

Endogenous endophthalmitis caused by *Cryptococcus neoformans* Var. *Gattii* mimicking choroidal tumor: From positron-emission tomography/computed tomography to histopathology

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A 60-year-old immunocompetent female with pneumonia history about 10 years ago suffered from blurred vision overall survival for 3 weeks. Common cold with headache and unintentional body weight loss was also noted recently. Choroidal detachment simulating choroidal tumor was observed in the temporal quadrant. The 18F-fluoro-2-deoxyglucose (FDG) positron-emission tomography/computed tomography (CT) scan showed focal, mild to moderate FDG uptake in the left lateral orbit, and an enhanced lesion was seen on the recent CT scan. The suspicious choroidal tumor became larger in a week. Phacoemulsification, vitrectomy, and retinal biopsies were performed. Histochemical study of the retinal specimens established the diagnosis of endogenous cryptococcal endophthalmitis. Vitreous culture yielded *Cryptococcus neoformans* var. *gattii*. Systemic and

topical voriconazole eliminated the infection. In the literature, endogenous endophthalmitis caused by *C. neoformans* var. *gattii* has not been reported in detail. The key to successful management lies in early diagnosis. If clinical improvement could not be achieved after conventional management and imaging studies have failed to yield a definite diagnosis, retinal biopsy can be considered.

Key words: 18F-fluoro-2-deoxyglucose positron-emission tomography/computed tomography scan, *Cryptococcus neoformans* var. *gattii*, endogenous endophthalmitis, Grocott's methenamine silver stain, periodic acid-Schiff stain

Cryptococcus neoformans, an encapsulated yeast, usually is found in the soil and affects immunosuppressed patients. However, it still can affect immunocompetent hosts.^[1-3] The primary site of infection is the lung, but the disease can disseminate through bloodstream to other organs. *Cryptococcus neoformans* can be divided into var. *neoformans* and var. *gattii*.^[4] These two varieties have quite different characteristics in human infection.

C. neoformans var. *neoformans* is present mainly in the soil, especially in pigeon droppings. It occurs worldwide but appears to be more common in Europe. Besides, it usually induces infection in the immunocompromised patients. In contrast, *C. neoformans* var. *gattii* mainly distributes in the tropics and subtropical regions. It has been isolated from wood, bark, leaves, and plant debris of the Eucalyptus trees.^[4] The infection occurs more frequently in immunocompetent people.

Ocular involvement usually occurs after cryptococcal meningitis and may represent hematogenous dissemination or extension through the leptomeninges. Intraocular manifestation includes vitritis, choroiditis, chorioretinitis, exudative retinal detachment, neuroretinitis, and endophthalmitis.^[1-3]

We report an immunocompetent case of endogenous endophthalmitis caused by *C. neoformans* var. *gattii* mimicking choroidal tumor and present the serial images

Access this article online	
Quick Response Code:	Website: www.ijo.in
	DOI: 10.4103/ijo.IJO_543_16

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Manuscript received: 05.10.16; Revision accepted: 27.05.17

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Cite this article as: Lin CJ, Chen WL, Lin JM, Tien PT, Tsai YY. Endogenous endophthalmitis caused by *Cryptococcus neoformans* Var. *Gattii* mimicking choroidal tumor: From positron-emission tomography/computed tomography to histopathology. Indian J Ophthalmol 2017;65:526-8.

including 18F-fluoro-2-deoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) scan and histochemical examination.

Case Report

A 60-year-old immunocompetent female with previous history of pneumonia about 10 years ago suffered from painless and progressively blurred vision overall survival for 3 weeks. Common cold with headache and body weight loss were also noted recently. She lived in the suburban area in the middle Taiwan and was a homemaker. Her best-corrected visual acuity (BCVA) was 20/25 in the right eye and counting finger at 20 cm in the left eye. A slit-lamp examination revealed mild lid edema, mild conjunctival congestion, mild corneal edema, anterior chamber cells 3+, cataractous lens, vitreous cells 3+, grade 2 vitreous haze in the left eye. Marked subretinal exudate simulating medium-sized choroidal mass (10–15 mm diameter) was observed in the temporal quadrant [Fig. 1a]. B-scan sonography was remarkable for a lenticular-shaped mass (6.6 mm × 11.8 mm) arising from the choroid with low to medium echogenicity [Fig. 1b]. Fluorescein and indocyanine angiography demonstrated blocked fluorescence within the choroidal lesion without late pooling [Fig. 1c]. Her right eye was normal.

