Successful Medical Treatment of Multiple Cryptococcomas : Report of a Case and Literature Review

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Abstract

We report a 35 year old man diagnosed as having CNS cryptococcosis with multiple cryptococcomas, presenting with headache, papilloedema and impaired mental function in a previously healthy man. Cerebrospinal fluid (CSF) examination revealed lymphocytic pleocytosis with low glucose level. Gram's stain, acid fast bacilli stain and Indian ink examination were all negative. CSF cryptococcal antigen was positive, however, several fungal cultures were negative. Early cranial CT scan showed focal cerebritis over the right temporal lobe while subsequent imaging studies showed multiple contrast-enhancing masses with severe surrounding brain oedema over bilateral frontoparietal areas. Brain biopsy showed cryptococcal granulomatous lesions. Treatment was successful with antifungal agents and steroids without surgical removal.

Key word : Cerebral Cryptococcosis, Cryptococcoma, CNS Cryptococcosis

Cryptococcus neoformans is the most common fungal central nervous system (CNS) infection. This encapsulated yeast has a worldwide distribution and is associated with soil enriched by pigeon droppings. Infections are mainly meningitis, but meningoencephalitis or cryptococcal mass are not uncommon(1-6).

Cryptococcal meningitis is found in association with human immunodeficiency viral infection and it ranks first in the opportunistic CNS infection in patients with AIDS(7). Initial infections occur through inhalation of yeast from the environment. The inflammatory reaction to inhaled cryptococci produces a primary lung-lymph node com-

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plex, which usually limits the spreading of organisms from this site. Most pulmonary infections are asymptomatic and often resolve slowly over weeks or months with or without treatment. Cryptococcus can remain dormant in the lung or lymph node for a long period after the initial infection and reactivates when the host defenses become weakened. *Cryptococcus neoformans* then spreads from the lung and intrathoracic lymph node to circulate into the blood stream. When distant infection occurs, the most common site to be involved is the CNS.

We report a patient with cryptococcal meningitis who also developed multiple cerebral cryptococcomas in spite of antifungal therapy in a previously healthy man, and review of the literature.

CASE REPORT

A 35 year-old man was admitted to Siriraj Hospital Medical School, Bangkok, Thailand in May 1998 with severe headache for 2 weeks and behaviour change for 3 days. He had a history of irritability, disinhibition, insomnia and severe amnesia and he could not even recognize his wife. Fever was observed one day prior to the admission. There was no history of tuberculosis in the family.

Physical examination revealed a body temperature of 38.5° Celsius, pulse rate of 84/min, respiration rate of 18/min, and blood pressure of 170/100 mmHg. He was drowsy with a Glasgow Coma Score (GCS) of 12/15 (E_4 V_3 M_5). He had no oral thrush, no skin lesion and no superficial lymphadenopathy. Examination of the cardiovasular, respiratory and alimentary systems were unremarkable. Neurological examination revealed stiffneck but Kerning's sign was negative. Papilloedema was prominent bilaterally. He had no definite motor weakness. Deep tendon reflexes were hyperreflexia.

Investigations showed seronegative for HIV with a CD_4 T-lymphocyte count of 430/mm^3 and immunological studies for T cell function were normal. CT brain scan demonstrated focal cerebritis at the right temporal area (Fig. 1A, 1B) and gyral enhancement of bilateral frontoparietal lobes with some oedema (Fig. 2). Initial lumbar puncture revealed an opening pressure of 440 mmH_2O, white blood cell of 110 cells/mm^3 mainly lymphocyte. CSF sugar of 46 mg/dl (blood sugar 117 mg/dl), protein of 149 mg/dl. Gram stain, acid fast bacilli (AFB) stain and Indian ink preparation were all negative. Cultures of CSF were negative but CSF cryptococcal antigen was positive at a titer of 1:16. Treatment of cryptococcal meningitis with intravenous amphotericin B (40 mg/day) was given initially. Repeated lumbar puncture was performed for reducing intracranial pressure. Cryptococcal antigen persisted at a low titer of 1:16 on June 23, 1998. and Indian ink preparation and CSF culture for fungus remained negative. His symptoms improved initially followed by fluctuation of consciousness. Amphotericin B was given to a total dose of 500 mg, but switched to oral fluconazole 400 mg per day due to its renal toxicity. Four weeks after admission, he had left hemiparesis. Repeated CT brain scan showed gyral enhancement and contrast enhancing lesions (size of 2x2 cm) at the right parietotemporal region, bilateral frontoparietal regions and hypodensity lesions over the left basal ganglia and the right thalamus (Fig. 3, 4).

