

## CASE REPORT

# Promising effects of corticosteroid treatment in combination with antifungal agents in a patient with *Aspergillus meningitis*

Parisa Aziz Jalali<sup>1</sup> | Ensieh Lotfali<sup>2</sup>  | Kamran Rezaei<sup>3</sup>  | Alireza Fatemi<sup>4</sup> | Farzad Ashrafi<sup>5</sup>  | Saeed Oraee-Yazdani<sup>6</sup> | Alimohammad Mirdehghan<sup>3</sup>

<sup>1</sup>Department of Neurology, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup>Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>5</sup>Functional Neurosurgery Research Center, Shohada-e Tajrish Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>6</sup>Department of Neurosurgery, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Correspondence

Parisa Aziz Jalali, Department of Neurology, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: [azizjalali.parisa@gmail.com](mailto:azizjalali.parisa@gmail.com)

## Funding information

None

## Abstract

Although *Aspergillus meningitis* is poorly responsive to current guidelines for treatment, we describe a dramatic response of *Aspergillus meningitis* in a patient to treatment using a combination of corticosteroids with guideline's suggested antifungal agents. Administration of corticosteroids in patients with *Aspergillus meningitis* is rarely reported in previous studies.

## KEYWORDS

aspergillosis, *Aspergillus*, corticosteroid, meningitis

## 1 | INTRODUCTION

About 10%–15% of cases of Invasive Aspergillosis (IA) affect the central nervous system (CNS) as neuroaspergillosis.<sup>1</sup> Being immunocompromised is the major risk factor for IA of the CNS with reported mortality rate of approximately 90% (compared with 10%–20% in immunocompetent individuals); and developing a proper medical approach for the treatment of neuroaspergillosis is very challenging because of its poor response to treatment.<sup>2</sup>

This could be due to intrinsic or acquired antifungal resistance, which is an emerging problem in current era, and even with current guideline of using new antifungal agents, outcomes of patients with this condition are not promising.<sup>3</sup> Patients with neuroaspergillosis present with a variety of signs and symptoms such as fever, headache, dizziness, seizure, lethargy, altered mental status, gait disorders, visual impairment, and diplopia.<sup>4</sup> One of the main manifestations of previously reported cases of IA involving the CNS is mass lesions seen in infectious meningitis.<sup>5</sup>

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

Herein, our case report describes a rare case of neuroaspergillosis in Iran, in which a dural aspergillus abscess is identified in cerebral aqueduct, and corticosteroid therapy is added to guideline's suggested antifungal agents.

## 2 | CASE REPORT

A 41-year-old female patient was admitted to the emergency department of hospital with chief complaint of frontal headache. Initially her headache had an on/off pattern that started 10 days earlier and progressed over time. She reports having fever and chills before onset of the headache and around 2 days prior to referring to our hospital. She developed delusion at the time. Her headache did not follow any specific patterns.

In her past medical history, she mentions being hospitalized due to a severe burn involving 35% of total body surface area around 5 months ago. Two months later, deep vein thrombosis developed in her right leg and rivaroxaban was prescribed as the treatment. She did not report any notable habitual and familial history as a predisposing factor for a specific headache pattern.

No signs of loss of consciousness and seizures were present. In neurological examination, only papilledema was observed. There was no sign of neurologic deficit.

A head computed tomography (CT) scan was taken, which showed mild triventricular hydrocephalus. The results of hematologic and cerebrospinal fluid tests are described in Table 1.

