Cryptococcal Meningoencephalitis Presenting With an Unusual Magnetic Resonance Imaging Appearance

—Case Report—

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Abstract

A 61-year-old female with a past history of gastric cancer presented with altered mental status, a few seizures, and low-grade fever. Lumbar puncture revealed elevated cerebrospinal fluid (CSF) pressure, lymphocytic pleocytosis, elevated protein level, remarkably decreased glucose level, and presence of cryptococcal antigen. *Cryptococcus neoformans* was identified by India ink staining and culture of CSF. The patient was given antifungal agents intravenously and intrathecally. CSF findings improved and *C. neoformans* could not be detected in CSF one month after the onset. Cerebral sulcal hyperintensity was identified in the bilateral frontal and parietal lobes on fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) imaging one month after the onset, but no leptomeningeal enhancement was detected in the affected sulci on T₁-weighted MR imaging. The sulcal hyperintensity on FLAIR imaging developed in the bilateral temporal and occipital lobes 2 months after the onset. CSF findings obtained by lumbar puncture were within the normal range except for pressure. However, neurological deterioration and reconfirmation of *C. neoformans* in CSF indicated recurrent cryptococcal inflammation. The sulcal hyperintensity on FLAIR imaging may indicate a high CSF protein concentration in the subarachnoid space. Such cerebral sulcal hyperintensity is an unusual MR imaging finding of cryptococcal meningoencephalitis, and may be an early sign of procrastinating process or recurrent inflammation even if the findings of CSF obtained by lumbar puncture are normal.

Key words: *Cryptococcus neoformans*, cryptococcal meningoencephalitis, magnetic resonance imaging, cerebral sulcal hyperintensity

Introduction

Cryptococcosis is a relatively common mycotic infection of the central nervous system (CNS). The causative agent is the ubiquitous mycocyte *Cryptococcus neoformans*, which usually occurs in soil heavily contaminated with bird feces. Inhalation is the primary route of entry of *C. neoformans*, and the primary result is pulmonary inflammation. Hematogenous dissemination from the primary infectious focus occurs if the host immune defenses are inadequate, or if there is overwhelming exposure to the organism in immunocompetent hosts. Cryptococcosis of the CNS may result in meningitis, meningoencephalitis, encephalitis, and ventriculitis depending on the distribution of the organism and

the inflammatory response.³⁾ The clinical course may be fulminant or chronic and insidious depending on the host resistance. Here, we present a case of cryptococcal meningoencephalitis showing unusual findings on magnetic resonance (MR) imaging.

Case Report

A 61-year-old female with a past history of gastric cancer was hospitalized for the treatment of non-insulin-dependent diabetes mellitus and decompensated liver cirrhosis. She had confused mental status and suffered a few partial seizures of her face with fever ranging from 37°C to 38°C. She was referred to our neurosurgical department. She presented with consciousness disturbance of 3 according to the Japan Coma Scale (JCS) and meningeal irritation signs without focal deficits.

Initial fluid-attenuated inversion recovery (FLAIR) MR imaging (repetition time/echo time/inversion time = 6882/110/1700 msec) showed ventricular dilation with hyperintense areas (cerebrospinal fluid [CSF] edema) around the anterior horns of the lateral ventricle, and an ovoid high intensity area in the left occipital lobe (Fig. 1 left) which was slightly enhanced by injection of 0.2 ml/kg of gadopentetate dimeglumine (not shown). The intensity of the CSF was clearly reduced in the subarachnoid space over the brain surface (Fig. 1 right).

Initial lumbar puncture revealed increased CSF pressure of 20.5 cmH₂O, lymphocytic pleocytosis of 50/mm³, elevated protein level of 100 mg/dl, remarkably decreased glucose level of 6 mg/dl (blood sugar level of 189 mg/dl), and presence of cryptococcal antigen. *C. neoformans* was identified by India ink staining and culture of CSF. The serum titer of cryptococcal antigen was 1:2048. No other fungi except for *C. neoformans* and no bacteria were detected by CSF culture. The titers of various viral antibodies in the serum and CSF were not significantly elevated.

The white blood cell count in the peripheral blood was 9300/mm³ with 16.0% lymphocytes. The CD4+ and CD8+ lymphocyte counts were 905/mm³ and 274/mm³, respectively. The CD4+/CD8+ ratio was 3.30 (control 0.50–2.30). Lymphocyte blastogenic responses against phytohemagglutinin and concanavalin A were normal, so no significant immunodeficiency was thought to be present, and the titer of human immunodeficiency virus antibody was not measured.

