

# Cerebral Cryptococcosis Mimicking Brain Tumor in an Elderly Woman Who was Seronegative for Human Immunodeficiency Virus Infection: The Need for A Multidisciplinary Approach

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## Abstract

Cerebral cryptococcosis is a deadly fungal infection, particularly, for elderly patients. Sometimes, the presentation of cerebral cryptococcoma mimics brain malignancy. It might confound diagnosis. To combat the disease progression, urgent and aggressive therapies with multidisciplinary support are beneficial. We report the case of an elderly woman with seronegative human immunodeficiency virus infection and cerebral cryptococcoma; she presented with symptoms that mimicked those of a brain tumor. She was treated with antifungal agents. We emphasize the need for multidisciplinary collaboration and care to manage cerebral cryptococcosis in elderly patients. (J Intern Med Taiwan 2016; 27: 163-169)

**Key Words: Cerebral cryptococcosis, Amphotericin B, Fluconazole, Multidisciplinary team**

## Introduction

The incidence of malignancy has been observed to increase with age. Brain tumors have been diagnosed more frequently in recent years as more individuals are undergoing neuroimaging for various reasons<sup>1,2</sup>. Taiwan became a World Health Organization-defined aging society in 1993, and the percentage of its population aged  $\geq 65$  years (aged population) is predicted to double by 2017<sup>3,4</sup>. The

presentation of cerebral cryptococcosis (CC), sometimes, mimics brain malignancy; this could confound diagnosis. In contrast to brain malignancy, CC can be cured; however, CC is not easily differentiated from brain malignancy<sup>5</sup>. Treatment for patients with CC requires an active collaboration of diverse specialists forming a multidisciplinary team (MDT); such a team could expedite communication concerning the required treatment, enable team members to share observations and perspectives,

and enhance their ability to care for patients. The MDT approach has emerged as a way of providing comprehensive medical care by bringing together professionals from a wide range of disciplines in a coordinated and effective manner<sup>3</sup>. Ben-Ami R et al. proposed an MDT model for management of invasive fungal disease, which aimed at facilitating communication among consultants, adherence to clinical pathways, and optimized use of resources available at each center<sup>3</sup>. This case report illustrates the challenges of managing CC in an elderly patient by using the MDT approach.

## Case Report

A 67-year-old, married Taiwanese woman experienced headache for many years, which was followed by the onset of left face weakness for 1 day. The characteristics of her headache were as follows: visual anesthesia score of 6–7/10<sup>6</sup>, duration of 1–2 hours, frequency of 2–3 times/day, aggravated by exercise, and relieved by rest. The headache was

not related to posture, cough, or exertion. The headache became more severe and frequent (2 times/day) without nausea and vomiting. Initially, she visited a local hospital, and brain computed tomography (CT) was performed. It revealed several hypodensities at the right parietal lobe. As brain tumor was suspected, she was referred to our institution for further management. Upon admission, she was afebrile; however, she had headache. Results of the laboratory-based tests conducted upon admission were within normal limits. Further, chest radiography performed upon admission revealed no significant abnormalities. The patient denied having a family history of cancer, environmental exposure history (including contact with decayed wood from tree bark, trunk hollow, soil, or pigeon droppings), or any remarkable travel history. On the first day following admission, her headache persisted. Brain magnetic resonance imaging (MRI) was performed (Figure 1A), and Grade III–IV astrocytoma was suspected. Therefore, stereotactic brain biopsy was conducted

