	289 U/L	973 U/L	332 U/L
Triglycerides	3.23 mmol/L	1.37 mmol/L	1.74 mmol/L	2.78 mmol/L
Serum ferritin	> 2000 ng/mL	> 2000 ng/mL	> 2000 ng/mL	> 2000 ng/mL
Procalcitonin	15 ng/ml	0.593ng/ml	0.169 ng/ml	0.17 ng/ml
Interleukin-6 (IL-6)	13.3 pg/ml	24.3 pg/ml	13.7 pg/ml	8.28 pg/ml
C-reactive protein (CRP)	0.95 mg/dl	0.45 mg/dl	3.44 mg/dl	7.25 mg/dl
Cerebrospinal fluid (CSF)				
White blood cell count (WBC count)	-	-	576×10^6/L	66×10^6/L
Glucose	-	-	2.88mmol/L	2.47mmol/L
Chloride	-	-	118.7mmol/L	129.2mmol/L
Protein	-	-	933 mg/L	464 mg/L

Case presentation

Fever and HLH

A 23-year-old male was admitted to Hainan Hospital of Chinese PLA General Hospital in late July 2023 due to fever. The patient had been in good health prior to this episode. Neurological examination revealed no abnormal signs. Laboratory results indicated decreased white blood cells, neutrophils, hemoglobin, platelets and fibrinogen, with elevated serum ferritin, triglycerides, D-dimer, aspartate aminotransferase, lactate dehydrogenase, total bilirubin, creatinine, urea nitrogen, procalcitonin, interleukin-6, and C-reactive protein (Table 1). Other tests including thyroid function, autoantibodies, tumor markers, respiratory virus, TORCHS, cryptococcal capsular antigen, G test, GM test, tuberculosis, arbovirus nucleic acid test and blood cultures were all negative. No abnormalities showed on brain MRI (Fig. 1A), PET-CT, and lung CT. Abdominal CT indicated splenomegaly. Based on the laboratory and imaging findings, HLH was considered. Further bone marrow biopsy showing NK cell activity: 15.73%, sCD25: 18,197 U/ml. Bone marrow smear revealed 1% phagocytic cells. The patient was diagnosed with HLH (Hscore: 265). The treatment regimen chosen was liposomal doxorubicin ($25mg/m^2$, day 1), etoposide ($100mg/m^2$, first day of every week) and methylprednisolone (15 mg/kg/d day 1–3, 0.75 mg/kg/d day 4–7, 0.25 mg/kg/d day 8–10, 0.1 mg/kg/d day 11–14). The treatment programme is repeated every 2 weeks, and resulted in significant symptom alleviation and normalization of body temperature, laboratory tests improved on subsequent examinations as well (Table 1).

Headache and CNS infection

In mid-November 2023, the patient was readmitted to hospital with fever, headache, and blurred vision. Brain MRI showed abnormal signals in the ventricles and ventricular dilation (Fig. 1B, C, D). Brain MRA and MRV

