



A case report of the metagenomics next-generation sequencing for early detection of central nervous system mucormycosis with successful rescue in patient with recurrent chronic lymphocytic leukemia

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Background: Central nervous system (CNS) mucormycosis is insidious and difficult to diagnose. It progresses rapidly and causes high mortality. Rare cases have been reported during ibrutinib use, which have poor prognosis. Through this case, we share the experience of successful diagnosis and treatment. We also emphasize the importance of focusing on high-risk groups, early diagnosis and prompt management.

Case Description: In this case, a 52-year-old patient was diagnosed with chronic lymphocytic leukemia (CLL) for more than 5 years. He was in remission after rituximab plus fludarabine and cyclophosphamide (RFC) regimen, and relapsed in the fourth year. During the ibrutinib monotherapy, the patient presented with sudden headache. Cranial imaging examination revealed a definite right occipitoparietal lobe mass with extensive edema. A rapid diagnosis of mucormycosis infection was made using metagenomic next-generation sequencing (mNGS). The patient at that time didn't have neutropenia, but he had hypogammaglobulinemia. The infection was treated with amphotericin B cholesteryl sulfate complex, posaconazole, and interventional surgery, and the treatment was successful. At the same time, we considered the control of disease progression in this relapsed patient with, as well as to the drug interaction with posaconazole. We chose the next generation Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib as the treatment, whose safety has been identified. As of the submission date, the patient has been followed up for nearly 1 year, and his disease is stable.

Conclusions: When new clinical problems arise in recurrent CLL patients, it is important to identify multiple factors, especially the insidious fungal infections. In particular, the immunocompromised patients should be concerned. CNS mucormycosis is extremely deadly, the early diagnosis will improve the prognosis. In clinical practice, the gold standard diagnosis of mucormycosis is difficult to obtain through pathology. In this case, mNGS was applied to quickly diagnose mucormycosis, enabling earlier treatment and ameliorating the prognosis. Thus, it will help us to early detect this group of people who may be potentially infected. Current guidelines do not recommend the prophylactic use of antifungal agents in treated CLL patients. However, in patients with prior severe infection or hypogammaglobulinemia, intravenous immunoglobulin is recommended to reduce the associated infection rate.

Keywords: Case report; chronic lymphocytic leukemia (CLL); central nervous system mucormycosis (CNS); metagenomic next-generation sequencing (mNGS); zanubrutinib

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Introduction

Relevant studies have shown that the annual incidence of mucormycosis is about 3.3 cases per 100,000 hospital admissions (1). The incidence of central nervous system (CNS) mucormycosis infection accounted for less than 0.04% of immunocompromised patients with central infection, which is extremely rare and fatal, with a mortality rate of 80% (2-4). Contemporary data show that the incidence of CNS mucormycosis is increasing (5). Thus, clinicians should be aware of the potential infections in immuno-impaired patients. The diagnosis of mucormycosis depends on histopathology and identification of microorganisms in tissue culture (6). In emergency situations, gold standard diagnostic methods in practical clinical application have limited value in improving prognosis. Cornely's study showed that rapid diagnosis and treatment of mucormycosis is critical for patient survival, with the risk of death doubling within a week due to delayed diagnosis and treatment (3).

Herein, we report a case in which a recurrent chronic lymphocytic leukemia (CLL) patient with CNS mucormycosis was successfully treated. Most patients with CLL have been shown to have defective humoral and cell-mediated immunity, and is more evident in progressive phase (7). When new clinical problems arise in CLL patients, it is important to identify multiple factors. Firstly, we need to rule out disease progression, and identify the presence of other conditions, such as invasive fungal infections that occur during ibrutinib treatment (8). Nervous system infections are uncommon, but they will develop insidiously during the application of ibrutinib and progress rapidly. In the face of difficulty obtaining pathological results, evidence of mucormycosis can be obtained using pathogenic microorganism DNA/RNA high-throughput genetic sequencing (PMseq) of cerebrospinal fluid (CSF).