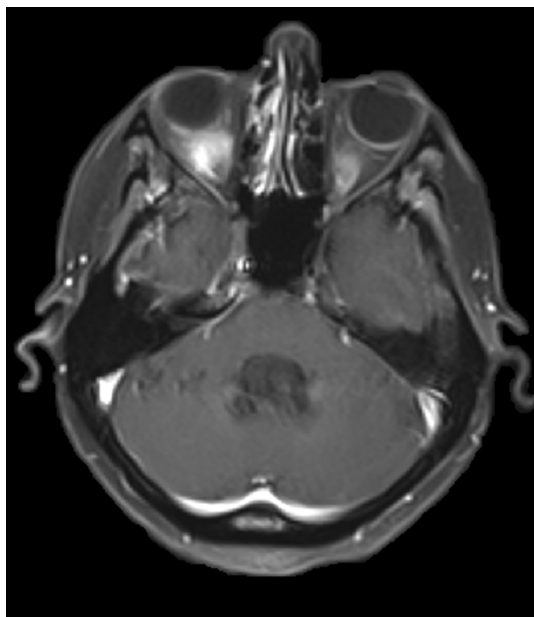
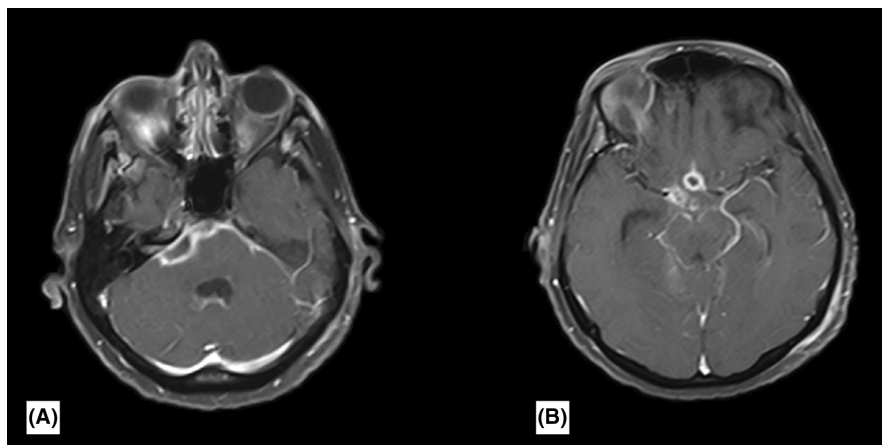
Based on the clinical and para-clinical suspicion of inflammatory or infectious meningitis, additional tests were performed for the patient and following results were obtained: PCR for *Cryptococcus neoformans* was negative, CSF and serum angiotensin converting enzyme (ACE) were normal, chest CT-scan showed no abnormality, tuberculosis (TB) PCR, CSF molecular-based (MTB) PCR, and PPD tests were negative. Malignancy work-up showed no abnormal results. Nested PCR<sup>6</sup> of the CSF was positive for *Aspergillus flavus*. Therefore, a non-contrast magnetic resonance imaging (MRI) of the brain was taken, in which a basal leptomeningeal enhancement in the area of pons and medulla, and a rim-enhancing lesion in the right cerebellopontine angle (CPA) was observed (Figure 1). Thus, a high degree of certainty for diagnosis of CNS aspergillosis was achieved. The antifungal susceptibility test was performed by the broth microdilution method using four antifungal agents, including voriconazole (VCZ; Merck, Germany), itraconazole (ICZ; Merck, Germany), fluconazole (FCZ; Merck, Germany), and amphotericin B (AMB; Merck, Germany). Based on the Clinical and Laboratory Standards Institute (CLSI) M38 3rd ed.,<sup>7</sup> *Candida parapsilosis* (ATCC 22019) was chosen as a quality control strain.

TABLE 1 Paraclinical laboratory tests performed on the patient

Test	Result	Unit
Basic hematology tests		
Quantitative CRP	42	mg/dl
CBC		
Hemoglobin	10.4	gr/dl
MCH	28.49	pg
MCHC	31.52	%
MCV	90.41	FL
Red blood cells	3.65	10 <sup>6</sup> cells/L
White blood cells	5.7	10 <sup>3</sup> cells/L
Platelet	246	10 <sup>3</sup> cells/L
Hematocrit	33	%
Biochemistry tests		
Blood sugar	112	mg/dl
BUN	10	mg/dl
Creatinine	0.71	mg/dl
K	3.7	meq/L
Na	142	meq/L
LDH	44	U/L
Alkaline phosphatase	148	U/L
Alanine transaminase	7.6	U/L
Aspartate transaminase	8.1	U/L
Ca	8.85	mg/dl
Phosphorus	5.8	mg/dl
Coagulation assay and PT		
PTT	35	Seconds
INR	1	
PT	13	Seconds
CSF analysis		
Anaerobic culture	No bacterial growth	-
Appearance	Clear	-
Aerobic culture	No bacterial growth	-
Color	Color-less	-
Direct smear	PMN = 0	-
Glucose	19	mg/dl
Gram stain	No bacteria were seen	-
Protein	87	mg/dl
RBC	0	-
WBC	0	-
Other tests		
RT PCR for SARS-CoV-2	Negative	-

The *A. flavus* strain showed resistance to FCZ, ICZ, with minimum inhibitory concentration MIC>16 and MIC>1 µg/mL, respectively. Furthermore, susceptibility

**FIGURE 1** (A) Axial T1W1C+MR shows basilar leptomeningeal enhancement and rim enhancing lesion in the right CPA with dilation of 4th ventricle. (B) Axial T1W1C+MR demonstrates rim enhancing lesion (abscess formation) in third ventricle



**FIGURE 2** Axial T1W1C+MR was obtained after starting antifungal treatment which shows enlargement of 4th ventricle with resolution of rim enhancing lesion and leptomeningeal enhancement in previous brain MRI

to voriconazole (MIC 0.313  $\mu\text{g}/\text{mL}$ ) and amphotericin B (MIC 0.313  $\mu\text{g}/\text{mL}$ ) was noted in this study.