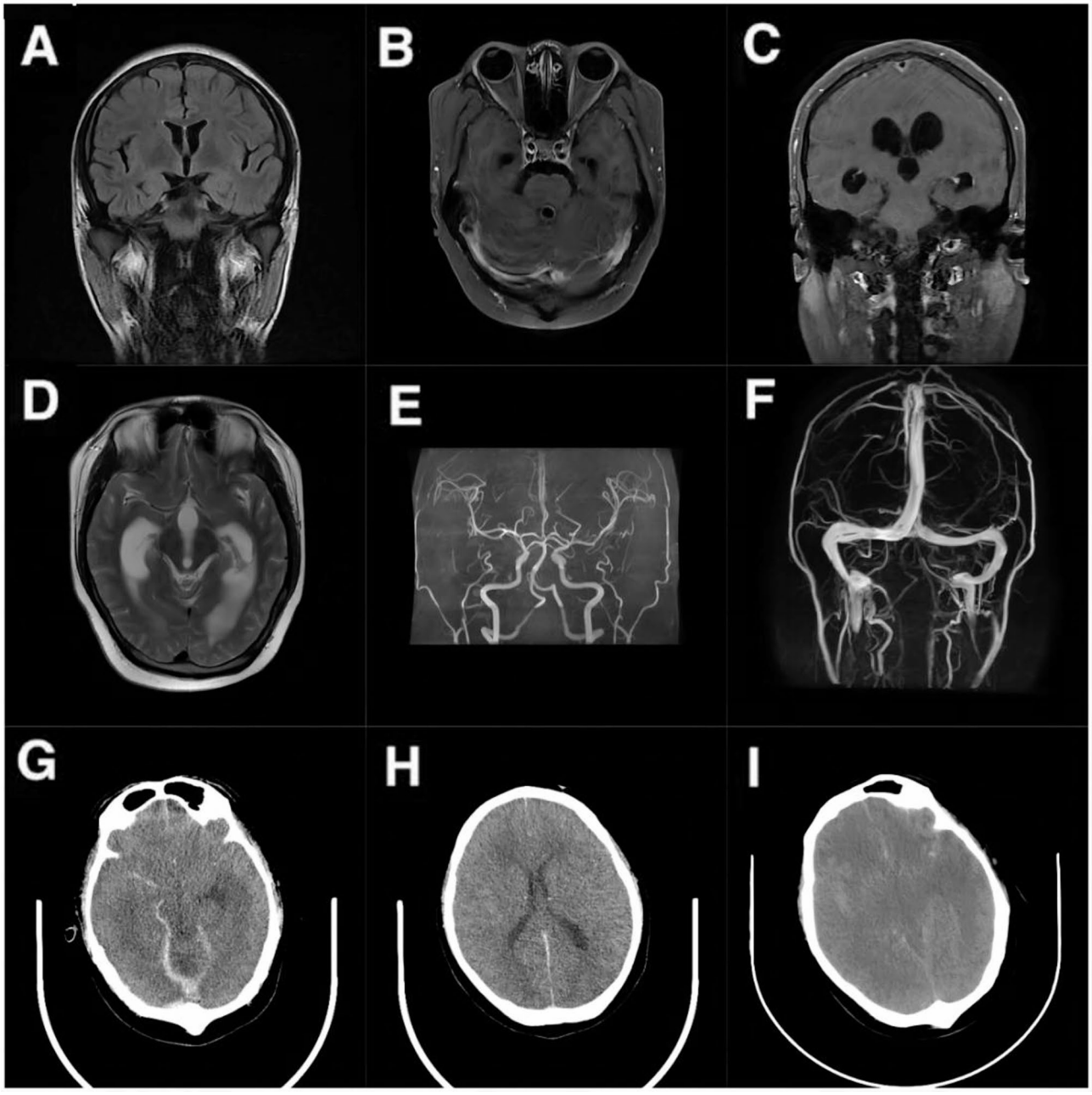

Fig. 1 Dynamic changes in imaging results for the patient. (**A**) Normal brain MRI. (**B**) Enhanced brain MRI suggests dilatation of the lateral and fourth ventricles, with enhancement seen in the fourth ventricle. (**C**) Coronal view of brain MRI suggests marked bilateral lateral ventricular dilatation. (**D**) T2 sequences of brain MRI suggests dilatation of the lateral and tertiary ventricles. (**E**) Normal brain MRA. (**F**) Normal brain MRV. (**G**) Brain CT indicate subarachnoid hemorrhage, compression and swelling. (**H**) Brain CT suggests swelling with significant compression of the lateral ventricles compared to previous scans. (**I**) Brain CT showed further progression of subarachnoid hemorrhage and significant brain swelling compared to previous scans

demonstrated no significant abnormalities (Fig. 1E, F). The lumbar puncture were performed and indicated significantly elevated intracranial pressure, increased cerebrospinal fluid white blood cells and protein levels, while glucose and chloride were within normal ranges (Table 1). No bacteria, fungi, or acid-fast bacilli were detected in the cerebrospinal fluid smear. Next generation sequencing (NGS) for cerebrospinal fluid suggested an *Aspergillus fumigatus* sequence count of 1038. Consequently, the patient was diagnosed with CNS *Aspergillus fumigatus* infection. Treatment included a combination of caspofungin (100 mg/d) and voriconazole (6 mg/kg, 1/12 h day 1; 4 mg/kg, 1/12 h from day 2) for antifungal therapy, along with mannitol for reduction of intracranial pressure. After treatment, the patient's body temperature normalized, although the headache persisted but was less

severe. We dynamically monitored cerebrospinal fluid results including NGS during the hospital stay (Fig. 2).