In the case reported here, in response to the pathological findings, we gave the patient amphotericin B cholesterol sulfate complex and posaconazole immediately for anti-infection, and interventional surgical treatment was performed to save the patient's life. Furthermore, CLL was kept in an ideal remission state by applying the next-

generation Bruton tyrosine kinase (BTK) inhibitor zanubrutinib. For CNS mucormycosis infection, we need the early introduction of effective drugs (like liposomal amphotericin B), appropriate surgical intervention, thus we are able to save patients' lives without delay. This case demonstrates successful treatment of hematologic malignancy complicated with CNS mucormycosis infection, which is extremely deadly. We can obtain the risk factors associated with invasive disease in patients receiving ibrutinib therapy through this case. And we also use new methods for rapid diagnosis of the disease, which was difficult to diagnose in the past, directly improving the prognosis of the patient. We present the following case in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2533/rc>).

Case presentation

The patient was a 52-year-old man with progressive lymph node enlargement and onset of fatigue. An ultrasound showed enlargement of the superficial lymph nodes. The maximum diameter of the left cervical lymph node was 4 cm. The spleen size was 80 mm × 211 mm × 91 mm. He was diagnosed with CLL/small lymphocytic leukemia (SLL) after left cervical lymph node biopsy in June 2015. Flow immunophenotype of the peripheral blood showed CD79b (dim), CD20 (dim), CD5 (+), CD10 (-), CD23 (+), FMC7 (-), CD200 (+), CD43 (+), and immunoglobulin light chain restricted expression. Fluorescence in situ hybridization (FISH) showed ATM (-), RB1 (-), CSP12 (-), D13S25 (-), and TP53 (-). The results of NGS of the genome showed mutated IGHV, SF3B1, and MYC. Assessment of the disease stage showed that it was Rai stage IIb and Binet stage B. The CLL International Prognostic Index score was 3 points, indicating moderate risk. At that time, the rituximab plus fludarabine and cyclophosphamide (RFC) regimen with standard doses [rituximab 500 mg/m² d0 + fludarabine 25 mg/m² d1-d3 + cyclophosphamide (CTX) 250 mg/m² d1-d3] was administered as treatment for a total of 6 cycles. The disease state was later evaluated as complete remission, and the patient was regularly followed up in the outpatient department for 4 years.

In September 2020, the patient had left cervical lymph node enlargement again, and the lymph nodes doubled in size within a month. Lymph node biopsy was led to the pathological diagnosis of CLL, and recurrence was thus considered. The RFC regimen was administered again. Due to the presence of hemolytic anemia during the treatment with fludarabine, the drug effect was considered, so the treatment program was changed to ibrutinib + rituximab (IR) (ibrutinib 420 mg qd plus rituximab 500 mg/m² d1, 28 d/cycle) in October 2020. After 4 cycles of the IR regimen, rituximab was terminated due to interstitial pneumonia. Prednisone and sulfamethoxazole (SMZ) maintenance therapy was followed for about 2 months, as recommended by a pulmonologist. The patient sustained remission with continued ibrutinib monotherapy, with the dose of 420 mg once daily. In mid-July 2021, the patient developed gait instability without obvious causes but did not have fever, disturbance of consciousness, headache, dizziness, purulent nasal discharge, nausea, vomiting, joint swelling or pain, deviated mouth opening, or drooling. He did not give much attention to this new symptom and no diagnosis or treatment was sought. In late July, he developed a feeling of fullness in the head originating in the occipital region and had a fever that reached 38 °C. However, the patient was not accompanied by any other uncomfortable symptoms. Complete blood count after admission showed that the white blood cell count was $5.92 \times 10^9/L$ (3.97×10^9 – $9.15 \times 10^9/L$) and the neutrophil cell count was $4.76 \times 10^9/L$ (2.00×10^9 – $7.00 \times 10^9/L$). The (1,3)-beta-d-glucan test and the galactomannan test were both unremarkable, and procalcitonin was <0.02 ng/mL. The lymphocyte subsets of the patient were decreased T cells and natural killer (NK) cells; CD4/CD8: 0.2 (1.0–2.5), the CD4 absolute count was 90/ μ L (384–1,346/ μ L), CD4/CD45RA: 0.6% (15.0–25.0%), and the patient presented with hypogammaglobulinemia, immunoglobulin G (IgG): 7.62 g/L (8.6–17.4 g/L).