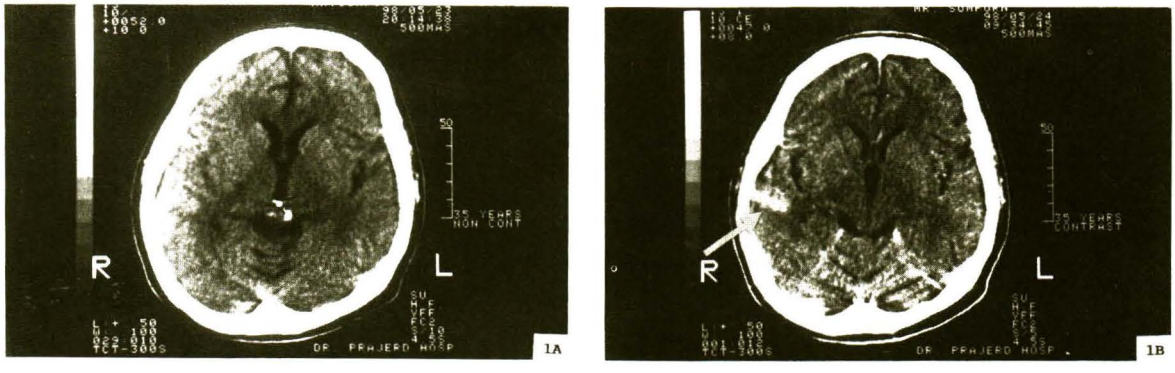

Fig. 1. Pre- (A) and post- contrast (B) axial CT scans showed a gyriform enchancement in the right temporal lobe with minimal surrounding oedema. An identical change with a lesser severity in the left temporal cortex was also noted.

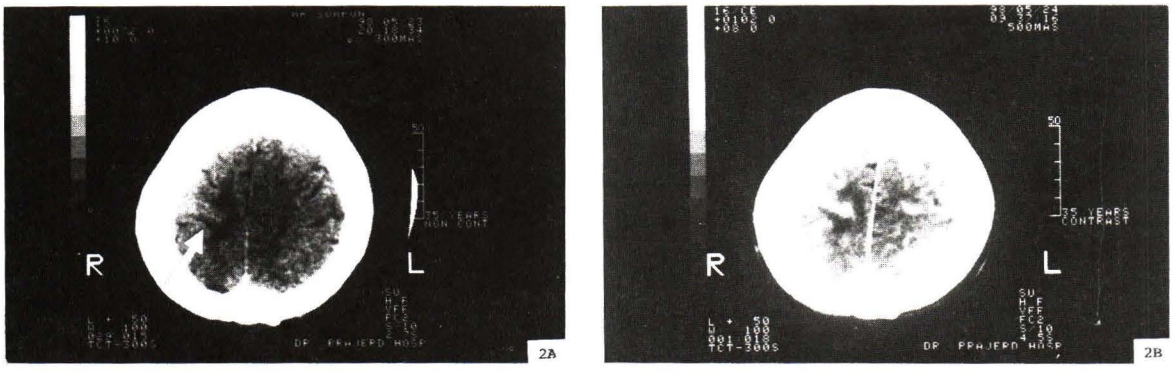

Fig. 2. Non-contrast (A) and contrast-enhanced (B) axial scans at higher level also demonstrated gyral enhancement of bilateral frontoparietal lobes with some oedema.