Due to the persistent headache symptoms and no significant reduction in *Aspergillus fumigatus* sequence counts observed in dynamic cerebrospinal fluid NGS, we initiated amphotericin B (0.1 mg/kg/d day 1, increased by 5 mg every other day starting on day 2 to dose of 1 mg/kg/d) for intensified antifungal treatment in early December. Following the treatment, the patient's headache symptoms were significantly alleviated. Cerebrospinal fluid NGS examination in late December indicated a substantial decrease in *Aspergillus fumigatus* sequence counts compared to previous results. Over the subsequent eight weeks, the patient's condition remained stable, with notable clinical symptom relief. Unfortunately, due to significant renal impairment, amphotericin B was discontinued in February 2024.

Coma and subarachnoid haemorrhage

On March 10, the patient exhibited a decline in consciousness level. Brain CT showed minimal changes compared to previous scans. On March 13, the patient experienced a sudden decrease in pulse oximetry and entered a comatose state. A follow-up brain CT scan indicated subarachnoid hemorrhage, brain compression, and significant brain swelling (Fig. 1G, H). Another follow-up brain CT scan in early April showed further progression of subarachnoid hemorrhage and significant brain swelling compared to previous scans (Fig. 1I). Ultimately, the patient died from brain herniation in mid-April.

Discussion and conclusions

HLH is a rapidly progressive inflammatory disease, usually caused by the activation of lymphocytes and histiocytes due to various etiologies, leading to a multi-organ hyperinflammatory response syndrome induced by the secretion of a large number of cytokines [1]. Clinically, secondary HLH is more frequent, with common causes including infections, malignancies, and autoimmune diseases, but a considerable number of patients still have an unclear etiology [6]. The diagnosis of HLH requires meeting 5 out of the following 8 criteria: (1) Fever persisting for > 7 days, body temperature > 38.5℃; (2) Splenomegaly; (3) Cytopenia involving two or three lineages in the peripheral blood, hemoglobin < 90 g/L, absolute neutrophil count $< 1.0 \times 10^9$/L, platelets $< 100 \times 10^9$/L; (4) Hypertriglyceridemia and/or hypofibrinogenemia: triglycerides > 3mmol/L, fibrinogen < 1.5 g/L; (5) Bone marrow biopsy or biopsy of the spleen, lymph nodes, skin showing hemophagocytic cells without evidence of malignancy; (6) Decreased NK cell activity or complete absence; (7) Serum ferritin ≥ 500 μg/L; (8) sCD25 ≥ 2400 U/mL [7–8]. It is worth noting that there is a high degree of overlap between tick-borne infections and HLH in terms of clinical presentation, with both presenting with fever and pancytopenia. The highest number of tick-borne infections associated with HLH has been reported in the United States, which may be related to tick-borne pathogen distribution and environmental exposure. While considering the diagnosis of HLH in the clinical setting, clinicians need to pay close attention to local epidemiology, patient habits, and rapid pathogenicity testing results [9–10]. In terms of HLH treatment, the most important therapeutic goal is to control the immune response. Even though there are currently few prospective studies on first-line treatment for adult HLH, there is a commonly used treatment regimen that combines corticosteroids with etoposide [11–12].

Currently, there are few reports on CNS *Aspergillus fumigatus* infection following the onset of HLH. *Aspergillus fumigatus* is an opportunistic pathogen and also an important pathogen causing fatal infections. Immunocompromised populations and patients with immunosuppressive related diseases such as hematologic malignancies, HIV infection, solid organ transplants, systemic lupus erythematosus and rheumatoid arthritis etc. are the most vulnerable. Risk factors for *Aspergillus fumigatus* infections also include age, ethnicity and long-term use of drugs, including corticosteroids immunosuppressants and a variety of broad-spectrum antimicrobial drugs [13–14]. It is important to note that CNS *Aspergillus fumigatus* infection differs from other types in terms of route of infection, clinical presentation, and prognosis. In terms of routes of infection, CNS *Aspergillus fumigatus* infection is most often caused by haematogenous dissemination or direct sinus invasion [15]. Pulmonary *Aspergillus* infection is mostly due to direct inhalation of spores, and exposure to water mist containing *Aspergillus* spores may also trigger infection [16]. Liver abscess *Aspergillus* infection is rarer and is mostly due to haematogenous dissemination or damage to the mucosal barrier of the gastrointestinal tract [17]. Clinical symptoms of CNS *Aspergillus fumigatus* infection often presents insidiously manifesting fever, headache, visual disturbances, hemiplegia and consciousness disorders. In terms of imaging characteristics, parenchymal space occupying lesions are generally more common than meningitis [18]. Pulmonary *Aspergillus* infection is mainly manifested by cough, haemoptysis, chest pain and dyspnoea. The main manifestations of liver abscess *Aspergillus* infection is fever, abdominal pain, weight loss, chills, night sweats, fatigue, and liver enzyme elevation [19]. In terms of prognostic differences, CNS *Aspergillus* infection carries a very high risk of mortality. Data from earlier studies have shown that the overall mortality rate from CNS *Aspergillus* in adults exceeds 90% [20]. With continuous improvement in *Aspergillus* treatment, systematic studies have shown improved prognosis in recent