The cranial magnetic resonance imaging (MRI) non-contrast scan results showed a space-occupying lesion in the right occipital parietal lobe with substantial edema and ischemic foci in the left frontal lobe and bilateral centrum semiovale. The contrast-enhanced cranial MR results (3 August 2021) revealed a space-occupying lesion in the right occipital parietal lobe with large edema. Based on the patient's medical history and imaging, it was suspected that the lesion was a metastatic tumor (*Figure 1*). Mannitol, glycerol fructose, and furosemide dehydration along with intracranial pressure reduction were administered for treatment, but the symptoms became further aggravated.

Specifically, the symptom of gait instability deteriorated. The patient developed left limb weakness and bradyesthesia. The results of lumbar puncture on 6 August 2021 showed that the intracranial pressure was higher than 300 cmH₂O (80–180 cmH₂O). The CSF analysis showed that the CSF was clear and colorless, Pandy's test was 1+, red blood cell count was $1 \times 10^6/L$, and white blood cell count was $<1.0 \times 10^6/L$. The CSF biochemistry showed the following: glucose level: 4.0 mmol/L (2.2–3.9 mmol/L), chloride level: 108 mmol/L (118–132 mmol/L), and protein level: 1,733 mg/L (<500 mg/L).

The fungal fluorescent staining smear showed that no fungi was detected in the direct smear. No acid-fast bacilli were detected in the acid-fast bacillus smear. The PMseq report for CSF, which can achieve a broader range of pathogen detection by metagenomic next-generation sequencing (mNGS) (9) suggested the presence of *Rhizomucor* (number of detected sequences: 3,842) and *Rhizomucor pusillus* (number of detected sequences: 3,771). Sample sequencing data and theoretical sensitivity to the pathogen showed that the total number of detected sequences was 43,797,028 and that the theoretical sensitivity (copies/mL) to the fungi (100 MB) was $1.00E+00$ (*Figure 2*). Combined with these results, we considered that the patient had CNS mucormycosis.

During this period, the symptoms of the patient were continuously aggravated, and he developed drowsiness and decreased muscle strength in the left arm and leg. Amphotericin B cholesterol sulfate complex combined with posaconazole treatment was started on 11 August 2021 (the dose of the amphotericin B cholesterol sulfate complex was gradually increased to 3 mg/kg/d; the initial dose of posaconazole was 600 mg and was later reduced to 300 mg qd for descending step therapy). On the second day of treatment, the patient regained consciousness and experienced defervescence of fevers. The muscle strength of his left side also continuously improved. The muscle strength recovered to grade 4 after approximately 1 week of medication and completely returned to normal after approximately 2 weeks. Examination of the disease lesion on 31 August by cranial MR showed that it had improved (*Figure 1*). Later, the patient's symptoms improved, his mental state improved, and his muscle strength completely returned to normal. Therefore, the treatment for CNS mucormycosis was effective.