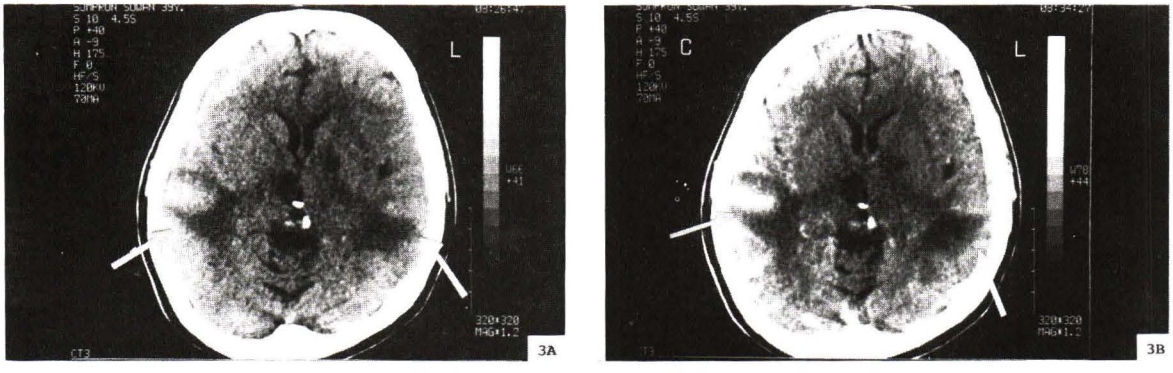

Fig. 3. The non-contrast (A) and contrast-enhanced (B) axial scans 2 months later revealed progressive oedematous change of bilateral temporal lobes. The right cortical enhancement was more pronounced. There were increased low density areas without enhancement at right anteromedial thalamus and left basal ganglia.

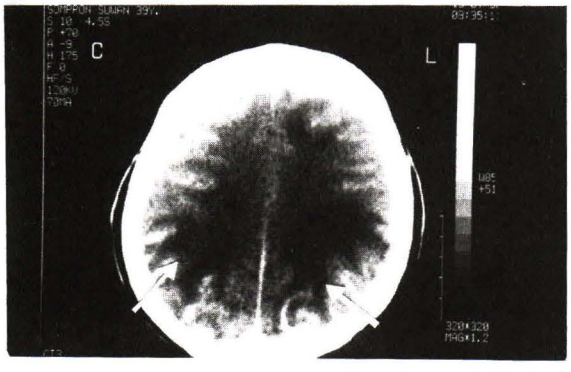

Fig. 4. Postcontrast axial CT scan at an upper level exhibited more diffuse white matter oedema and increased both gyriform and sulcal enhancement bilaterally.

Treatment with intravenous amphotericin B was reinstituted. However, definite diagnosis of cryptococcosis was confirmed by brain biopsy at the right temporal area. Pathological sections revealed granulomatous lesion of the meninges and numerous encapsulated yeast cells were found, confirming the diagnosis of cerebral cryptococcosis (Fig. 7). His consciousness and hemiparesis deteriorated after the operation. Hyperventilation and intravenous dexamethasone were given instantly. Magnetic resonance imaging (MRI) of the brain revealed hypersignal area in T_1W and T_2W over the left basal ganglia, right thalamus, and hyposignal area in T_1W with enhancement in the left basal cistern, interpeduncular cistern, pineal region, and right temporoparietal region (Fig. 5, 6). These were compatible with