Based on the result of antifungal susceptibility tests and, intravenous (IV) VCZ, intrathecal, and IV AMB were prescribed for the patient, and IV dexamethasone was added to her antifungal treatment.

Brain CT-scans taken on consecutive days showed a progressive triventricular hydrocephalus, and brain non-contrast MRI showed progression of the leptomeningeal enhancement to basal and suprasellar cisterns (with pressure effect on the optic chiasm). In addition to the CPA, rim enhancement progressed to the right internal auditory canal (IAC) and enhancement of the basilar and circle of Willis vessels were also observed. Because of the patient's

hydrocephalus and rise of ICP neurosurgery consult was obtained following which an external ventricular drainage (EVD) was placed in patient's left lateral ventricle to drain excessive CSF.

After 5 weeks on the mentioned combination therapy, resolution of lesions was observed on imaging (Figure 2), and a few days later, the patient's hydrocephalus reduced, so her condition improved dramatically.

### 3 | DISCUSSION

Among all the reported sites of IA, CNS is considered to be the most devastating, which accounts for 10%–15% of cases of aspergillosis<sup>1</sup>; and using corticosteroids to manage a fungal infection-mediated hydrocephalus is a controversial.<sup>8</sup> Previously, the initial treatment of choice for IA affecting the CNS was systemic antifungal treatment with AMB, but now guidelines have switched to VCZ as the initial treatment, given that VCZ is more capable of reaching the proper concentration required for antifungal activity in the CSF. It also has lower toxicity potential compared with AMB.<sup>1,9</sup> Also, ICZ and isavuconazole (ISZ) were used in some previous cases; Tattevin et al. reported 3 patients with neuroaspergillosis and underlying diseases, receiving ICZ in combination with other agents. One of the patients (a known case of Wegener granulomatosis) was cured with AMB (29 days)+ICZ (410 days), another individual (suffering from laryngeal cancer) receiving AMB (25 days)+ICZ (13 days) died, and the last one (a case of systemic lupus erythematosus and end-stage renal disease) was cured by receiving liposomal AMB (44 days)+VCZ and ITZ (380 days).<sup>10</sup> Taking into consideration that outcomes of monotherapy vs. combination therapy could be an important point of comparison in previous reports of neuroaspergillosis, Karthic et al. reported an expired case that was treated with VCZ,<sup>11</sup> Haroon and colleagues mentioned another expired case who received AMB,<sup>12</sup> but the

overall results of combination therapy were more promising; Gruter et al. reported a neuroaspergillosis patient (who also had thyroid cancer) receiving VCZ+ AMB+ ISZ who was cured.<sup>5</sup> Leroy et al.<sup>13</sup> and Turki et al.<sup>14</sup> both reported cured cases of neuroaspergillosis treated with VCZ + liposomal AMB, and of 5 cases described in Tattevin and colleagues' study, 3 were cured by combination therapy.<sup>10</sup>

In addition to the above-mentioned antifungal agents, using corticosteroids draws attention which is rarely reported previous cases. Although not recommended in current guidelines, corticosteroids may improve outcomes in *Aspergillus*-related meningitis presenting with hydrocephalus; even with consideration of the fact that corticosteroids have an anti-inflammatory nature and may apply a minimizing effect on immune cells. Hiraga et al. reported a case of meningitis caused by *Aspergillus* infection in an immunocompetent woman that was complicated by respiratory failure, which was dramatically cured by VCZ and corticosteroids and no relapse was observed.<sup>15</sup> The mentioned study and our experience of positive outcomes with combination therapy using corticosteroids and antifungal agents may provide an evidence for potentialities of this combination therapy to treat fungal meningitis. Surgical debridement is considered to reduce mass effect caused by abscess, and EVD may be placed to treat hydrocephalus.<sup>10</sup>

#### AUTHOR CONTRIBUTION

PA has made substantial contributions to conception and design, revised, and gave final approval of the version to be published. EL has made substantial contributions to conception and design and participated in drafting the manuscript. KR Involved in collaboration between hospital and laboratory and participated in drafting the manuscript. AF involved in conception and revise of the manuscript. FA agreed to be 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. SO involved in conception and revise of the manuscript. AM involved in drafting the manuscript.

