

LETTER TO THE EDITOR

OCULAR COMPLICATIONS CAUSED BY *Cryptococcus gattii* AFLP4/VGI MENINGITIS IN AN IMMUNOCOMPETENT HOST

Changhua, June 15, 2016

Dear Editor

The *Cryptococcus gattii* complex has been recognized as an endemic pathogen since the 1990s and has caused multiple outbreaks since then<sup>1</sup>. Cryptococcal meningitis (CM) is a globally occurring invasive mycosis associated with significant morbidity and mortality<sup>2,3</sup>, including papilledema and visual loss<sup>1,3</sup>. We present a case of CM caused by *C. gattii sensu stricto* (AFLP4/VGI) that was complicated by visual loss under the continuation of antifungal therapy (AFT).

A 45-year-old woman complained of neck stiffness and headaches for two weeks. She was admitted to a community hospital. Her opening intracranial pressure (ICP) was 230 mmH<sub>2</sub>O. A cerebrospinal fluid (CSF) study revealed the following values: protein, 53 mg/dL (reference range, 10–45 mg/dL); glucose, 62 mg/dL (45–75 mg/dL); white blood cells (WBCs), 84/mL (<5/mL); lymphocytes, 79% (63–99%); and neutrophils, 17% (0–2%). The *Cryptococcus* antigen titer in both CSF and serum were positive, at 1:8 and 1:64, respectively. With the impression of a diagnosis of CM, the patient received intravenous amphotericin B (AmB; 0.7 mg/kg/day) with flucytosine (5-FC; 100 mg/kg/day) for two weeks, followed by intravenous AmB (1 mg/kg/day) for another two weeks. Then, a consolidation therapeutic regimen with oral fluconazole (FLC; 450 mg/day orally) was administered for the following three months. She was rehospitalized because of seizures, unfavorable CSF data, and progression of the brain MRI finding. Her opening ICP was 180 mmH<sub>2</sub>O. A follow-up CSF study revealed the following values: protein, 140 mg/dL; glucose, 68 mg/dL; WBCs, 468/mL; lymphocytes, 69/mL; and neutrophils, 16/mL. The cryptococcal antigen titer in CSF was 1:128, and staining the CSF with India ink revealed positivity for the pathogen. Hence, CM was still present. We prescribed a combination therapy for reinduction, but she noticed floaters and blurred vision (ou) since the first day of the second admission. Her eye findings were as follows: visual acuity, no light perception (ou), and fungus with: papilledema, subhyaloid hemorrhage, and retinal hemorrhage. Her fundus color photograph and follow-up MRI scan are presented in Figure 1. The cryptococcal isolate 44-6 was identified as *C. gattii sensu stricto* according to the findings of the culture using canavanine-glycine-bromothymol blue medium. Molecular identification by sequencing the *URA5* gene revealed that the isolate was genotype AFLP4/VGI, representing the recently described species *C. gattii sensu stricto*<sup>4</sup>. She received consolidated oral FLC (450 mg/day) at home in the following years. No new neurological sequelae were found after a follow-up period of 3 years, except for visual loss.