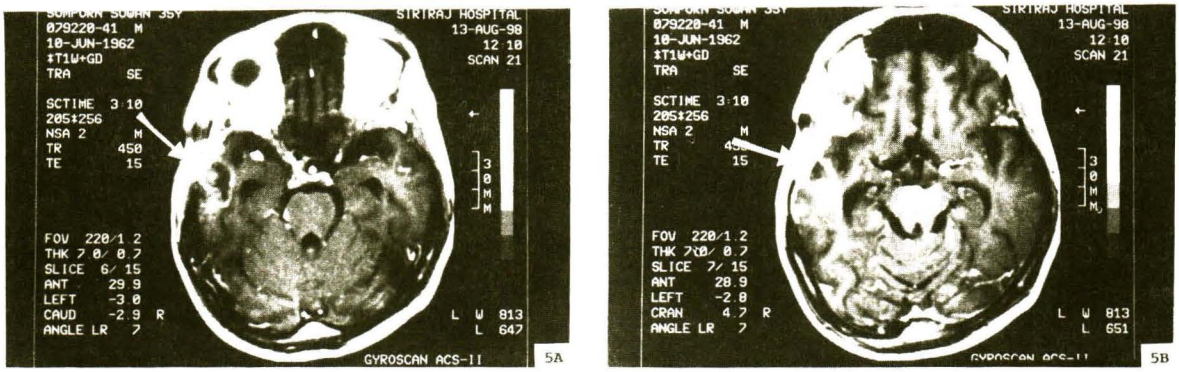

Fig. 5. (A, B) Axial postcontrast T1 - weighted scans showed subtle meningeal enhancement over the right temporal lobe with an ill-defined contrast enhancing area that represented cerebritis (compare to CT scan in Fig. 3).

Noted also an inflammatory lesion in the interpeduncular fossa and diffuse oedema of left temporal lobe.