To further clear the lesion, on 14 October 2021, intracranial abscess drainage and biopsy were performed under intravenous general anesthesia. The conclusion of

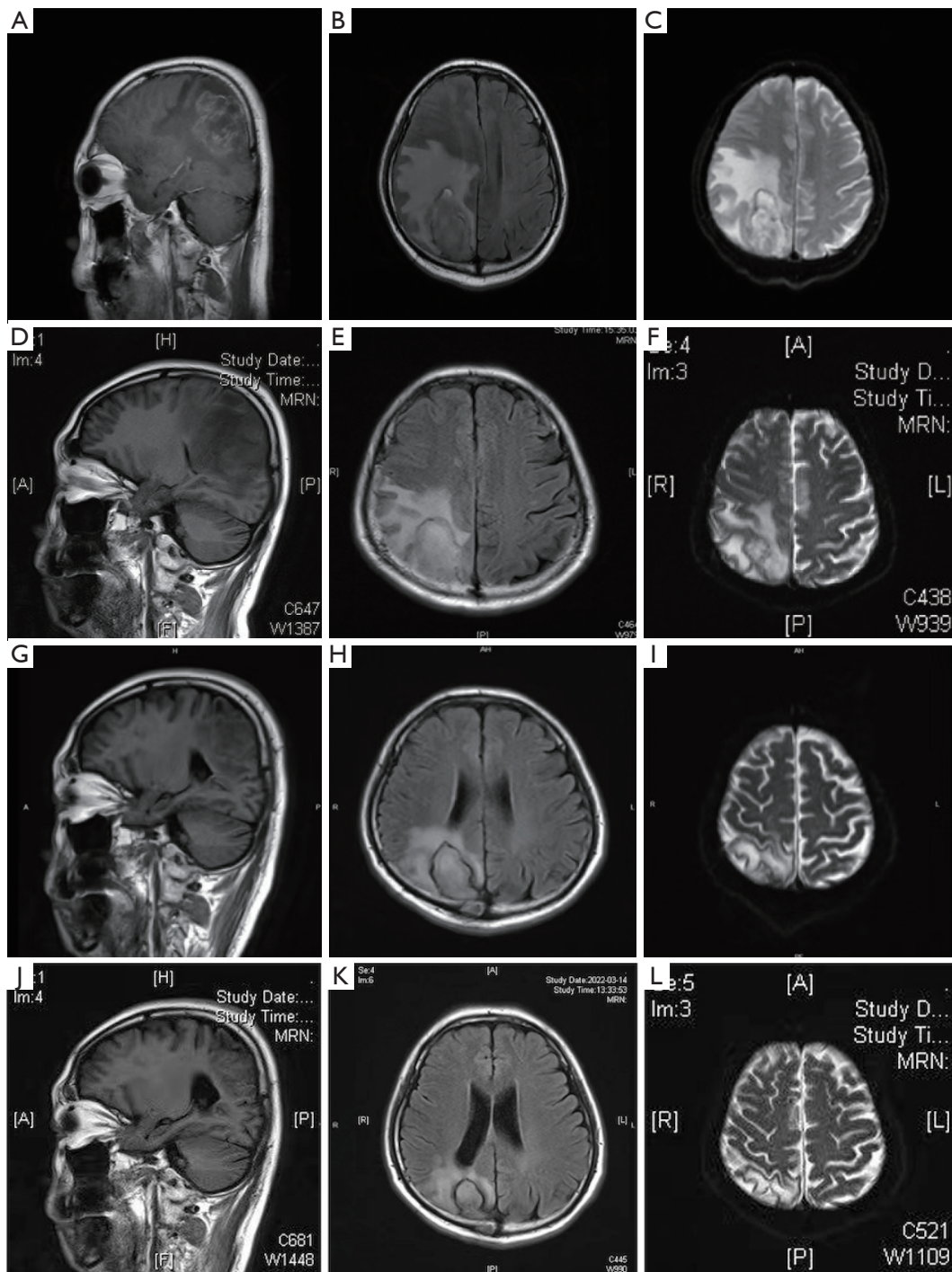


Figure 1 Changes in the cranial MRI of the patient. (A) MRI of the cerebellum (16 August 2021), T1W FLAIR; (B) MRI of the cerebellum (16 August 2021), T2W FLAIR; (C) MRI of the cerebellum (16 August 2021), DWI; (D) MRI of the cerebellum (31 August 2021), T1W FLAIR; (E) MRI of the cerebellum (31 August 2021), T2W FLAIR; (F) MRI of the cerebellum (31 August 2021), DWI; (G) MRI of the cerebellum (15 November 2021), T1W FLAIR; (H) MRI of the cerebellum (15 November 2021), T2W FLAIR; (I) MRI of the cerebellum (15 November 2021), DWI; (J) MRI of the cerebellum (14 March 2022), T1W FLAIR; (K) MRI of the cerebellum (14 March 2022), T2W FLAIR; (L) MRI of the cerebellum (14 March 2022), DWI. MRI, magnetic resonance imaging; T1W FLAIR, T1-weighted-fluid-attenuated inversion recovery; T2W FLAIR, T2-weighted-fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging.

pathology was that the right parietal region staining results were consistent with mucormycosis. Biopsy did not yield any evidence of lymphoma. The special staining results showed both periodic acid Schiff and silver stain were