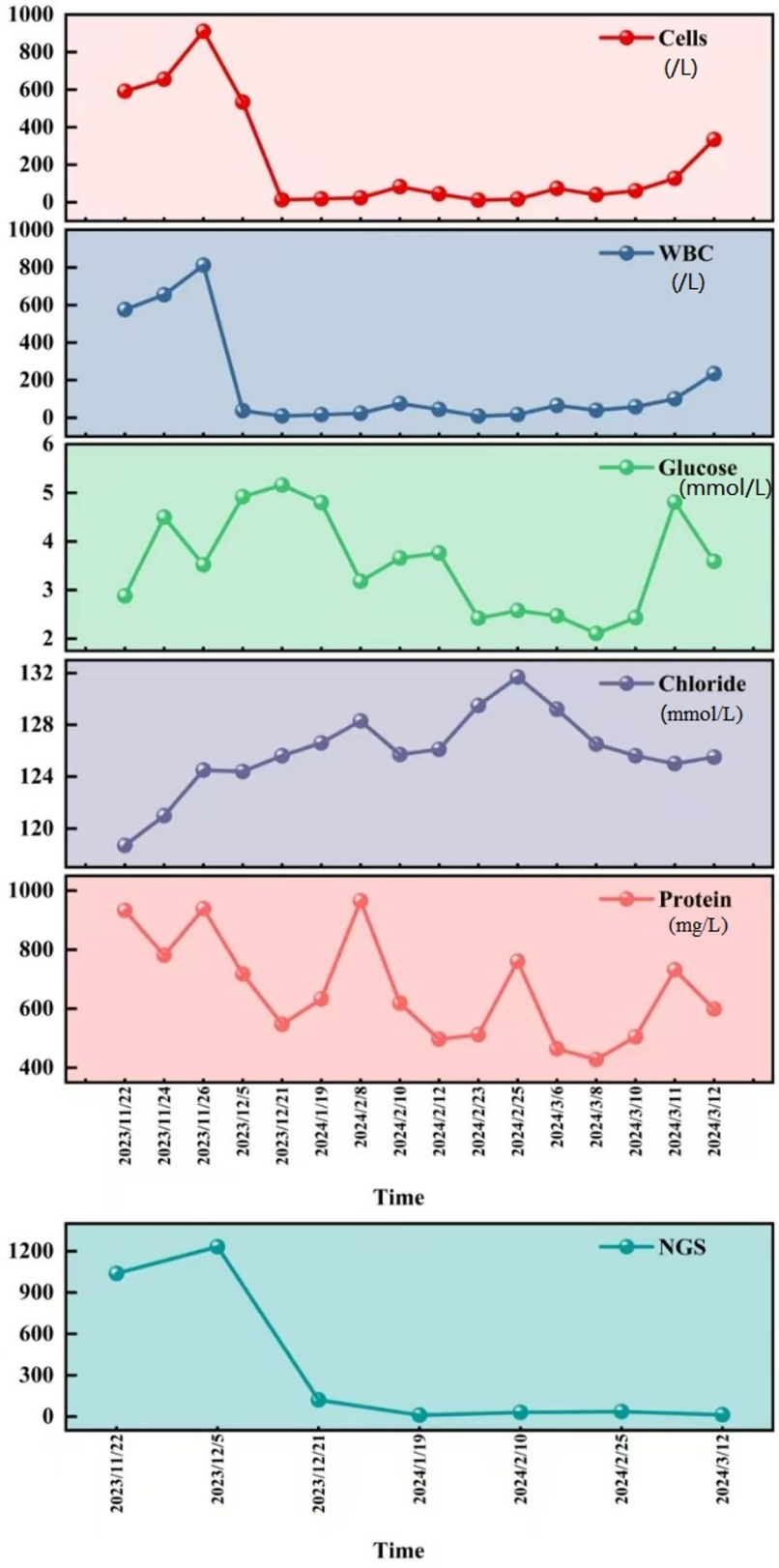

Fig. 2 Dynamic changes in cerebrospinal fluid test indicators for the patient

years. In a study that included 235 patients, the overall mortality rate for CNS *Aspergillus* infection was 45.1% [21]. In a retrospective study, Kourkoumpetis found that patients with CNS *Aspergillus* had a 57.1% mortality rate during hospitalisation, and only 14.28% of patients achieved a survival of more than 2 years [22].