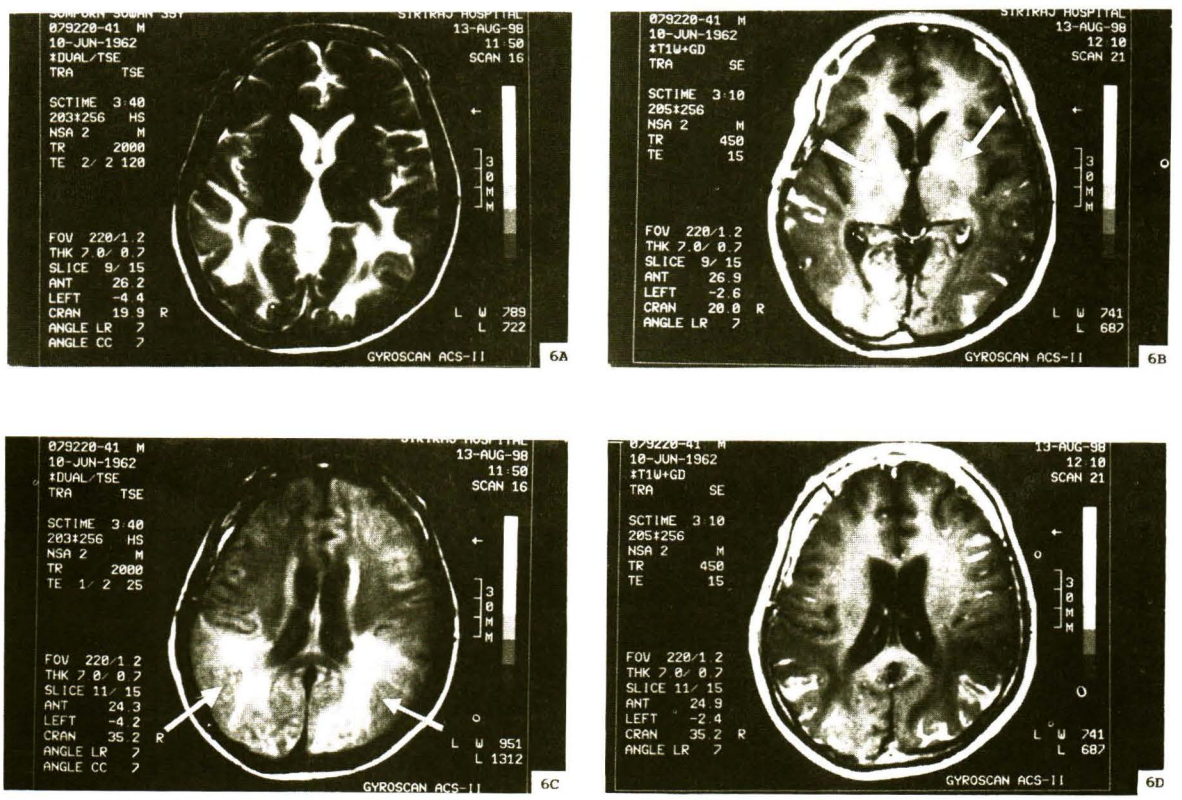

Fig. 6. Axial T2 - weighted (A), proton density (C) and postcontrast T1 - weighted images, at the same level of A and B, C and D. The bilateral diffuse oedema in the temporal, occipital and parietal lobes presented with thickened, enhancing leptomeninges and extension of inflammatory infiltration deep into the sulci which indicated meningitis. There were other two small nodular enhancing lesions in the right thalamus and left basal ganglia.

multiple cryptococcomas. Magnetic resonance angiography (MRA) of the intracranial and neck vessels showed no occlusion or abnormal vessels.

He was treated with amphotericin B for 8 weeks to a total dosage of 1,500 mg. He was finally extubated and his left hemiparesis improved and maintenance treatment with itraconazole 200 mg/day was given. Follow-up CT brain scan revealed marked reduction of the lesions except the left basal ganglia. He was discharged home on September 23, 1998, in the self-ambulation state with normal mentation. Repeated lumbar puncture showed WBC of 37 cells/mm^3 with low CSF sugar, slightly increased CSF protein, and negative CSF cryptococcal antigen.

Review of literature

Cryptococcus neoformans infection can occur both in immunocompetent and immunocompromised hosts. Since the report of acquired immunodeficiency syndrome (AIDS), the incidence of CNS cryptococcosis has increased tremendously. In Thailand, cryptococcal meningitis ranks second to tuberculosis in AIDS patients. The incidence rate of cryptococcal meningitis as an opportunistic infection is approximately 24 per cent in AIDS patients, especially the one with CD_4 count below 100/mm^3. In non HIV cases most patients have the predisposing factors such as corticosteroid therapy or underlying diseases but some patients may not have any such factors.

Cryptococcus neoformans is divided into two varieties, i.e. *C. neoformans* var. neoformans and *C. neoformans* var gattii. Serotypes B and C are more likely to cause disease in nonimmunocompromised hosts and to invade brain parenchyma, causing cerebral mass or cryptococcomas. The disease caused by var. neoformans occurs throughout the world and var. gattii is found mainly in tropical and subtropical areas(9,10,12).

Cryptococcal meningitis should be included in the differential diagnosis of chronic meningitis syndrome. Its symptoms last from days to a few months; prolonged duration is more common in a nonimmunocompromised host(6).

Meningoencephalitis is the most common presentation of CNS cryptococcosis. The common initial symptoms are headache and fever, however, these may be the only clinical manifestations of cryptococcal meningitis especially in some patients with AIDS. Nausea and/or vomiting, neck stiffness, disturbance of consciousness and the impairment of higher mental functions (memory, language, and cognitive processes) are also often found at initial presentation and are more frequently present in nonimmunocompromised hosts than in patients with AIDS(8,9). Central nervous system cryptococcosis is reported more frequently among males. Chronic meningitis is caused by tuberculosis, cryptococcosis and other infectious or noninfectious. The presentation of headache with no other definite focal neurological deficits may make it difficult to distinguish intracerebral mass lesions from meningitis. CNS cryptococcosis and cerebral toxoplasmosis may cause similar clinical manifestations(7).

Papilloedema, commonly found in nonimmunocompromised patients leads to the suspicion of intracranial mass lesions . Cranial nerve palsies are also frequently found in CNS cryptococcosis; the third, fourth and sixth cranial nerves are commonly affected.