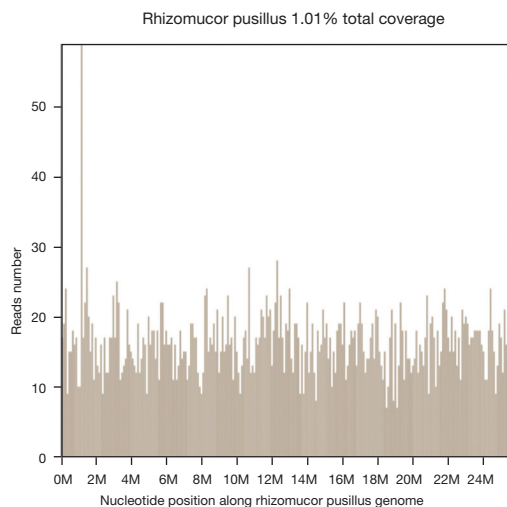


Figure 2 Report of PMseq of CSF (distribution of the locations in the pathogen genome). PMseq, pathogenic microorganism DNA/RNA high-throughput genetic sequencing; CSF, cerebrospinal fluid; The “M” on the x-coordinate means the location of the genome.

positive. Examination using contrast-enhanced cranial MRI on 15 November 2021 showed that the lesion had reduced (*Figure 1*). Currently, de-escalation therapy with oral posaconazole is underway. A re-examination of the head MRI in March 2022 showed improvement in the infected lesions (*Figure 1*).

The patient had moderate-risk CLL combined with hemolytic anemia. Zanubrutinib has greater selectivity in relative inhibition of BTK, and its safety and efficacy have been confirmed (10). Therefore, zanubrutinib was chosen for controlling the primary hematologic tumor and was applied together with triazole drugs. The oral dose of zanubrutinib was adjusted to 80 mg bid. As of this writing, the hematologic tumor is stable. On November 18, CLL was evaluated; hematology suggested peripheral blood measurable residual disease was negative and the disease was currently in complete remission. *Figure 3* shows the diagnosis and treatment administered in this case.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

