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CASE REPORT

Case Report: Successful Treatment of Recurrent Candida Albicans Meningitis with Kimura's Disease Using Amphotericin B Colloidal Dispersion Combined with Fluconazole

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Background: *Candida albicans* meningitis is a fungal infectious disease of the central nervous system that most often occurs in immunodeficient populations. Kimura's disease is an IgE-mediated inflammatory reactive disease that is a chronic immune disorder with predominantly lymph node, soft tissue, and salivary gland damage, the treatment of which is hormone-based. The combination of Kimura's disease with *C. albicans* meningitis is relatively uncommon. Herein, we report a case of *C. albicans* meningitis in combination with Kimura's disease.

Case Presentation: The case is a 26-year-old male with a medical history of Kimura, who presented with symptoms of dizziness, headache, and double vision. Lumbar puncture and cerebrospinal fluid examination revealed an increased white blood cell count. Further analysis through cerebrospinal fluid culture and metagenomic second-generation sequencing (mNGS) led to the final diagnosis of *C. albicans* meningitis. The patient was treated with fluconazole after the onset of *C. albicans* meningitis and had a good response. During the treatment, changes in the pathogen genome sequences were monitored dynamically using metagenomic next-generation sequencing. After 1 year, the patient had a recurrence of *Candida* meningitis. Treatment with fluconazole alone was ineffective, while antifungal treatment with amphotericin B colloidal dispersion was effective with no detectable renal injury.

Conclusion: *Candida* meningitis can occur in the context of Kimura disease. In patients with mild disease, the possibility of recurrence exists with fluconazole treatment alone, and the efficacy of amphotericin B colloidal dispersion combined with fluconazole is better than fluconazole alone in patients with a recurrence. No nephrotoxicity was observed during amphotericin B colloidal dispersion treatment. The mNGS allows dynamic monitoring of pathogen sequencing reads, and for *Candida* meningitis, there may be a mismatch between peak sequencing reads and disease during treatment, the basis for which is unclear.

Keywords: *Candida* meningitis, angiolymphoid hyperplasia with eosinophilia, amphotericin B colloidal dispersion, metagenomic next-generation sequencing, case report

Background

Candida meningitis is caused by *C. albicans* infection of the central nervous system and presents with fevers, headaches, convulsions, and impaired consciousness, which most often occurs in immunocompromised populations.[1] Amphotericin B is the preferred for treatment of *Candida* meningitis, although fluconazole can be used in mild cases or when amphotericin B is not tolerated.[2] According to previous case reports, *Candida* meningitis can be well-managed using standardized treatment with fluconazole alone,[3] voriconazole,[4,5] and amphotericin B combined with flucytosine.[3,6] Clinical studies have also shown that amphotericin B colloidal dispersion (ABCD) has similar efficacy[7] and less nephrotoxicity[8] compared to liposomal amphotericin B with respect to antifungal activity. During the course of antifungal treatment, the therapeutic effect is primarily

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assessed by clinical symptoms and cerebrospinal fluid testing indicators.[9] Dynamic and in real time detection of changes in sequencing reads of pathogen by metagenomic next-generation sequencing (mNGS) has been less frequently.[10]

Kimura's disease, also known as eosinophilic lymphogranuloma, mainly presents as a painless subcutaneous mass of the head and neck. The microscopic mass is lymphoid hyperplasia with eosinophilic infiltration. It is a rare, chronic disease of unknown cause that was first reported by Kim et al in 1937[11] and described in more detail by Kimura in 1948.[12] The disease has a low incidence and is a chronic immune disease causing lymph node, soft tissue, and salivary gland damage.[12,13] In some cases, Kimura disease may be associated with renal damage, and treatment is mainly hormonal. The combination of Kimura disease with *C. albicans* meningitis has not been reported.

mNGS is a technique that allows for the simultaneous sequencing of thousands to billions of DNA or RNA fragments.[14,15] This technique offers a fast detection of pathogens, addressing the limitations of traditional diagnostic methods. It has the ability to identify all potential pathogenic microorganisms in a sample, which is valuable for diagnosing diseases.[16] Moreover, mNGS is less influenced by prior antibiotic exposure, enabling doctors to promptly and accurately treat infectious diseases.[17]

We report a case of *C. albicans* meningitis with Kimura's disease in a mildly ill patient. At the time of onset, the patient was treated with oral fluconazole (800 mg once a day). After 1 month of treatment the clinical symptoms resolved and the cerebrospinal fluid test results improved. During the same period of time, however, the cerebrospinal fluid mNGS showed a significant increase in the number of pathogen sequences which did not match the treatment outcome. After 6 months of treatment with the original dose of fluconazole, the clinical symptoms were significantly relieved and the number of pathogen sequences were significantly decreased. Mainte-nance therapy was continued with oral fluconazole 800 mg once daily. One year later, the patient had a recurrence of *C. albicans* meningitis, which responded poorly to fluconazole, while ABCD combined with fluconazole treatment resulted in rapid improvement and no renal injury or recalcitrant hypokalemia throughout treatment.