Cranial imaging should be done in patients with papilloedema before performing lumbar puncture. Abnormal enhancing lesion over the right temporal area was demonstrated in the first cranial CT study of our patient. This could be early brain abscess or focal cerebritis. Lumbar puncture was done and revealed high openning CSF pressure (440 mm H_20) with lymphocytic pleocytosis (wbc 110 cells/mm^3), an elevated protein level (149 mg/dl), a low CSF-blood glucose ratio (46/117 mg/dl), negative Indian ink preparation, negative Gram's stain, negative AFB stain, and CSF culture and polymerase chain reaction for tuberculosis were all negative. However, cryptococcal antigen was positive at a titre of 1:16.

Cerebrospinal fluid findings of cryptococcal meningitis have been well documented. Most cases have a predominant mononuclear pleocytosis, ranging between 20-500 cells/mm^3. In immunocompromised hosts, especially those with AIDS or who are receiving high dose corticosteroid, very low or even normal CSF leukocyte count may be found. The proportion of polymorphonuclear leukocytes is variable, usually well below 50 per cent. Eosinophilic pleocytosis is rarely seen. CSF protein levels are generally elevated and the glucose levels are mostly reduced.

The essential laboratory tests for diagnosis of CNS cryptococcosis are direct microscopy, culture of CSF and serodiagnosis. Indian ink preparation is the easiest technique with a sensitivity rate of 60-80 per cent (more than 90 per cent in immuno-

compromised hosts). CSF cultures are usually positive in 75 to 90 per cent. The isolation of organism from the CSF may not be successful and a large volume of CSF (10 to 30 ml) should be taken for culture. Positive culture is the gold standard for the diagnosis of CNS cryptococcosis, but usually takes several days. Serological test is important for a rapid diagnosis.The latex agglutination test for cryptococcal polysaccharide antigen is both sensitive and specific in more than 90 per cent of patients[15,16]. Cryptococcal antigen may be positive in the early phase of infection, even when the culture is negative. A titer of 1:8 or greater is considered positive, but any titers are significant if the proper control is applied. False positive tests can be due to other infection such as disseminated *Trichosporon beigelii* infection, paravertebral bacterial infection and positive rheumatoid factor. False negative tests are uncommon, but can occur in the early stage of infection with a low burden of organisms in the CSF and as a prozone phenomenon resulting from antigen excess. Titers during therapy often fall but they are not valuable markers to predict the success of treatment. Haemocultures are positive in more than one half of the patients in disseminated cryptococcosis.

Elevation of intracranial pressure is found in more than 60 per cent of patients and a high opening pressure of above 400 mmH_2O is found more frequently in non-AIDS patients. Papilloedema and visual deficit are common in both immunocompetent and immunocompromised hosts. Other complications of cryptococcal meningitis include alteration of consciousness, impairment of higher mental function, cranial nerve lesions, focal neurological deficits visual deficits, seizure, hydrocephalus, cerebellar signs, decreased hearing and arteritis[6,9,13].

Difference in the clinical findings in cryptococcal meningitis between AIDS and non-AIDS patients is well established. In addition, Wachirutmanggur L et al showed that cryptococcal antigen in the CSF was very sensitive for the diagnosis of cryptococcal meningitis[17]. Meningeal and brain biopsies are sometimes needed for definite diagnosis. In addition to the usual histopathological techniques, specimens should be stained for fungi and cultured.

Cryptococcal intracerebral mass is a rare form of CNS infection due to *Cryptococcus neoformans*. It may be associated with meningitis and pulmonary involvement. The incidence of cryptococcal intracerebral mass associated with cryptococcal meningitis is about 4 to 25 per cent. The commonest symptom is headache and less frequently mental status change, weakness, seizure, nausea, vomiting, visual disturbance and unsteady gait. In autopsy reports, there were 4 per cent of cases without CNS symptoms. Moreover, asymptomatic intracerebral mass lesions may have been missed in patients who survived an episode of cryptococcal meningitis or disseminated cryptococcosis, if appropriate diagnostic tests were not done[18,21,23,35].