Her routine serum biochemistry was within normal limits. Rapid plasma regain, anti-Toxoplasma IgM, anti-Toxoplasma IgG, HIV, and HLA-B27 were negative. Erythrocyte sedimentation rate (ESR) and C-reactive protein were elevated. Antinuclear antibody (ANA) was checked using indirect fluorescent antibody method to rule out the systemic autoimmune disorders which was positive at 1:160 dilution with a nucleolar pattern. Leukocytosis (14700/ μ l) with a left shift (neutrophil count: 78.8%) and elevated high-sensitivity C-reactive protein (1.34 mg/dL) and ESR (32 mm/1 h) were found. Chest X-ray revealed decreased volume of right lung, pleural fibrosis, and thickness in the right middle lung field. The pulmonologist was consulted. Her breath sound was normal and the right apical pleural thickening was just the resolved lesion of the previous pneumonia. No active pneumonia was diagnosed. The brain CT was unremarkable, but orbit CT showed thickened left eyewall. Because malignancy could not be ruled out, The FDG PET/CT scan was arranged which showed focal, mild to moderate FDG uptake in the left lateral orbit [Fig. 1d], and an enhanced lesion on the recent CT scan, possibly of benign etiology, weak-avid malignancy or partial volume effect. PET scan showed no uptake in the brain. Approximately symmetrical, mild to moderate increased FDG uptake was noted in the mediastinum and bilateral bronchopulmonary regions, possibly due to inflammation or physiological aging changes. Sinus CT showed mucus retention in the left frontal sinus, bilateral ethmoid, and maxillary sinuses. The otolaryngologist was consulted and sinusitis-related headache was diagnosed.

Because the choroidal detachment became larger in 1 week, phacoemulsification, vitreous sampling for cultures, and retinal biopsies by endodiathermy to achieve hemostasis and cut by vertical scissors in a precise manner were performed. The yellow-whitish viscous substance was found adherent to the undersurface of the retina which could not be aspirated by the extrusion needle easily during vitrectomy. The mass

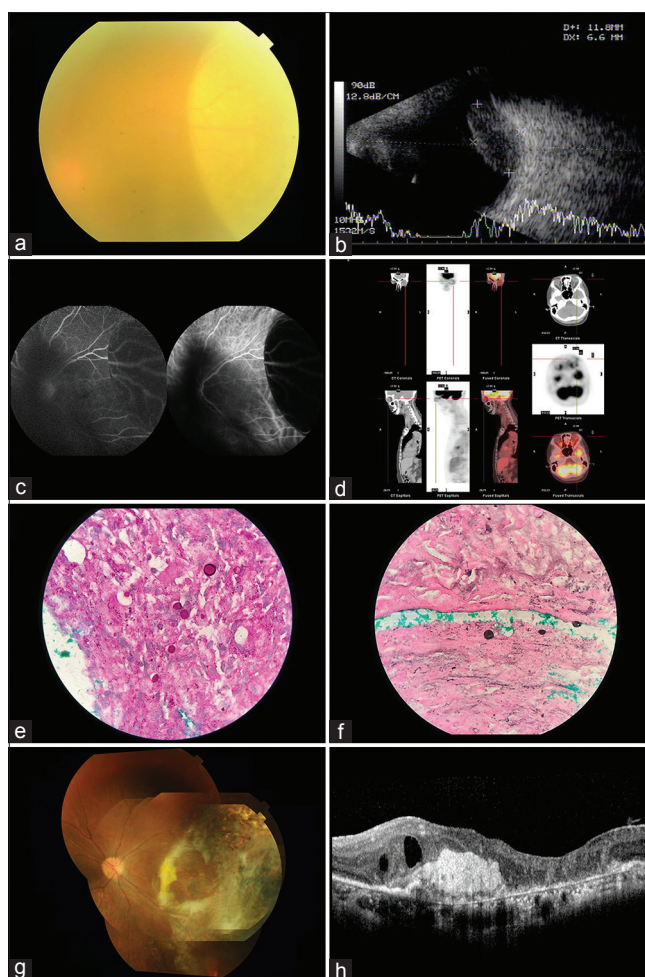


Figure 1: (a) Marked subretinal exudate simulating choroidal tumor in the temporal quadrant. (b) A lenticular-shaped mass arising from the choroid with low to medium echogenicity. (c) Fluorescein angiography and indocyanine green angiography demonstrated blocked fluorescence without late pooling. (d) 18F-fluoro-2-deoxyglucose positron-emission tomography/computed tomography scan showed focal, mild to moderate 18F-fluoro-2-deoxyglucose uptake overall survival. (e) Periodic acid–Schiff stain revealed cryptococci in the retinal specimens. (f) Grocott's methenamine silver stain revealed cryptococci. (g) The retina remained attached with cicatricial change. (h) High-definition-optical coherence tomography demonstrated intraretinal cysts and disorganization of retinal layers

lesion was sticky, so it could not be excised completely. The intact 1 mm × 1 mm × 1 mm retinal sections were flattened and spread on the filter paper. Then, laser retinopexy around the biopsy sites was applied, possible peripheral breaks were checked, and silicone oil was placed for tamponade.