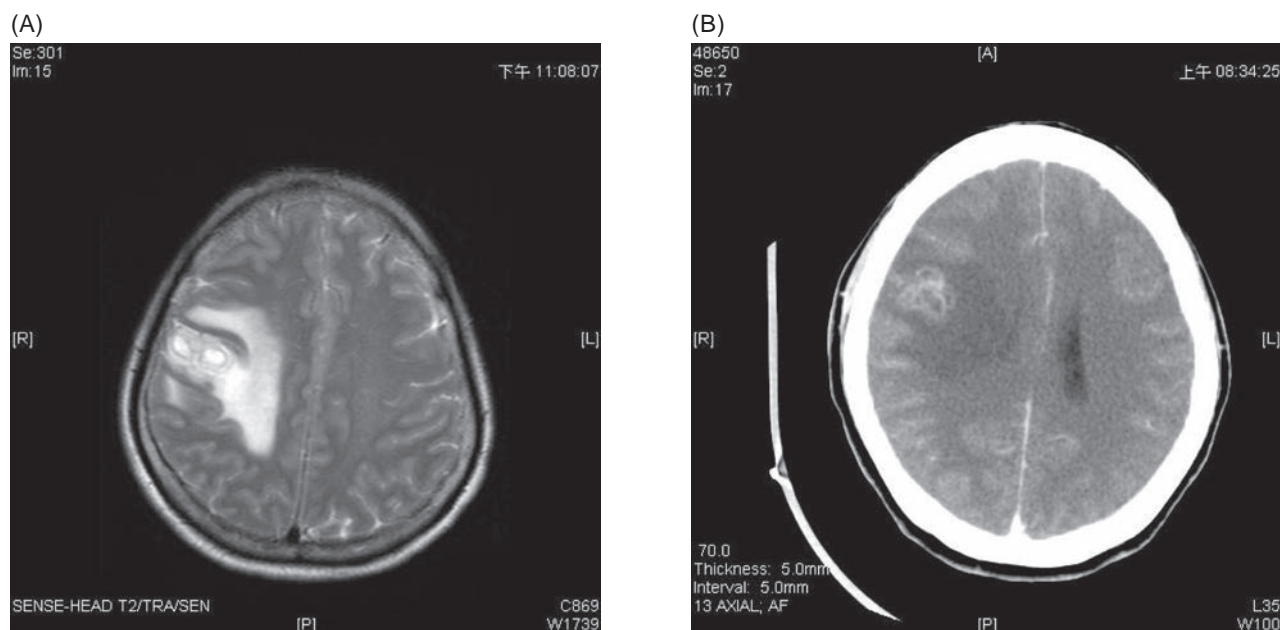


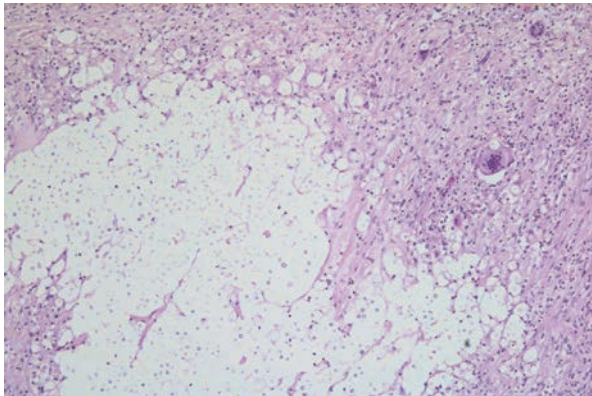
Figure 1. (A) The image of the brain during the first admission. Magnetic resonance imaging of the brain reveals presence of a cystic lesion (2.3 x 2.0 cm) in the right frontal lobe with perifocal edema and mass effect observed with ipsilateral lateral ventricle compression and ipsilateral pending uncus herniation. (B) The image of the brain at re-admission. Computed tomography of the head reveals a lobulated peripheral enhancing lesion, 2 x 1.5 cm in size, in the right frontal lobe with extensive perifocal edema in the fronto-parieto-temporal lobe.

for tissue examination, which revealed an irregular and rim-enhanced lesion located at the right parietal lobe. After 1 week of admission, she was discharged from our hospital before the results of the pathologic examination were obtained.

The patient experienced a sudden tonic–clonic seizure after going home. She was re-admitted to our hospital for seizure control and pre-operation survey. On admission (day 0) to the emergency department, laboratory-based tests were conducted that revealed the following: white blood cell count,  $18,500/\text{mm}^3$ ; erythrocyte sedimentation rate (ESR), 88 mm/h; and C-reactive protein level, 11.0 mg/dL. Urgent CT of the head was performed that revealed a lobulated, peripheral, enhancing lesion in the right

frontal lobe (Figure 1B). Cerebritis, abscess, or tumor was suspected. Craniotomy and total excision of the mass lesion were performed on the first day of admission, and the operative findings indicated a subcortical brain tumor. Microscopic histo-pathological examination of the tumor revealed numerous cryptococci (Figure 2). The serum sample tested positive for cryptococcal antigen (titer, 1:512). Subsequently, the diagnosis of cryptococcosis was confirmed. The patient was transferred to the intensive care unit and referred to an infectious disease specialist. Intravenous amphotericin-B (AMB) (0.7 mg/kg per day) with flucytosine (5-FC) (100 mg/kg per day for four times a day) was prescribed immediately. The MDT approach was subsequently ini-

(A)



(B)