The diagnosis was cryptococcal meningoencephalitis based on the findings of CSF examination and MR imaging. Intravenous administration of 0.25–1.0 mg/kg/day of amphotericin B and 100–200 mg/kg/day of flucytosine were given for 14 days, followed by intrathecal injection of 0.025–0.5 mg/day of amphotericin B for the next 7 days. She was also given 12–14 U/day of isophane insulin and 15–24 U/day of neutral insulin for control of blood sugar, 500 ml/day of branched chain amino acid supplement for hyperammonemia, and 100 mg/day of potassium canrenoate and 20 mg/day of furosemide for ascites. Her blood sugar level ranged from 100 to 300 mg/dl and serum NH₃ level from 40 to 200 µg/dl, and these levels were maintained during the administration of the agents. During the antifungal treatment, the CSF examination found pleocytosis from 38 to 1090/mm³, protein level from 58 to 114 mg/dl, and glucose level from 0 to 58 mg/dl (blood sugar level from 120 to 153 mg/dl). The CSF pressure ranged from 12 to 25 cmH₂O, and about 30–50 ml of CSF was drained at every lumbar

Fig. 1 Initial fluid-attenuated inversion recovery images showing ventricular dilation associated with cerebrospinal fluid (CSF) edema and an ovoid high intensity area (arrow) in the left occipital lobe (left). The signal from CSF in the subarachnoid spaces is clearly suppressed (right).

Fig. 2 Fluid-attenuated inversion recovery images about one month after the onset showing cerebral sulcal hyperintensity in the bilateral frontal and parietal lobes (right). The ventricles have progressively dilated and cerebrospinal fluid edema has also developed (left). Hyperintense areas of various sizes are also observed in the cerebral white matter (right and left).

puncture.

About one month after the onset, she suffered mental alternation and motor weakness of the bilateral upper and lower extremities. Follow-up FLAIR MR imaging showed cerebral cortical atrophy with moth-eaten appearance in the bilateral frontal and temporal lobes (Fig. 2 left) and cerebral sulcal hyperintensity localized in the bilateral frontal and parietal lobes (Fig. 2 right). T₁-weighted MR

Fig. 3 Fluid-attenuated inversion recovery images about 2 months after the onset clearly showing cerebral sulcal hyperintensity (arrows) in the bilateral temporal and occipital lobes (left). Cerebral sulcal hyperintensity was still present in the bilateral frontal and parietal lobes (center). T₁-weighted image shows no abnormally enhanced areas in the affected sulci (right).

imaging detected no leptomeningeal enhancement in the affected sulci (not shown). Multiple hyperintensity areas of various sizes were also observed in the cerebral subcortical white matter. The ventricles progressively dilated, and CSF edema extended despite intermittent spinal drainage of CSF (about 50 ml/day) two or three times weekly. CSF examination revealed pressure of 29.0 cmH₂O, cell count of 18/mm³, protein level of 50 mg/dl, and glucose level of 40 mg/dl (blood sugar level of 146 mg/dl).

Within the next few weeks, the patient's general condition gradually worsened with increase of blood sugar level to 250–450 mg/dl in spite of intensive insulin therapy and occurrence of general edema due to hypoalbuminemia (1.5–2.3 g/dl). Her poor general condition was accompanied by pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Her consciousness level deteriorated to 20–30 on the JCS, and a few partial seizures also occurred. CSF examination showed a pressure of 25 cmH₂O, cell count of 19/mm³, protein level of 39 mg/dl, and glucose level of 66 mg/dl (blood sugar level of 158 mg/dl). Recurrence of cryptococcal meningoencephalitis was suspected because *C. neoformans* was simultaneously identified in the CSF. The patient could not be given any additional antifungal agents since we feared that their side effects would significantly worsen her general condition. We could not obtain written informed consent for the surgical treatment of hydrocephalus because of her seriously poor general condition. Only intermittent spinal drainage of 50–100 ml/day two or three

times weekly was continued for the hydrocephalus.

About 2 months after the onset, follow-up FLAIR MR imaging showed that sulcal hyperintensity in the bilateral frontal and parietal lobes still persisted (Fig. 3 center), and was conspicuous in the bilateral temporal and occipital lobes (Fig. 3 left). T₁-weighted MR imaging detected no abnormally enhanced area (Fig. 3 right). The size of the lateral ventricle had slightly decreased compared to one month after onset, but the CSF edema was more extensive (Fig. 3 left). At this time, CSF examination showed increased pressure of 31.5 cmH₂O, cell count of 19/mm³, protein level of 32 mg/dl, and glucose level of 82 mg/dl (blood sugar level of 183 mg/dl).

Severe MRSA pneumonia caused respiratory insufficiency, and hepatorenal syndrome also developed despite intensive medical treatment. The patient died of significant cardiopulmonary insufficiency about 3 months after onset of the CNS cryptococcal infection. Autopsy was not performed.