#### ACKNOWLEDGEMENTS

Published with written consent obtained from the patient.

#### CONFLICTS OF INTERESTS

There are no conflicts of interest related to this case report.

#### DATA AVAILABILITY STATEMENT

Data are available on request.

#### CONSENT

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images and videos. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

#### ORCID

Ensieh Lotfali  <https://orcid.org/0000-0001-6709-1320>

Kamran Rezaei  <https://orcid.org/0000-0002-0451-3175>

Farzad Ashrafi  <https://orcid.org/0000-0002-5959-5462>

#### REFERENCES

1. Anciones C, de Felipe A, de Albóniga-Chindurza A, et al. Acute stroke as first manifestation of cerebral aspergillosis. *J Stroke Cerebrovasc Dis.* 2018;27(11):3289-3293.
2. Antinori S, Corbellino M, Meroni L, et al. Aspergillus meningitis: a rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases. *J Infect.* 2013;66(3):218-238.
3. Rudramurthy SM, Paul RA, Chakrabarti A, Mouton JW, Meis JF. Invasive aspergillosis by aspergillus flavus: epidemiology, diagnosis, antifungal resistance, and management. *J Fungi.* 2019;5(3):55.
4. Mohanty P, Lenka A, Govardhan T, Panigrahi S. A diagnostic challenge of invasive sellar neuroaspergillosis in an immunocompetent patient. *Formos J Surg.* 2021;54(3):111.
5. Grüter BE, Reuss AM, Rushing EJ, Pangalu A, Oertel MF. An unexpected intracerebral lesion—case report of a superinfected aspergillosis mimicking a brain metastasis. *BMC Infect Dis.* 2021;21(1):1-5.
6. Hummel M, Spiess B, Kentouche K, et al. Detection of aspergillus DNA in cerebrospinal fluid from patients with cerebral aspergillosis by a nested PCR assay. *J Clin Microbiol.* 2006;44(11):3989-3993.
7. Wayne P. Clinical and laboratory standards institute. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. CLSI Document M38-A2 Clinical and Laboratory Standards Institute, 2008. 2008.
8. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by aspergillus. *Clin Infect Dis.* 2000;30:696-709.
9. Fattahi A, Sayyahfar S, Lotfali E, Ghasemi R, Mortezaeian H. Aspergillus flavus endocarditis and meningitis in a child with marfan syndrome. *Curr Med Mycol.* 2020;6(4):70-74.
10. Tattevin P, Bruneel F, Lellouche F, et al. Successful treatment of brain aspergillosis with voriconazole. *Clin Microbiol Infect.* 2004;10(10):928-931.
11. Kulanthavelu K, Prasad C, Reddy YVK, Mahadevan A. Holohemispheric invasive aspergillus granulomatous cerebritis of the brain. *World Neurosurg.* 2020;134:170-175.
12. Haroon K, Taher T, Alamgir A, et al. Cerebral aspergillosis in an immunocompetent patient: a case report. *Bangladesh J Infect Dis.* 2017;4(2):52-55.
13. Leroy J, Vuotto F, Le V, et al. Invasive rhino-orbital-cerebral aspergillosis in an immunocompetent patient. *J Mycol Med.* 2020;30(3):101002.

14. Turki AT, Rashidi-Alavijeh J, Dürig J, Gerken G, Rath PM, Witzke O. Successful treatment of cerebral aspergillosis: case report of a patient with T-cell large granular lymphocytic leukemia (T-LGL). *BMC Infect Dis.* 2017;17(1):797. doi:[10.1186/s12879-017-2877-8](https://doi.org/10.1186/s12879-017-2877-8)
15. Hiraga A, Aoki R, Nakamura K, Kuwabara S. Rapidly progressive aspergillus meningitis successfully treated with voriconazole and corticosteroids. *Neurol Sci.* 2018;39(3):577-579.

**How to cite this article:** Jalali PA, Lotfali E, Rezaei K, et al. Promising effects of corticosteroid treatment in combination with antifungal agents in a patient with *Aspergillus* meningitis. *Clin Case Rep.* 2022;10:e05993. doi: [10.1002/ccr3.5993](https://doi.org/10.1002/ccr3.5993)