A Flow Chart Proposed for Early Diagnosis of Cryptococcal Infection as a Cause of Stroke

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Abstract- An 82 year-old woman had a transient ischemic attack and stroke of the left middle cerebral artery syndrome that turned out to be attributed to cryptococcal meningoencephalitis (CM). An initial presentation of central nervous system infection, such as fever and headache, was absent. It was masked by chronic use of corticosteroids and immunosuppressants for her rheumatoid arthritis. The diagnosis was made by the clinical setting of stroke-in-evolution and progression of hydrocephalus on the second brain imaging study. In this case, we discuss the atypical presentation of CM in an immunosuppressed patient and offer a flow chart for early diagnosis, thus improving outcome and survival rates.

Key Words: Cryptococcus, Stroke, Immunosuppressed, Afebrile, Stroke-in-evolution, Hyponatremia, Hydrocephalus

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INTRODUCTION

Cryptococcal meningoencephalitis (CM), presented as a sudden onset of focal neurological deficits, has been documented for at least four decades [(1)]. It implies that a concomitant vascular accident in the central nervous system (CNS) has occurred. Although non-invasive evaluation has shown a cerebral hemodynamic change during CM treatment [(2)], underlying CM may sometimes be missed as a cause of stroke initially when immunity is suppressed. As the strategy of treatment is quite different, early recognition of this underlying problem is crucial. Here, we report an immunosuppressed patient who had atypical manifestation of CM mimicked a stroke syndrome and also propose a flowchart for early diagnosis of CM when encounter an acute ischemic stroke.

CASE REPORT

An 82 year-old woman was taken to our emergency room after a left humerus fracture, caused by a fall. She was discharged from our ward under the diagnosis of transient ischemic attack of sudden dysarthria and numbness on the right face, hemibody and limbs, 3 weeks before the event. Left middle cerebral artery

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stenosis was confirmed by transcranial color-coded duplex sonography. After management with clopidogrel (75 mg/day), her symptoms and signs recovered within 12 hours, without recurrence. She had a 10-year history of type-2 diabetes mellitus, treated by insulin injections. She had also had chronic, stable hepatitis C for three years and rheumatoid arthritis, treated with corticosteroids and immunosuppressants (cyclosporine and hydroxychloroquine) for 8 months. She underwent orthopedic surgery and discontinued clopidogrel on the first day of hospitalization. Delirium state was noted during the first four days. Her laboratory data on admission included a peripheral white blood cells count (WBC) of 10500 per microliter (normal range 3600-11000), a segment/lymphocyte (S/L) ratio of 77/13, serum creatinine of 0.6 mg/dl (normal range 0.6-1.1 mg/dl), sodium of 126 meq/L (normal range 136-145 meq/L) and GPT of 61 IU/L (normal range 7-35 IU/L). She had improved mental status in the next 2 days. A sudden onset of drowsiness with right hemiplegia, conjugated eyeballs deviating to the left side and right upgoing plantar reflex occurred on the seventh day of hospitalization. Emergent cranial computerized tomography scan showed a mild hydrocephalus only though left supratentorial ischemic stroke was impressed clinically. Atrial fibrillation with rapid ventricular response and afebrile leukocytosis with WBC 21200 per microliter, S/L ratio of 87/7, serum C-reactive protein of 2.7 mg/dl (normal range 0-0.5 mg/dl), and sodium of 124 meq/L were noted. Her condition kept deteriorating with a gradually limited doll eye test in all directions despite reinstitution of clopidogrel and correction of hyponatremia. Brain magnetic resonance imaging (MRI) on the twelfth day of hospitalization revealed an increased ventricular size without parenchymal signal changes. (Fig. 1) Lumbar puncture was performed immediately, which showed an opening pressure of 110 mmH_2O and a clear appearance. Cerebrospinal fluid (CSF) analysis reported a red blood cell count of 130 per microliter, a white blood cell count of 78 per microliter with a neutrophil ratio of 14%, a lymphocyte ratio of 86%, a protein level of 184 mg/dl and a glucose level of 12 mg/dl (serum glucose 352 mg/dl). India ink demonstrated cryptococcal organisms. Since the amphotericin test dose provoked a drop in blood pressure, she received fluconazole (400 mg/day) intravenously. Sepsis with lung infection by Candida albican developed and she expired on the sixteenth day of hospitalization.

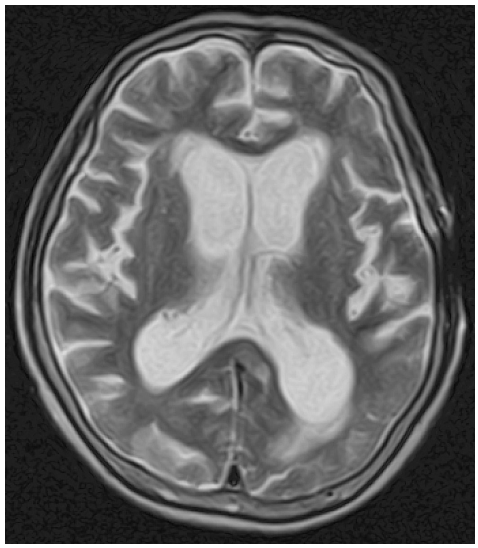

Figure 1. A T2-weighted axial non-contrast brain magnetic resonance image shows increased ventricular volume not proportionate to enlargement of cortical sulci.