Case Presentation

A 26-year-old male was admitted to the hospital for evaluation of dizziness and headaches for 10 days that was aggravated by diplopia for 2 days. He had a history of Kimura disease 4 years before the onset of the current symptoms. He had taken prednisone acetate orally for 1 year (starting at 30 mg/day and gradually decreasing). The physical examination showed limited abduction of the eyes with the right side being dominant, diplopia, and neck rigidity There are no abnormalities in the heart, lungs and abdomen, the muscle strength of the limbs is normal, the nervous position is negative, there are no disorders of consciousness, movement, sensation or small brain defects. Serologic testing showed a normal white blood cell count (3.9×109/L; eosinophils, 0.5×109/L) and a normal rheumatic profile. The cranial MRI did not reveal any significant abnormalities. A lumbar puncture was significant for an elevated cerebrospinal fluid (CSF) opening pressure >330 mmH2O, an increased white blood cell count (690×106/L), decreased glucose (1.54 mmol/L), and elevated cerebrospinal fluid protein (0.56 g/L). Cerebrospinal fluid cultures were negative. To identify the pathogen, CSF mNGS was performed and only C. albicans was detected (sequencing reads 954). Combining the clinical symptoms, signs, and CSF positive for *C. albicans*, the diagnosis of *Candida* meningitis was evident.

In this case, the patient had mild disease and a history of Kimura disease. Due to the patient's concern about the increased risk of nephrotoxicity with amphotericin B and the sensitivity of the CSF culture to fluconazole, treatment was initiated with fluconazole alone (800 mg daily), as recommended by the treatment guidelines. The symptoms gradually improved after 1 month of antifungal treatment, and the results of the repeat lumbar puncture showed that the CSF opening pressure, white blood cell count, and biochemical indices were improved, in agreement with the clinical symptoms; however, mNGS of the CSF during the same period showed a significantly higher sequencing reads of *C. albicans* (sequencing reads 8141). Six months after the original dose of fluconazole treatment, mNGS showed that the sequencing reads of *C. albicans* was decreased (sequencing reads 743). The oral fluconazole treatment was continued for 1 year without recurrent symptoms, then the fluconazole was discontinued. One month after stopping the fluconazole, fevers and headaches recurred, a lumbar puncture showed an elevated CSF opening pressure >330 mmH2O, the white blood cell count increased to 450×106/L, the glucose concentration decreased to 0.36 mmol/L, and the protein content increased to 1.02 g/L. Moreover, CSF mNGS showed that the *C. albicans* sequencing reads increased (sequencing reads 1178), thus recurrence was considered. The patient was administered 800 mg of fluconazole daily. After 2 weeks, the clinical symptoms improved slightly, and the biochemical characteristics of CSF were slowly restored; the CSF

glucose level changed from 0.36 mmol/L to 0.48 mmol/L. Considering the ineffective treatment by fluconazole, the patient finally received antifungal treatment with ABCD combined with fluconazole due to the unavailability of flucytosine. After 5 days of ABCD treatment, the CSF glucose level increased (2.46 mmol/L), and after 2 weeks the clinical symptoms and CSF examination improved significantly. The CSF glucose level returned to normal (4.11 mmol/L). No adverse effects, such as renal injury and hypokalemia, occurred during the treatment period, and the patient was discharged after 1 month of induction phase ABCD treatment. There was no recurrence at the 6-month follow-up evaluation.

Discussion

Kimura disease is an IgE-mediated inflammatory reactive disease with a low incidence. Kimura disease is prevalent in Asian populations and is more common in young adult males, with 80% of patients having an age of onset between 30 and 40 years.[18] Approximately 20% of patients with Kimura disease have renal injury, with nephrotic syndrome being the most common type.[19] The combination of Kimura disease with *Candida* meningitis has not been previously reported. Herein we reported a case of *Candida* meningitis with Kimura disease in a male patient at 22 years of age due to enlarged lymph nodes in the neck, as suggested by puncture biopsy. The patient was treated with oral hormones for 1 year, and the lymph nodes shrank after treatment with normal serum IgE values. No recurrence of Kimura disease occurred before the onset of meningitis. *Candida* meningitis occurs mostly in patients with immunodeficiencies. The patient in this case had Kimura disease and an oral steroid history, suggesting that Kimura disease may be one of the causes of susceptibility to *Candida* meningitis.