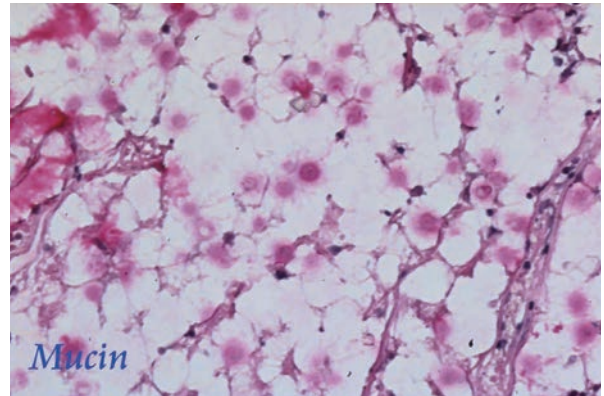
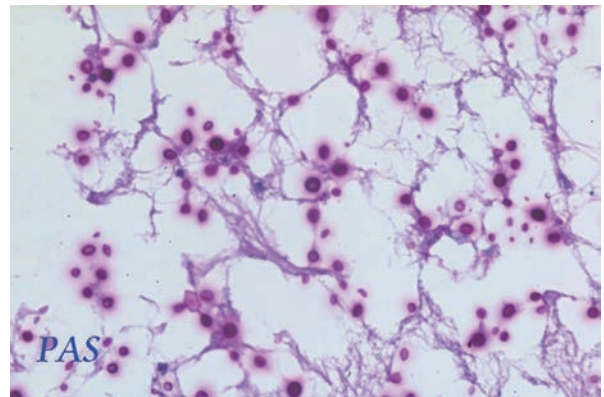


Figure 2. (A) Typically, in cryptococcosis cases, numerous round microorganisms (arrow) are present. The brain parenchyma elsewhere reveals dense lymphoplasmacytic infiltration in the fibrous stroma with granulomatous inflammation. (B) Subcortical brain tumor about 2 x 2 x 3 cm in size. The microscopic histo-pathological examination reveals cryptococcosis (arrow), which is manifested as the presence of numerous round microorganisms; this is confirmed by mucin stain. The brain parenchyma elsewhere reveals dense lymphoplasmacytic infiltration in the fibrous stroma with granulomatous inflammation. (C) Subcortical brain tumor about 2 x 2 x 3 cm in size. The microscopic histo-pathological examination reveals cryptococcosis (arrow), which is manifested as numerous round microorganisms are present; this is proved by Periodic acid-Schiff stain. The brain parenchyma elsewhere reveals dense lymphoplasmacytic infiltration in the fibrous stroma with granulomatous inflammation.

(C)



tiated; the team included medical, surgical, and intensive care members. The team discussed the patient's progress every morning, viewed her test results, and established the treatment plan for that day (Table 1). Her blood sample was tested to detect anti-human immunodeficiency virus (HIV) antibodies and serum *Toxoplasma* antibodies; the results were negative. Tissue obtained during biopsy was cultured, and *Cryptococcus neoformans* isolation was conducted based on the gross and microscopic appearance, biochemical test results, and growth at 37°C (Figure 3). The minimum inhibitory concentration of *C. neoformans* is shown in Additional File 1. During the entire course, the patient was closely monitored for signs and symptoms of AMB and 5-FC toxicity; additionally, complete blood count, ESR, electrolyte levels, and kidney and liver function were monitored weekly. With the stabilization of her general condition, she was transferred to the regular hospital ward and treated by a simplified MDT approach. Each morning, the medical-surgical team visited the patient to discuss her condition. The clinical pharmacist recommended that the concurrent use of fluconazole (FLC) and haloperidol was

not beneficial; it might result in increased haloperidol exposure and risk for QT interval prolongation. The nutritionist provided individualized nutritional supplements. The social workers provided the economic support. The clinical symptoms subsided 2 weeks later. Consolidation therapy including oral administration of FLC (600 mg per day) was provided for the following 3 months after she was discharged. She received maintenance therapy of oral FLC at home in the following year; her clinical condition stabilized and no recurrence or relapse was observed.

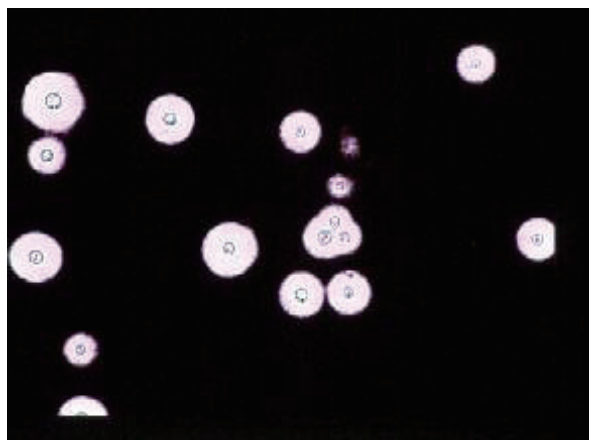


Figure 3. The tissue culture shows a yeast-like fungus.