DISCUSSION

In Taiwan, cerebral infarction accounts for 32% of CM cases[3]. The estimated mortality and morbidity in nonimmunosuppressed patients with CNS cryptococcosis are high, especially among those with cerebral infarcts. The major contributing factors to the poor outcome are delayed diagnosis, suboptimal initial antifungal therapy and relatively intact host immune responses[4]. Thus increased recognition and timely diagnosis of this condition may be critical to the improvement of outcome and survival rates though they are challenging in clinical practice.

CM comprises an infection of the subarachnoid space accompanied with involvement of the brain parenchyma, possibly through a microvascular endothelial transcellular crossing of the blood-brain barrier[5]. Its clinical features are not specific. Patients usually present with headache, fever, malaise and altered mental status,

over the course of several weeks. Signs are often absent, but may include meningism, papilloedema, cranial nerve palsies and other focal neurological deficits, and a depressed consciousness level[6]. Headache (91%) and fever (91%) are the most common symptom and sign respectively, in CM patients[7]. Regarding brain imaging of CM, CT scans may be normal or reveal enhancement, single or multiple nodules, cerebral edema, or hydrocephalus[6]. Hydrocephalus was found in 11 of 12 cases of CM with cerebral hemodynamic changes, in one study[2], and was consistent with the findings of a higher incidence of hydrocephalus among CM patients with cerebral infarction[3] than general CM[8], which is often not well-recognized on the first brain image of a stroke patient. The absence of left cerebral infarction on brain MRI was out of our expectation and realization. It may be a special presentation of ischemic penumbra which will be better demonstrated by perfusion-weight imaging but this technique was not available in our hospital. Although hyponatremia is not uncommon in elderly patients and stems from a variety of clinical disorders, including CNS infections, literature regarding CM-related syndrome stemming from inappropriate anti-diuretic hormones is limited[9]. Hyponatremia alone in a stroke patient has no sufficient indication for a CSF study before the workup of other more common medical causes. A flow chart to make early diagnosis of underlying CM in stroke patients is illustrated in Fig. 2.

Atypical presentation with afebrile headache in the stroke as an initial sign in CM had been reported[10]. There was also delayed revealing of CSF pleocytosis and cryptococcal microorganisms on the second lumbar puncture[10]. Another case of midbrain infarction, as an presentation of CM, experienced a stroke-in-evolution

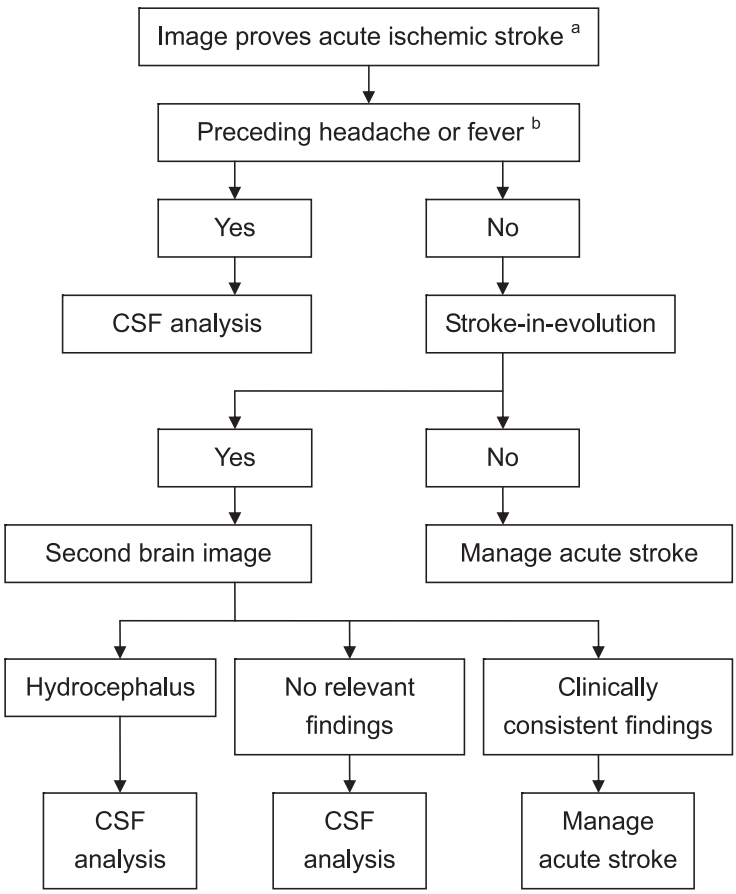

Figure 2. A flowchart for early diagnosis of CM as a cause of an ischemic stroke.
[a]: First brain imaging findings compatible with acute ischemic stroke.
[b]: Preceding headache or fever represents a recent onset of new headache or change of past headache behavior, with or without inexplicable fever.
CM: cryptococcal meningoencephalitis; CSF: cerebrospinal fluid.

with deteriorated consciousness into a comatose state, five days after stroke[11]. Considering the flow chart, either of them met one of the screening steps proposed on our chart and CSF study would be indicated for the critical diagnosis. In our case, the absence of headache and fever would pass the first screening step but the presence of a stroke-in-evolution and hydrocephalus on the second brain image would meet the next step. Lumbar puncture, as the flow chart indicates, was out of our expectation with normal opening pressure in this CM-related hydrocephalus. We think the chronic usage of corticosteroids was responsible for this by down-regulating Cryptococcus-induced vascular endothelial growth factor production[12] and may also have caused the absence of headache and fever.

With current medical care advancements, immunosuppressed patients will be increasingly encountered in the future. CM may be an atypical and critically-masked cause of stroke in these patients, and physicians should raise their awareness of this condition. Early diagnosis may be facilitated through the flow chart proposed here.

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