Histopathological study including periodic acid–Schiff (PAS) [Fig. 1e] and Grocott's methenamine silver (GMS) [Fig. 1f] stains revealed cryptococci of the retinal specimens. Besides, Gram's stain found that yeast-like structures and vitreous cultures (Sabouraud dextrose agar, micro cell culture, and brain–heart infusion with blood agar) all yielded *C. neoformans* var. *gattii* which established the diagnosis of endogenous cryptococcal endophthalmitis. Cryptococcal antigen of blood was also positive ($\times 1:64$). Polymerase chain reaction was not done. The infection specialist was consulted. Her sputum

acid-fast stain was negative and *Mycobacterium tuberculosis* culture showed no growth. CD3 total T-cells, CD19 total B-cells, CD4 helper/inducer cells, CD8 suppressor/cytotoxic cells, and CD4/CD8 ratio were all within normal range to confirm her immunocompetent status.

Intravitreal voriconazole injection was not used due to silicone oil tamponade. Systemic voriconazole 400 mg daily was given for 1 month and tapered to 300 mg daily for another 5 months. The infection subspecialist decided to stop voriconazole; however, her blood cryptococcal antigen elevated to $\times 1:64$. Hence, voriconazole was given for another 6 months to eliminate the infection. The retina remained attached in the postoperative period. Silicone oil removal was performed 1 year postoperatively. The patient has been followed up for 2 years. The retina remained attached with cicatricial change [Fig. 1g]. High-definition-optical coherence tomography (OCT) demonstrated intraretinal cysts and disorganization of retinal layers due to scar formation [Fig. 1h]. Her BCVA improved to 20/1000. Cryptococcal antigen of blood was 1:16x.

Discussion

C. neoformans is a ubiquitous encapsulated yeast found largely in the soil. The main route of infection is through the inhalation of dust with cryptococci into lung and cause pneumonia, then transfer to other organs hematogenously, such as the central nervous system, skin, bone, prostate, and eye. Endogenous cryptococcal endophthalmitis is rare in the absence of simultaneous central nervous system involvement.^[1-3,5,6]

Intraocular cryptococcal infection is characteristic as granulomatous inflammation, so it could present as choroidal tumor-like lesion. Choroidal tumors might be presented as serous choroidal detachment and vice versa. Therefore, choroidal detachment simulating choroidal tumor should be carefully studied to access the possibility of malignancy.

A positive ANA test result meant that autoantibodies were present. In a person with signs and symptoms, this might suggest the presence of an autoimmune disease, but further evaluation was required to assist in making a final diagnosis. The ANA of this patient was false positive.

Apart from CT and MRI, PET/CT can assess both anatomical morphology and cell metabolism in one single examination. Standardized uptake value-positive lesions are clinically correlated and evaluated for the suspicion of malignancy versus other benign causes, including inflammation, infection, and muscle movement during examination. In this case, only mild to moderate FDG uptake in the left lateral orbit was noted; hence, benign etiology was most likely. PET/OCT may not be useful to rule out malignancy completely as inflammatory lesions can also have positive uptake value. Since the choroidal mass increased in size within a week, endogenous endophthalmitis was suspected and vitrectomy with retinal biopsy was carried out.

In the literature, endogenous endophthalmitis caused by *C. neoformans* var. *gattii* has not been reported in detail

in ophthalmology literature.^[6] The possible risk factors in this patient included her weaker pulmonary defense against infection (previous pneumonia history) and present illness (common cold and unintentional body weight loss). The possible primary route of infection was the respiratory system and the disease disseminated through bloodstream to the eye. Special histochemical stains (GMS, PAS, alcian blue) and electron microscope of the retinal specimens showing budding form of *C. neoformans* and thick polysaccharide capsule can confirm the diagnosis. Moreover, the vitreous culture yielded *C. neoformans* var. *gattii* makes the final differentiation from *C. neoformans* var. *neoformans*.

The key to successful management of endogenous cryptococcal endophthalmitis lies in early diagnosis, which is difficult because it can mimic choroidal tumors. If conventional investigations and treatment of endogenous endophthalmitis (which includes smears and cultures, intravitreal antibiotics) fail to archive clinical improvement, retinal biopsy can be considered to rule out cryptococcus and other organisms. The blood test for cryptococcal antigen could be checked first before proceeding to surgery in cases of suspicious choroidal tumors enlarging in a relatively short time. Voriconazole, a new generation triazole, has been studied to be a powerful weapon against cryptococcal endophthalmitis with good safety profiles and few side effects.^[7,8] The patient was also followed up regularly by the infection subspecialist and did not develop serious side effect after 12 months of voriconazole treatment. After vitrectomy, systemic and topical voriconazole treatment, the infection was well controlled and her vision improved.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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