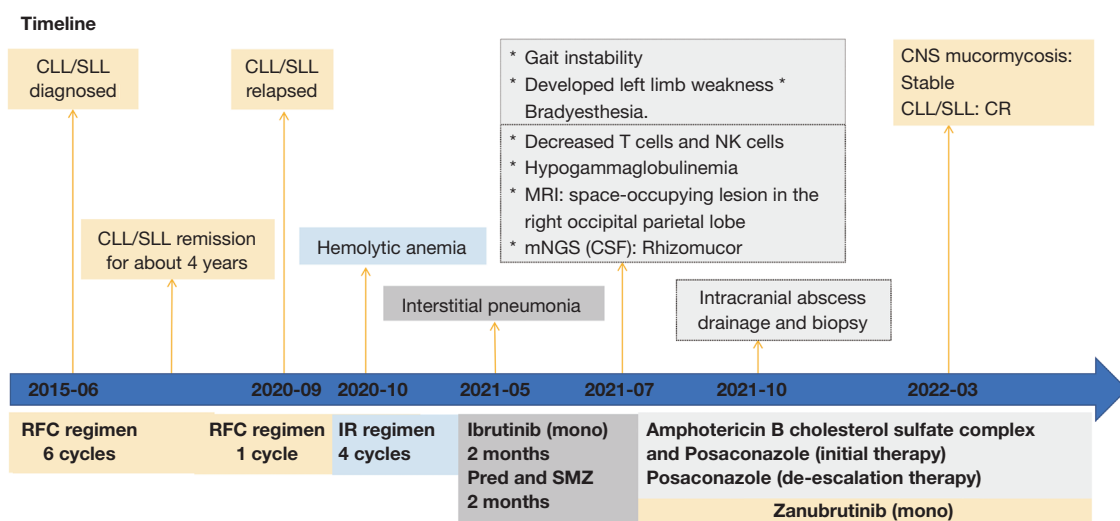


Figure 3 Flow of diagnosis and treatment. CLL/SLL, chronic lymphocytic leukemia/ small lymphocytic leukemia; CR, complete remission; RFC, rituximab plus fludarabine and cyclophosphamide; IR, ibrutinib and rituximab; mNGS metagenomics Next-Generation Sequencing; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; SMZ, sulfamethoxazole; Pred, prednisone; mono, monotherapy; CNS, central nervous system.

Table 1 Review of reported cases of mucormycosis in patients on ibrutinib therapy (17–23)

Clinical features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, years	52	72	71	72	70	68	67
Gender	Female	Male	Male	Male	Male	Male	Male
Malignancy	CLL	CLL	CLL	CLL	CLL	CLL	CLL
Methods of diagnosis	Biopsy	Biopsy	Autopsy	Biopsy	Autopsy	Biopsy	Biopsy
Site of mucormycosis involvement	Renal	Cutaneous	Brain, lung, kidney, pancreas	Thyroid	Liver	Cutaneous	Lung
Outcome	Survival	Survival	Died	Survival	Died	Survival	Died
Active malignancy treatment	Ibrutinib	Ibrutinib	Ibrutinib	Ibrutinib	Ibrutinib	Ibrutinib	Ibrutinib

CLL, chronic lymphocytic leukemia.

Discussion

Discussion among physicians from Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

We conducted intradisciplinary and multidisciplinary consultation of this case. As CNS mucormycosis is rare and deadly, early diagnosis and treatment are important for improving the prognosis of patients. Patients with recurrent CLL relapsing after multiple line treatments, they are usually immunocompromised. During the application of BTK inhibitors, we need to monitor immune function and associated clinical symptoms, which will help us recognize underlying fungal and other related infections. For symptomatic, highly suspected patients with infection, new diagnostic methods can be used to identify them, appropriately with early drug intervention. Although prophylactic fungal therapy is not routinely recommended during ibrutinib treatment in CLL patients, we need to monitor indicators of immune function in these patients. If the patient is complicated with hypogammaglobulinemia, whose acquired humoral immunodeficiency should be corrected and improved. However, the underlying causes and new methods for early diagnosis and treatment should be further investigated.

Department of Epidemiology

Rhizopus is a thermophilic fungus of the order *Trichoderma* (2). Humans can be infected with *trichoderma* and *rhizopus*. Rare infections are caused by *Trichoderma hamia* and *Absidia* (reclassified as *Lichtheimia*, *Saksenaea*, and *Apophysomyces*) (11–14). Mucormycosis infection is a relatively rare cause of

human infection, with an overall mortality of approximately 62% (2), of which mucormycosis infection of the CNS is rare and fatal (15). In China, the understanding of mucor infection is somewhat limited, especially the central mucor infection, its related mortality has not been reported.

An international epidemiological survey running from January 2010 to January 2017 showed that in addition to diabetes, hematologic tumors were the second most common factors for mucormycosis infection, accounting for 32%. Especially when patients receive tumor chemotherapy and immunotherapy, the incidence of immunosuppression will be higher (16).

