INTRODUCTION

Influenza infection involving central nervous system lesions was reported previously and is hereafter referred to as “influenza-associated encephalitis/encephalopathy (IAE)” (1). Magnetic resonance imaging (MRI) findings of encephalitis associated with influenza A virus have been described previously (2). Reports of necrotizing encephalopathy in children with influenza. However, few reports have described multifocal hemorrhages in both cerebral hemispheres in adults with concomitant infection with influenza A and B. Here, we describe a case of influenza A- and B-associated encephalitis accompanied by numerous cerebral hemorrhages.

CASE REPORT

A 19-year-old woman with diabetes was admitted to another institution after 3 days of fever, cough, rhinorrhea, headache, and diarrhea. She was diagnosed with influenza types A and B subtypes H1N1 and H3, respectively, by nasopharyngeal swab. Other initial laboratory results were unremarkable. On the 8th day after symptoms developed, the patient developed respiratory distress and became unresponsive. Her blood count indicated thrombocytopenia (0.8 × 10^4 cells/mL) and anemia (8.5 g/dL). No peripheral blood smear was done. Prothrombin time and activated partial thromboplastin time were within normal limits. Fibrinogen was elevated and D-dimers were mildly elevated. A urine analysis showed proteinuria (4+) and hematuria (4+) with >50% dysmorphic red blood cells. A cerebrospinal fluid (CSF) analysis revealed monocytes (98%). Results of a reverse-transcription polymerase chain reaction (PCR) analysis were negative for influenza. Her serum creatinine was elevated to 5.7 mg/dL (normal, 0.9–1.3 mg/dL), so the patient was transferred to our institution and intubated for immediate hemodialysis. The patient remained neurologically unchanged. The results of a repeat CSF analysis remained unremarkable.
including negative results for enterovirus, herpes simplex virus, and human herpes virus 6 by PCR. Blood and urine cultures taken upon admission showed no growths. Her C-reactive protein level was elevated to 12.89 mg/dL (normal, ≤0.5 mg/dL).

MRI obtained on a 1.5T system (Intera, Philips Healthcare, Best, the Netherlands) on the 8th day of illness (Fig. 1) demonstrated bilateral thalamic lesions with slightly restricted diffusion (Fig. 1A) and diffuse leptomeningeal and pachymeningeal enhancement in both cerebral hemispheres (Fig. 1B, C) with hemorrhagic foci in both frontal lobes (Fig. 1D-F).

She was treated with intravenous acyclovir and oseltamivir, cephalosporin, and mannitol, and was placed on continuous renal replacement therapy.

Her consciousness level was consistently improving 1 week later but voluntary movement and speech remained impaired. A 2-week follow-up MRI on the same 1.5T unit demonstrated numerous newly-developed, dark, low-signal-intensity foci on gradient-echo images in subcortical white matter in both cerebral hemispheres, suggesting microbleeds (Fig. 2A, B). A susceptibility-weighted image was taken on a 3T MRI unit the same day which showed the striking appearance of multiple microbleeds (Fig. 2C, D). The diffuse leptomeningeal enhancement and thalamic lesions had disappeared (Fig. 2E), and the previously noted hemorrhagic lesions in both frontal lobes had evolved to the subacute stage (Fig. 2F).

The patient had recovered mental alertness at the 4-month follow up but some cognitive dysfunction and motor weakness remained.

Fig. 1. Hemorrhagic influenza-associated encephalitis in a 19-year-old woman. Magnetic resonance diffusion-weighted images taken on day 8 of illness show restricted diffusion (A) at both thalami (arrows), diffuse leptomeningeal (B) and pachymeningeal (C) enhancement (arrows), and a few hemorrhagic lesions (D) along the subcortical frontal white matter (arrows) showing T1 iso-signal intensity (E) and T2 high-signal intensity (F).
DISCUSSION

Several reports of neurological complications caused by influenza infection, especially those involving children, have been published. Kimura et al. (6) divided influenza-related brain changes into five categories based on computed tomography and MRI findings: normal (category 1), diffuse involvement of the cerebral cortex (category 2), diffuse brain edema (category 3), symmetric involvement of the thalamus (category 4), and post-infectious focal encephalitis (category 5). In our patient, bilateral thalamic lesions and persistent microbleeds were present, so we categorize this case as a combination of categories 1, 2, and 5.

Our patient showed reversible bilateral thalamic lesions and cerebral and meningeal enhancement, which are suggestive of meningoencephalitis. Several reports have described these findings in patients with influenza infection. However, our patient showed hemorrhagic foci diffusely scattered in both cerebral hemispheres. Only a few reports have described IAE in adults. Additionally, we found only three cases of acute hemorrhagic leukoencephalitis in a review of the literature (3-5).