The incidence of *Candida* meningitis is low. The Infectious Diseases Society of America recommended in the 2016 clinical practice guidelines for the management of candidiasis that the drugs of choice for the treatment of central nervous system candidiasis are amphotericin and flucytosine, with optional fluconazole for milder cases or in patients who cannot tolerate amphotericin B nephrotoxicity.[2] In this case, the initial onset of symptoms was mild and the patient declined amphotericin B treatment for fear of renal injury. Thus, 800 mg of fluconazole was selected for treatment. After treatment, the fevers and headaches were relieved, and the patient was treated continuously with oral fluconazole for 1 year; however, 1 month after discontinuation of fluconazole the patient developed headaches and low-grade fevers again, and the recurrence of *Candida* meningitis was considered after an auxiliary examination. Based on the CSF culture and drug sensitivity results, 800 mg of fluconazole daily was administered, but the CSF glucose level improved slightly (0.36–0.48 mmol/L) after 2 weeks of treatment. After communication with the patient, the treatment was altered to the relatively less nephrotoxic ABCD at a dose of 3 mg/kg/day. A significant therapeutic effect was achieved after 5 days of treatment, with a significant improvement in the CSF glucose level (from 0.48 to 2.46 mmol/L). More importantly, no renal impairment or recalcitrant hypokalemia side effects were observed during 1 month of continuous ABCD treatment.

mNGS detects pathogenic nucleic acids by DNA or RNA sequencing in the CSF with a sensitivity of 73% and specificity of 99%, which is of great value in the diagnosis of pathogens in infectious diseases of the CNS.[20] The percentage of pathogens detected by CSF mNGS ranged from 15.7%-57.0%,[20–22] and the percentage of simultaneous positive mNGS and conventional pathogenic techniques ranged from 22.5%-52.6%, where the number of specific sequences detected by mNGS can respond to the pathogen load.[10] At present, the evaluation of the therapeutic effect of infectious diseases is mainly assessed by clinical manifestations and CSF testing indicators,[23] and less often by dynamic changes in the number of sequences detected by mNGS.[10] In 2018, Ai et al[10] reported, for the first time, using mNGS to diagnose and monitor the dynamic changes of the pathogen sequencing reads in four patients with central infections, and the results showed that the changes in mNGS detection sequencing reads were closely related to the progression and improvement in disease status. Zhang et al,[24] used mNGS to dynamically monitor the number of pathogen sequences in patient CSF, and the results showed that when patients received effective antimicrobial therapy, the number of mNGS sequences decreased or even became negative within a few weeks. This change was consistent with a simultaneous decrease in CSF leukocyte levels and an increase in the increased glucose ratio. These results suggest that mNGS provides a somewhat direct and accurate indication of dynamic changes in pathogen load and is consistent with trends in disease regression; however, no dynamic changes in the number of mNGS sequences in patients with *Candida* meningitis have been reported in the above studies with clinical relevance. The patient in the present case study was definitively diagnosed with *Candida* meningitis by mNGS with a Candida-specific sequencing reads of 954 before treatment. After administration of fluconazole (800 mg daily for 1 month), the clinical symptoms improved and the abnormal CSF

indicators gradually recovered; however, the number of mNGS specific sequences increased to 8141, even though the patient was symptom-free. After 6 months of continued maintenance treatment, the number of specific sequences for *Candida* albicans in the CSF was significantly reduced to 743 according to mNGS. At the time of relapse, the patient developed fevers and headaches, and repeat mNGS revealed a specific sequencing reads of 1178 and an elevated CSF cell count and decreased glucose concentration. After treatment, mNGS showed a trend of significantly higher, then lower CSF *Candida* sequencing reads, which did not agree with the clinical symptoms. Previous studies have reported that patients with fungal meningitis can have elevated CSF WBC counts after antifungal treatment, which decreased after continued treatment.[23] The phenomenon of peak pathogen count by mNGS dynamic detection during treatment of *Candida* albicans meningitis has not been retrieved. The cause and significance of these findings are unclear and warrant further observation and study in the future.

Unfortunately, the patient refused to undergo cerebrospinal fluid mNGS after significant remission. Sequence readings of *Candida albicans* in this patient after cure are not known, which is a major limitation of this study.

Conclusion

In conclusion, *Candida* meningitis can occur in the context of Kimura disease. In patients with mild disease, the possibility of recurrence exists with fluconazole treatment alone, and the efficacy of ABCD combined with fluconazole is better than fluconazole alone in patients with a recurrence. No nephrotoxicity was observed during ABCD treatment. The mNGS allows dynamic monitoring of pathogen sequencing reads, and for Candida meningitis, there may be a mismatch between peak sequencing reads and disease during treatment, the basis for which is unclear.

Abbreviations

ABCD, amphotericin B colloidal dispersion; CSF, cerebrospinal fluid; mNGS, metagenomic next-generation sequencing.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report. And the consent form is avail able for reviewing by the editor when needed. Details of the case can be published without institutional approval.

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Disclosure

The authors report no conflicts of interest in this work.

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