Cryptococcal mass lesions are found mainly in the cerebral cortex and the basal ganglia. Intraventricular cryptococcoma rarely occurs. Thirty-five per cent of patients with cryptococcoma have multiple lesions. Size of the lesions varies between 1 to 6 cm in diameter, but most are greater than 1 cm in diameter. The abnormalities demonstrated in CT scan include diffuse atrophy, hydrocephalus, diffuse brain oedema and mass lesions. Magnetic resonance imaging is more sensitive than CT scan in detecting these lesions[19,20]. Four basic morphology types of cryptococcomas were described in CT : abscess (9%), gelatinous mass (24%), fibrogranulomatous mass (15%) and mixed-type (43%). Cryptococcal granulomas may also appear hypodense or isodense and show little or no contrast enhancement in the CT scan.

The standard treatment of cryptococcal meningitis consists of intravenous amphotericin B (0.6 - 1.0 mg/kg/day, maximum 50 mg/day) for a minimum of 6 weeks. Flucytosine plus amphotericin B (150 mg/kg/day and 0.3 mg/kg/day, respectively) is as effective as amphotericin B alone but culture conversion is more rapid with the combination, However, flucytosine alone has no benefit[25]. A four-week combination regimen was found to be successful for those patients without underlying diseases or neurological complications[27]. Fluconazole has been shown to be as efficacious as amphotericin B alone in treatment of early or mild, uncomplicated cases[26,28,29]. In addition, itraconazole is also useful in the treatment of cryptococcal meningitis and cryptococcosis, however, it cannot penetrate into the CSF as well as fluconazole[24]. The current recommendation for management of cryptococcal meningitis in AIDS and non-AIDS patients includes initial therapy with amphotericin B (0.7 mg/kg/day) with or without flucytosine (100-150 mg/kg per day) for two or more weeks as an induction regimen, then switch to oral fluconazole 400 mg per day or itraconazole 400-600 mg per day

for 8-10 weeks. Treatment should be continued for at least 6 weeks until evidence of CNS infection (symptoms and abnormal CSF parameters, positive CSF or blood culture, unremitting antigen titers) have disappeared. Persistence of mild CSF pleocytosis and protein elevation may be acceptable at the termination of therapy. However, it is safe to continue treatment until three or four consecutive weekly CSF cultures are sterile.

At present, flucytosine is no longer available in Thailand, a problem in the management of cases not responsive to monotherapy. Maintenance therapy should be given in complicated cases or in AIDS patients to prevent relapse[30,32,34]. There are three regimens of maintenance treatment : the first regime is amphotericin B intravenously 1 mg/kg once weekly, the second is oral itraconazole 200-400 mg/d, and the third is oral fluconazole 200 mg/d. Intravenous amphotericin B once weekly is less effective than oral itraconazole and fluconazole in maintenance therapy.

Amphotericin B can cause a variety of adverse effects, including fever, chills, nausea, vomiting, hypokalemia, anaemia, phlebitis and nephrotoxicity. Nephrotoxicity from amphotericin B is reduced with a low dose regimen of 0.3 mg/kg per day. Flucytosine has toxicity to bone marrow, liver, and gastrointestinal tract. Sodium supplementation (e.g. intravenous saline) and avoiding dehydration, sodium depletion and diuretic drugs appear to be a safe and effective means of reducing the risk of nephrotoxicity associated with amphotericin B administration[31]. During the course of treatment, serial blood tests should be done weekly or twice weekly, which include complete blood count, blood urea nitrogen, creatinine, electrolytes, magnesium. If nephrotoxicity occurs, amphotericin B must be discontinued. Liposomal amphotericin B has less adverse reactions than the conventional amphotericin B. Liposomal amphotericin is still in clinical trial, and the cost-effectiveness should be considered[33].

Cryptococcomas in the brain parenchyma are treated with antifungal chemotherapy alone if the lesions are small and multiple. However, large cryptococcomas (more than 3 cm in diameter) that are located in the surgically accessible areas warrant surgical removal. Occasionally these lesions enlarge during therapy because of inflammatory response or continuing growth[18].