Our patient was a refractory CLL treated with ibrutinib. The peripheral blood cell analysis of the patient at the time of infection showed that he did not have neutropenia. The lymphocyte subsets of the patient were decreased T cells and NK cells, and he also had hypogammaglobulinemia, which displayed high-risk factors of mucormycosis infection. After controlled mucormycosis infection, the patient was given intravenous immunoglobulins (IVIG) at 1 g/kg per month (for 1 week) to correct the humoral immunity.

Department of Infectious Diseases

There are many host factors that may contribute to invasive mycosis, among which therapy-related immunosuppression that identifies B cells is also a common cause, such as the BTK inhibitor ibrutinib (8). Previous cases of mucormycosis infection during BTK inhibitor use have shown that infection can involve various sites (Table 1) (17–23). Common infection sites are the lungs and skin. The site of infection reported in our case is a rare infection of the CNS.

The onset of CNS mucormycosis is usually insidious. Once related infection symptoms are present, the disease

is invasive and life-threatening. Therefore, early diagnosis is beneficial to improve prognosis. Fungal culture and tissue biopsy are the gold standards for the diagnosis of mucormycosis. The global guideline for the diagnosis of mucormycosis published by the European Confederation of Medical Mycology (ECMM) (3) in 2019 describes the diagnosis of mucormycosis using a combination of tissue culture, molecular technology, and in situ hybridization as well as species identification and drug susceptibility testing. The recommended methods for genus and species identification are ITS sequencing and matrix-assisted laser desorption ionization time of flight (MALDI-TOF). These two types of genus and species identification have certain limitations. Especially for high-risk clinical patients, these methods have low diagnostic rates and are time-consuming (24,25). Fehr *et al.* (17) reported the case of a 71-year-old patient with CLL who developed CNS mucormycosis and died rapidly during treatment with irutinib. It was finally identified as mucormycosis by polymerase chain reaction (PCR) after autopsy, which delayed medical treatment (17). The PCR is a hypothesis-driven molecular testing method that can involve numerous individual tests for specifically targeted organisms but may still miss a rare pathogen or use primers containing mismatches to the microbial strain involved, which decreases the sensitivity of detection. However, mNGS is an unbiased diagnostic approach that has the potential to detect nearly any organism, which could lead to a dramatic paradigm shift in microbial diagnostic testing (26).

In our case, we sent the CSF of the current patient for PMseq. The report was available after 48 hours and showed the presence of *Rhizomucor pusillus*, which provided a basis for early medication. The consensus is that CSF mNGS is more available than traditional gold standard methods. At the same time, it has advantages in the identification of meningitis pathogens, especially in species identification, and is recommended for the diagnosis of infectious CNS diseases (27).

Department of Neurology

The disease presentation of our patient was CNS infection. The onset was insidious, but the progression was rapid. Hence, rapid diagnosis and treatment were required to improve his prognosis. Although DNA sequencing that can directly localize the infected region in the tissue is a promising approach, the method has high requirements for laboratory equipment (28). In clinical practice, sometimes there are difficulties obtaining histopathological tissue. At

this time, CSF mNGS is recommended as the second-line detection method.

The reporting of the use of NGS in CNS infections is currently mainly in the form of case reports, there are few large-scale studies to refer to. In previous studies on pathogen NGS in CSF, the diagnostic rate was not high, partly because only acellular virus or acellular microbial nucleic acid could be detected in CSF supernatant, and the detection rate was low (29-33). Therefore, CSF should be correctly used as sequencing specimens in clinic to improve the detection rate (34). A study by Miller *et al.* (35) showed that NGS had a sensitivity of 73%, specificity of 99%, positive predictive value of 81%, and negative predictive value of 99% compared to traditional clinical laboratory results.

Our case was successfully diagnosed by NGS, for which relevant international reports are sporadic. The efficacy and clinical value need to be further explored. Clinical trials with larger sample sizes are still needed to verify the efficacy of NGS for fungal infections of the CNS, and the results should be interpreted and verified in close combination with patient clinical manifestations and laboratory test results.