Table 1. Members of the multidisciplinary team and their roles

Members of multidisciplinary team	Role
Infectious diseases specialist, team leader	primary care, prescribe antibiotics
Neurosurgery	craniotomy and total excision of the mass lesion
Intensive care unit specialist	intensive care
Medical radiologist, p.r.n.	interpretation of CT and MRI findings
Pathologist, p.r.n.	interpretation of pathological specimen
Clinical microbiologist, p.r.n.	interpretation of microbiological specimen
Clinical pharmacist	adjust medications, including antibiotics
Social workers	economic support
Clinical pastoralist	mental support
Nutritionist	nutritional supply
Nurse practitioner, coordinator	primary care
Primary registered nurse	nursing care

Abbreviation: CT, computed tomography; MRI, magnetic resonance imaging; p.r.n., pro re nata.

## Discussion

To our knowledge, this is the first case report to focus on a multidisciplinary approach to manage CC in an elderly patient in central Taiwan. The incidence of cryptococcosis is not rare in Taiwan. The average incidence of cryptococcosis was around 4.7 per million person-years in Taiwan<sup>5,7,8</sup>. Lin reported many risk factors for cryptococcosis<sup>9</sup>; however, approximately 15.4% of patients with seronegative HIV infection who developed cryptococcosis were not predisposed to any underlying diseases, such as liver diseases, diabetes mellitus, malignancy, kidney diseases, solid organ transplantation<sup>10</sup>. Consistent with this observation, our patient had no such history; however, she was old. It is remarkable that successful treatment of CC was achieved with an MDT approach. Based on our experience, an MDT approach has the potential to correct fundamental problems that are associated with patient care; for example, the clinical pharmacist suggested to avoid the concurrent use of FLC and haloperidol, which might have led to insomnia. Implementation of daily visits of multidisciplinary doctors and expansion of attendees for the multidisciplinary review committee meetings improved care related to heart transplantation<sup>11</sup>. The National Quality Forum reported that the healthcare system in United States is fragmented, complex, and inefficient; the failure to coordinate care could increase costs, errors, and complications<sup>12</sup>. As shown in O'Daniel's study, good communication encourages collaboration and helps prevent errors<sup>13</sup>. The MDT approach is paramount to decrease errors and length of stay as well as improve patient experience. Wensing et al.<sup>14</sup> reported overall improvement in outcomes when an MDT approach was incorporated compared with conventional care. Kim *et al.* observed that daily visits by an MDT were associated with lower mortality among medical intensive care units<sup>15</sup>.

An MDT is especially important for patients

with complex conditions such as CC. During CC treatment, incomplete communication can lead to inaccurate usage of antifungal agents and other postoperative hemodynamic management problems. Implementing the MDT approach for management of patients with CC at our institution has significantly benefited the quality of care being delivered; the comprehensive care model helps facilitate active participation and daily collaboration of diverse specialists. It mobilizes consultation and necessary ancillary services to produce valuable results. Additionally, this model has improved the long-term survival of patients with CC. By caring for the patient with the MDT approach, we experienced benefits similar to those shown in previous studies<sup>3,14-15</sup>.

Our case report accentuates the need for adopting the MDT approach to cure CC in elderly patients. Despite the medical and surgical interventions, CC causes immense morbidity in patients who survive. Owing to the awareness of our patient's need for effective multidisciplinary cooperation and support, we continued to monitor her condition for 6 months and achieved a positive outcome.

We emphasize that physicians should consider the possibility of cryptococcoma in patients presented with brain tumor-like symptoms. Further, there is a need for multidisciplinary collaboration and care to cure CC in elderly patients.

## Acknowledgement

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Additional File 1. Minimum inhibitory concentration of different antibiotics on *Cryptococcus neoformans*

Drug	Minimum inhibitory concentration
Amphotericin B	0.5 µg/mL
Fluconazole	16 µg/mL
Flucytosine	8 µg/mL
Itraconazole	0.12 µg/mL
Posaconazole	0.25 µg/mL
Voriconazole	0.06 µg/mL

Reference method is the one recommended by the Clinical and Laboratory Standards Institute (M27-A3) for broth dilution and antifungal susceptibility testing for yeasts.

# 非愛滋老人以類似腫瘤表現的腦部隱球菌感染： 需要整合治療

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## 摘 要

在目前癌症越來越被重視的時代，隱球菌感染有時候表現的很像癌症。因為腦部隱球菌感染這樣的病患，疾病變化多端，需要積極治療並且整合不同科別共同治療。在這裡我們報導一位非愛滋病患的女性老人，以類似腫瘤表現的腦部隱球菌感染的病例個案，接受兩周 amphotericin B 治療，接著使用口服的 fluconazole 治療三個月，病患恢復得相當好。臨床醫師應當在診斷癌症病患時，多考慮其他的鑑別診斷，例如隱球菌感染。我們的經驗強調，挽救腦部隱球菌感染，需要整合跨領域的醫療團隊共同治療，更能成功地拯救這樣的病患。