The optimum length of medical therapy and the efficacy of systemic antifungal therapy in the management of cryptococcal intracerebral mass lesions require further study. Therefore, a prolonged course of systemic antifungal agents with close monitoring is appropriate at present. The intrathecal administration of antifungal drug is not effective and can cause clinical spinal arachnoiditis. Generally, there is no role for corticosteroid therapy.

Elevated intracranial pressure increase morbidity and mortality, should be treated with repeated lumbar punctures or intraventricular drainage[8,11]. If hydrocephalus occurs, a shunt should be inserted. The mortality rate for this condition is about 30-35 per cent and death is found in patients with altered consciousness, convulsion prior to treatment, a maximum systolic blood pressure more than 150 mmHg on admission, raised intracranial pressure, positive blood culture and CSF white cell count less than 20 cells/mm^3. Mortality may be reduced if efforts are made to lower intracranial pressure in those patients who present with factors of poor prognosis. In survivors, residual focal neurological deficits have been found in about 40 per cent of patients[8,10,11,22].

Among patients who do not have HIV infection, rates of relapse after initial treatment of cryptococcal meningoencephalitis range from 15 to 25 per cent. Patients with immunosuppression steroid therapy are associated with a greater chance of relapse. In patients with HIV infection, relapse increases to 50 per cent, warranting suppressive therapy. Relapses mainly occur within the first year of treatment, but may be as late as 30 months.

In conclusion, we presented a rare case of cryptococcal meningitis and multiple cryptococcomas in an immunocompetent host. Although repeated CSF examinations were negative for Indian ink preparations as well as fungal cultures, cryptococcal antigen was persistently positive, leading to a long course of antifungal drug administration. This resulted in a complete recovery without surgical removal.

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การรักษาคริพโตคอคโคมาหลายก้อนโดยไม่ต้องผ่าตัด : รายงานผู้ป่วย 1 ราย และทบทวนวารสาร

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ได้รายงานผู้ป่วยไทย อายุ 35 ปี ซึ่งได้รับการวินิจฉัยโรคว่ามีการติดเชื้อคริพโตคอคคัสของระบบประสาทส่วนกลางเป็นแบบคริพโตคอคโคมา ผู้ป่วยมีอาการปวดศีรษะรุนแรง ความดันในกะโหลกศีรษะสูง พร้อมทั้งมีอาการสับสนและหลงลืม. ผลการตรวจน้ำไขสันหลังพบว่ามีเม็ดเลือดขาวชนิดลิมโฟไซท์เพิ่มจำนวน และมีระดับน้ำตาลต่ำ ผลการตรวจย้อมสีโดยวิธีต่าง ๆ ไม่พบเชื้อ แต่ตรวจพบคริพโตคอคคอล แอนติเจนในน้ำไขสันหลัง ส่วนผลการเพาะเชื้อราหลายครั้งไม่พบเชื้อ การตรวจคอมพิวเตอร์สแคนของสมองเมื่อแรกรับพบลักษณะของภาวะสมองอักเสบบริเวณกลีบเทมเพอรัลข้างขวา ซึ่งต่อมากลายเป็นก้อนคริพโตคอคโคมาหลายก้อนในสมอง พร้อมทั้งมีภาวะสมองบวมน้ำอย่างมากโดยรอบ ผลการตรวจชิ้นเนื้อของสมองพบว่าเป็นแกรนูโลมาจากเชื้อราคริพโตคอคคัส. ผู้ป่วยได้รับการรักษาด้วยยาต้านเชื้อราและสตรีรอยด์พบว่าได้ผลดีคือ รอยโรคยุบหายไปโดยไม่ต้องผ่าตัดเอาออก.

คำสำคัญ : คริพโตคอคโคสิสของสมอง, คริพโตคอคโคมา, คริพโตคอคโคสิส ระบบประสาทกลาง

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