Determining the etiology of fungal infections can be expedited through a combination of methods such as NGS to achieve an early diagnosis, start effective and systemic antifungal treatment sooner, and treat the underlying diseases. Early and effective disease control can improve the prognosis. During treatment, we can monitor the condition of disease control through the number of sequences found in the CSF. The titer reduction can also reflect the disease condition to a certain extent. Due to the high sensitivity of metagenomics, metagenomic testing results can show the status of disease control and may guide drug withdrawal after the clinical symptoms of the patient improve and imaging results become negative. If the patient requires long-term application of immunosuppressants or the disease progression necessitates further treatment such as cell-mediated immunity, metagenomics can be applied to monitor the activity of mucormycosis.

Several issues regarding the diagnosis and treatment of this patient were further discussed as follows

- (I) For patients with recurrent and refractory CLL, which methods can best monitor their immune function during treatment?

Goyal Gaurav: Typically, only through complete blood count (CBC) differential and sometimes

checking serum immunoglobulins. However, it hardly changes management.

Fabiana Perna & Manuel Espinoza-Gutarra: Cellular immune function is best monitored through standard CBC, as neutropenia and lymphopenia have been associated with an increased risk of infection, particularly in patients receiving traditional chemotherapy (36). Regarding humoral immunity, low immunoglobulin levels, specifically IgG have been associated with infection risk (37).

- (II) Are there any means to prevent latent fungal infection in patients with recurrent and refractory CLL during treatment?

Goyal Gaurav: Currently, it is not recommended to use prophylactic antifungals unless there is neutropenia.

Fabiana Perna & Manuel Espinoza-Gutarra: Currently guidelines do not recommend prophylactic use of antimicrobials or antifungals in CLL patients undergoing treatment, with a few exceptions: patients with prior history of significant infection requiring Intravenous antibiotics and an IgG level <500 mg/dL have decreased rates of bacterial infections when treated with intravenous IVIG to a target level of 500–700 mg/dL, this data has sometimes been extrapolated to fungal infections; however, no trial has specifically studied this (38). Prophylactic antifungals are recommended when patients receive alemtuzumab-based treatment; however, given newer therapeutic options in CLL, this drug is rarely, if ever, used (39). Finally, the use of myeloid-derived growth factors (G-CSF, GM-CSF) in neutropenic CLL patients has been shown to decrease the rate of infections, particularly for regimens where the risk of neutropenia is greater or equal to 20% (40).

- (III) How long should the treatment of CNS mucormycosis be maintained? Could mNGS be used to monitor subsequent mucormycosis activity in patients and determine when to stop?

Goyal Gaurav: This question would be best addressed to infectious disease. I have never seen mNGS used at our center before.

Fabiana Perna & Manuel Espinoza-Gutarra: There are no clear guidelines on when to stop antifungal therapy in this setting, a generally accepted approach is to begin to de-escalate therapy once clinical recovery and radiographic resolution of infection takes place, which often takes several weeks (41).

There is currently no evidence that mNGS can be used to determine duration of therapy in invasive fungal infections, although its usefulness is certainly intriguing and should be investigated in clinical trials.

- (IV) If the patient needs further treatment for CLL progression, should antifungal therapy be used prophylactically?

Goyal Gaurav: That would be an open question, and would have to be discussed with infectious disease. There is no clear recommendation on this.

Fabiana Perna & Manuel Espinoza-Gutarra: Given the life-threatening nature of invasive fungal CNS infections and the potential for recurrence, even at later stages of treatment, long term prophylactic therapy with a mold active agent is recommended (42), particularly in patients with a chronic condition that will require long-term treatment such as CLL.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2533/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-2533/coif>). FP received grants/contracts from Lonza, Leukemia Research foundation, Indiana University School of Medicine (payments were made to her institution), and received consulting fees from NGMBio. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as

revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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