MRI findings of encephalopathy with numerous microbleeds

Fig. 2. Follow-up magnetic resonance imaging (2 weeks later) demonstrates numerous dark low-signal-intensity foci on gradient-echo (A, B) and susceptibility-weighted images (C, D) in subcortical white matter in both cerebral hemispheres; micro- and macrobleeds, normalized bilateral thalamic diffusion restriction (arrows) (E), and small T1 (not shown)/T2 high-signal-intensity lesions (F) in the left frontal lobe; and late subacute hemorrhage (arrow).
in a patient with both influenza A and B infection have not been reported.

The pathogenesis of IAE is unclear because influenza is rarely detectable in CSF, and pleiocytosis is often absent. Autopsy findings are mainly obtained from patients with necrotizing encephalopathy. Such autopsy results show that the integrity of the blood-brain barrier (BBB) is an important prognostic factor (7), and disruption of the BBB promotes neuronal degeneration with severe clinical findings. The levels of proinflammatory cytokines and soluble cytokine receptors are increased in serum and CSF in patients with IAE. Toxic-mediated aberrant immune activation causing endothelial injury, microvascular angiopathy, and perivascular edema or release of inflammatory cytokines from virus-stimulated glial cells causing rapid breakdown of the BBB is responsible for the neurotoxic effects (8). However, the ineffectiveness of steroids or intravenous immunoglobulins in IAE does not support this mechanism of action.

Our patient showed neurologic deterioration with acute renal failure, mild anemia, thrombocytopenia, and elevated fibrinogen. These findings could suggest a mild form of thrombotic microangiopathy (TMA). TMAs encompass a groups of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia associated with hyaline thrombi (comprised primarily of platelet aggregations in microcirculation), and varying degrees of end-organ failure. TMA includes a spectrum of entities, such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Many genetic and secondary etiological predisposing factors have been described, including pregnancy, autoimmune disorders, cancer, drugs, antineoplastic therapy, bone marrow/solid organ transplantation, and infection. In the setting of infectious diseases, the association with Shiga or the Shiga-like exotoxin of Escherichia coli 0157:H7 or Shigella dysenteriae type 1-induced typical HUS is well known. However, an increasing body of evidence suggests that viruses may also trigger of TMA. TMA induced by influenza A infection has been reported several times during the recent H1N1 influenza epidemic (9). The exact pathophysiology of viral-associated TMA remains to be elucidated. However, direct endothelial cell injury appears to play an important role. This proposed TMA pathophysiology includes the production of IgG-type anti-ADAMTS13 inhibitors, which indicate TTP. Host genetic or ambient susceptibility factors may create a favorable environment for the virus to trigger a cascade of events that culminate in TMA (10).

Although our patient’s intermediate degree of thrombocytopenia and anemia did not completely fit the diagnostic criteria for TTP, HUS, or disseminated intravascular coagulation, and she progressively recovered without plasmapheresis or fresh frozen plasma transfusion, the possibility of such an association cannot be ruled out.

Treatment includes antiviral agents, such as M2 inhibitors (amantadine, rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir). The prognosis is not favorable. According to Morishima et al., many patients develop multiple organ failure, and rates of mortality (31.8%) and disability (27.7%) are high.

In conclusion, encephalopathy is a rare neurological complication of influenza infection in adults. Neuroimaging findings in a case of IAE may be normal, but abnormalities in severe cases can include diffuse cerebral edema, bilateral thalamic lesions, and multiple hemorrhagic lesions. IAE must be considered as a diagnosis in patients with an influenza-like illness and altered mental state. In addition, influenza-associated TMA should also be suspected when a patient presents with encephalopathy and acute renal failure, anemia, and thrombocytopenia. Radiologists and clinicians should be aware of this possibility and its appearance on MRI scans, particularly during an epidemic.

REFERENCES

인플루엔자 관련 뇌염에서 보인 다발성 뇌출혈: 증례 보고

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인플루엔자 관련 뇌염의 합병증 중 뇌출혈은 드문 합병증으로 인플루엔자 감염에 동반되는 가장 흔한 합병증 중 하나로 비해 희귀한 합병증으로 보고된 바 있다. 현재까지 인플루엔자 A, B 양성의 성인 환자에서 보고된 뇌출혈의 보고는 없었다. 이에 저자들은 증례보고를 통해 인플루엔자 관련 뇌염의 뇌출혈의 형태를 보고하고자 한다.

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