The diagnosis of CNS *Aspergillus fumigatus* infection is highly challenging. Currently, the gold standard for diagnosis remains pathological diagnosis. Due to the operational difficulties associated with invasive examinations, more and more cases relied mainly on cerebrospinal fluid NGS for diagnosis. NGS is a DNA sequencing technology developed based on PCR and gene chips. With its high throughput rapid efficiency and high precision in describing the transcriptome and genome of pathogens, it can accurately analyze the type of pathogen. In recent years, NGS has developed rapidly, making it possible to confirm the infectious pathogen at an early stage, especially improving the detection rate of rare pathogens like CNS *Aspergillus fumigatus*, thereby better guiding clinical diagnosis and treatment [23]. We found that in this patient, the early changes in cerebrospillular fluid NGS correlated positively with clinical symptoms. As the clinical symptoms improved significantly, the levels of cerebrospinal fluid NGS also decreased significantly, thus we believe that the level of cerebrospinal fluid NGS in the early stages of the disease can reflect the effectiveness of treatment to some extent. However, in the later stages of the disease, although there was significant progression in clinical symptoms, the changes in cerebrospinal fluid NSG were not very significant.

Regarding the treatment strategy for CNS *Aspergillus fumigatus* infection, it is generally believed that voriconazole combine with Amphotericin B may effective. Amphotericin B is highly toxic and has poor CNS penetration, but is an effective treatment for neuroinfections caused by fungi which are not susceptible to agents with good CNS penetration (e.g., voriconazole). Among antifungal drugs, voriconazole, fluconazole, and flucytosine readily penetrate into the CNS, but itraconazole and posaconazole only penetrate to a minor degree. Voriconazole is recommended as primary therapy for CNS *Aspergillus*, while amphotericin B are reserved for intolerant or refractory patients [24]. Literature reports that combining amphotericin B lipid complex with voriconazole for the treatment of *Aspergillus fumigatus* patients is an effective treatment regimen with fewer adverse reactions and lower costs [25].

CNS *Aspergillus fumigatus* infection can cause cerebrovascular complications. On the one hand, hyphae can directly block cerebral blood vessels, leading to ischemic stroke. On the other hand, *Aspergillus fumigatus* can release elastase to break down elastin in the vessel walls while hyphae penetrating the vessel wall and growing, further leading to thinning of the vessel wall and ultimately forming mycotic aneurysms [26]. Both ischemic stroke and aneurysm impose a significant burden on patients, with ruptured aneurysms leading to subarachnoid hemorrhage, significantly increasing the patient's mortality rate [27–28]. For mycotic aneurysm rupture leading to subarachnoid hemorrhage, there is currently no unified and standardized treatment protocol.

In conclusion, this case review underscores the necessity of comprehensive etiological screening in patients with HLH. Patients with HLH on immunosuppressive therapy may be at increased risk of invasive fungal infections, including CNS *Aspergillus fumigatus*, and close follow-up is necessary. Early diagnosis and monitoring of CNS *Aspergillus fumigatus* can be facilitated through cerebrospinal fluid NGS. In the present case, amphotericin B administration yielded notable therapeutic benefits. However, vigilant renal function surveillance is essential. Sudden clinical exacerbations in CNS *Aspergillus fumigatus* infection patients warrant consideration of potential cerebrovascular complications. It is important to acknowledge the limitations of this study. While the HLH case discussed herein exhibited a rare complication of CNS *Aspergillus fumigatus* infection which ultimately resulted in subarachnoid hemorrhage, it should be emphasized that such outcomes are not indicative of HLH as a whole. In fact, HLH cases with these specific characteristics are exceptionally uncommon.

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Author contributions
SW, JL, and FC developed the concept of the article. WZ, NZ, YL, and JL investigated and followed up the patient. YL and WZ supervised the project. FC and WZ authorised the project. SW, NZ and YL wrote the original draft. SW, NZ and JL reviewed, revised and edited the original draft. SW, NZ and JL confirmed the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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