Discussion

The present case of cryptococcal meningoencephalitis showed normal CSF findings except for pressure and negative culture of *C. neoformans* in the CSF, but abnormal findings progressively developed on MR imaging one month after treatment with antifungal agents. A few weeks after discontinuation of the antifungal agents, the patient's general condition (diabetes mellitus and liver cirrhosis) seriously worsened and her consciousness level decreased

and partial seizures occurred, indicating recurrent cryptococcal inflammation of the CNS. Reconfirmation of *C. neoformans* in the CSF also supported the recurrence of inflammation. Her general condition deteriorated and MRSA pneumonia occurred subsequent to discontinuation of the antifungal agents, so whether their side effects were involved remains unknown. Shunt operation for hydrocephalus could not be performed, so intermittent lumbar drainage was continued two or three times a week. The final outcome was poor. Retrospectively, intraventricular administration of small amounts of antifungal agents via an Ommaya reservoir into the lateral ventricle may have been more effective for this serious condition.²⁾

CNS cryptococcosis primarily manifests as meningitis, especially at the base of the brain. Hydrocephalus, both communicating and noncommunicating, is a common but nonspecific representation of CNS cryptococcosis. The infection provokes little inflammatory reaction, owing to the host immunity and to the immunosuppressive effect of the organism capsule. The main MR findings are dilated Virchow-Robin spaces, gelatinous pseudocyst, "cryptococcoma", and miliary enhanced nodules.^{1,4,6,8,10)}

Cryptococcal infection spreads along the Virchow-Robin spaces that accompany the perforating arteries, so the perivascular spaces may become distended with mucoid, gelatinous material that originates from the organism capsule.¹⁰⁾ The dilated Virchow-Robin spaces are located relatively symmetrically in the basal ganglia, midbrain, and deep white matter.^{1,6,10)}

Gelatinous pseudocyst represents a proliferation of the fungi and gelatinous capsular material in the Virchow-Robin spaces,^{4,10)} and is thought to be an "unreactive" form of meningoencephalitis preferentially located in the basal ganglia, thalami, midbrain, and dentate nuclei.⁹⁾ Gelatinous pseudocyst is a nonenhanced lesion and appears similar to CSF on all MR imaging sequences. Some cases appear as intermediate signal intensity on T₁-weighted imaging due to the presence of mucin or mucoid material that shortens the T₁ relaxation time.⁹⁾

"Cryptococcoma" has been used to describe cryptococcal parenchymal lesions with or without contrast enhancement, usually appearing as hypodense on computed tomography, low intensity on T₁- and high intensity on T₂-weighted imaging. "Cryptococcoma" includes gelatinous pseudocyst^{4,6)} and granuloma.^{1,9)} Granuloma can be observed throughout the brain parenchyma,^{1,10)} along the ependyma, in the choroid plexus,^{1,7)} and shows solid or ring-like enhancement with contrast medium.⁹⁾

Miliary enhanced nodules are observed in the brain parenchyma and leptomeningeal-cisternal spaces. These lesions are microabscesses containing amorphous debris and cryptococcal organisms encased by an outer fibrous capsule.⁸⁾ Gelatinous pseudocyst and cryptococcoma (granuloma) in the choroid plexus are relatively specific for CNS cryptococcosis.¹⁾

The cerebral sulcal hyperintensity on FLAIR imaging shown in the present case is an unusual MR imaging finding that has not been reported in cryptococcal meningoencephalitis. This finding may imply a high protein concentration in the CSF resulting from the inflammation in the localized subarachnoid space. FLAIR pulse sequences have an inversion time designed to nullify or markedly reduce the signal from CSF but to allow recovery of most of the brain magnetization. Long echo time versions can be used to produce heavy T₂ weighting. Changes of T₁ and T₂ relaxation times resulting from increased CSF protein concentration are more conspicuous on FLAIR imaging than on the standard T₁- and T₂-weighted spin-echo sequences. Heavy T₂ weighting preferentially suppresses the signal intensity in the brain parenchyma as compared with the abnormal CSF (because of differences in T₂ decay). Therefore, when an effective echo time is used in FLAIR sequences, the abnormal CSF with a high protein concentration becomes hyperintense compared to the brain parenchyma.⁵⁾ Our FLAIR sequence was always constant (repetition time/echo time/inversion time = 6882/110/1700 msec), and thus the appearance of sulcal hyperintensity indicates increased CSF protein concentration in the subarachnoid space caused by recurrent inflammation. Sulcal hyperintensity on FLAIR imaging may be an early sign of a procrastinating process or recurrent inflammation even if the findings of CSF obtained by lumbar puncture are normal.

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