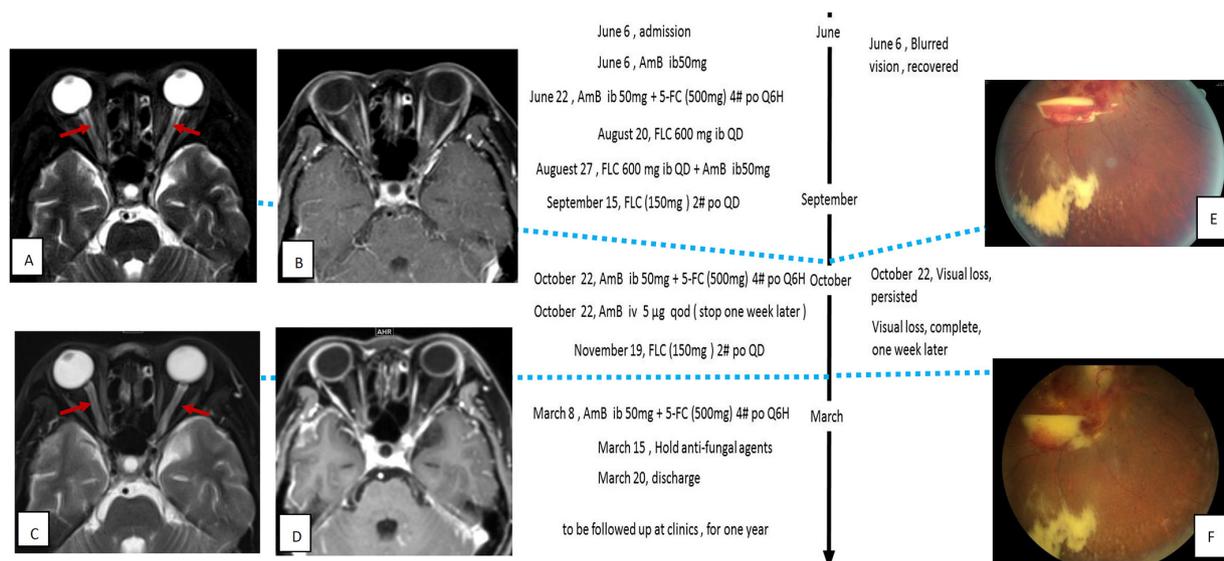
To our knowledge, this is the first case report to describe ocular complications of CM caused by *C. gattii* AFLP4/VGI under continuation of AFT in Taiwan. In general, *C. gattii* AFLP4/VGI tends to produce larger and more numerous cryptococcomas in the central nervous system<sup>1</sup>. Seaton *et al.* suggested that the high rate of visual loss in immunocompetent patients with *C. gattii* AFLP4/VGI infections may reflect immune-mediated optic nerve dysfunction in *C. gattii* meningitis caused by either compression due to arachnoid adhesions or edema and inflammatory cell-mediated damage<sup>5</sup>. The optic nerve lesion can be due to direct destruction by this pathogen<sup>5</sup> or indirectly caused by increased intracranial pressure<sup>6</sup>. Our case was treated in accordance with the recommendation in the guidelines<sup>3</sup>, but her eye condition continued to deteriorate, most likely due to optic nerve damage (Fig. 1). Use of corticosteroids could be recommended for immunocompetent patients with severe *C. gattii sensu stricto* (AFLP4/VGI) meningitis.

CM due to *C. gattii* AFLP4/VGI can cause significant neurological morbidities, including ocular complications. We emphasize that physicians should pay attention to the possible complications of CM in patients, even during active AFT.

Chang-Hua CHEN(1)  
Shao-Hung WANG(2)  
Wei Liang CHEN(3)  
Wang-Fu WANG(4)  
San-Ni CHEN(5)

- (1) Changhua Christian Hospital, Division of Infectious Disease, Department of Internal, Changhua, Taiwan.  
(2) National Chiayi University, Department of Microbiology, Immunology and Biopharmaceuticals, Chiayi City, Taiwan.  
(3) Changhua Christian Hospital, Department of Medical Imaging, Changhua, Taiwan.  
(4) Changhua Christian Hospital, Department of Neurology, Changhua, Taiwan.  
(5) Changhua Christian Hospital, Department of Ophthalmology, Changhua, Taiwan.

**Correspondence to:** Chang-Hua Chen, Division of Infectious Disease, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan. E-mail: 76590@cch.org.tw



**Fig. 1** - Timeline of the *C. gattii* AFLP4/VGI infection, a serial brain magnetic resonance image, and serial fundus color photographs. The magnetic resonance image (A, B, October) and 1-month follow-up magnetic resonance image (C, D, November) were analyzed. The axial, short tau inversion recovery (STIR) image (A, C) and axial, fat-suppressed, post-contrast, T1-weighted image (B, D) demonstrate a faint but increased signal in both the non-expanded optic nerves (A, arrow). Enhancement (B) in the follow-up STIR image (C, arrow) shows progression of the high-signal change and mild atrophy of both the optic nerves. The lesser enhancement (D) is consistent with progression of visual loss. The initial fundus color photograph (E, October) and 1-month follow-up fundus color photograph (F, November) show retinal hemorrhage.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## ETHICS STATEMENTS

This study was approved by the Changhua Christian Hospital (CCH) Institutional Review Board [CCH IRB No. 131221] for human subjects

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## AUTHORS CONTRIBUTION:

CHC and WFW conceived and designed this study. CHC and WFW analyzed the data, wrote the paper, prepared figures and/or tables. CHC, WFW, SNC, and WLC served this patient. SHW performed the experiments. All authors reviewed drafts of the paper.

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