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Letter to the Editor

An autopsy case of elderly-onset acute necrotizing encephalopathy secondary to influenza

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Dear Sir,

Influenza-associated encephalopathy (IAE), which can lead to acute necrotizing encephalopathy (ANE), often appears as low-density areas (LDAs) in the thalamus bilaterally on brain CT. In addition, histopathological examination of LDAs reveals necrotic tissue compatible with ANE [1]. In previous studies, most patients with IAE were under 5 years of age; adult-onset IAE is globally very rare [2]. Here, we present the first case of elderly-onset IAE–ANE confirmed by autopsy. The study protocol was approved by the Ethics Committee of the University of Miyazaki. Written informed consent was obtained from the patient's family member.

1. Case report

An 80-year-old man, whose past and social history included diabetes for a few years, cerebral infarction at the age of 52 and smoking for 40 years, was admitted for acute altered mental status and recurrent seizures. Four days before admission, he had fever and upper respiratory symptoms. On the morning of the day of admission, he was diagnosed with influenza type B using ELISA, and laninamivir and acetaminophen were initiated in an outpatient clinic. That night, he was found to be unconscious and having generalized tonic–clonic seizures.

On admission to our hospital, his level of consciousness was E1V2M4. His temperature was 39.0 °C, blood pressure was 86/36 mm Hg, pulse was 113 beats/min, respiratory rate was 28/min, and SpO_2 was 98%. A general physical examination revealed no abnormalities. Neurological examination showed preserved pupillary functions, but diminished corneal and oculocephalic reflexes. There was no neck stiffness and the Babinski sign was negative. His extremities moved in response to painful stimuli symmetrically. Laboratory studies showed a normal white blood cell count and a slight elevation in C-reactive protein (1.28 mg/dL, reference range: 0–0.3 mg/dL). Other blood test results were normal, including plasma ammonia levels. Head CT and MRI revealed no focal lesions except for generalized brain atrophy. Anti-epileptic drugs were initiated for recurrent seizures.

On hospital day 2, his level of consciousness did not improve and electroencephalography showed a diffuse contribution of slow wave activity (2–5 Hz) but no epileptiform activity. LDAs in the thalamus were found bilaterally in serial head CT (Fig. 1A). Laboratory tests revealed disseminated intravascular coagulation (DIC) and acute liver and renal failure. Serum IL-6 level was markedly elevated at 2180 pg/mL (reference range: <4 pg/mL), which lead to multiple organ failure. Cerebrospinal fluid analysis was not performed due to DIC. He was diagnosed with IAE, and treated with pulsed intravenous prednisolone (1 g, 3 days), intravenous immunoglobulin therapy (400 mg/kg/day, 5 days), and peramivir (100 mg/day, 2 days). However, the patient's condition never improved and he died from pneumonia on hospital day 11. Autopsy was performed on the same day.

2. Brain neuropathology

Grossly, the cerebrum had widespread necrosis with multiple petechiae in the white matter and the thalamus bilaterally (Fig. 1B). Histologically, there was coagulation necrosis accompanied by ring hemorrhages around the small vessels (Fig. 1C, D). Edematous changes were seen mainly in the border regions between necrotic and non-necrotic areas. Lymphocytic and neutrophilic infiltrates were not observed. These lesions did not correspond to any arterial territory. Immunohistochemically, numerous PG-M1 (anti-CD68 antibody) positive macrophages were observed (Fig. 1E). Glial fibrillary acidic protein (GFAP) staining revealed only a mild gliosis (Fig. 1F). These findings were compatible with ANE.

3. Discussion

IAE is an acute encephalopathy. Approximately half of its clinicopathological subtypes are ANE and Reye-like syndrome caused by hypercytokinemia [3]. It is reported to occur mainly in infants, and it is very rare in elderly patients [2].

In infants, typical symptoms of IAE–ANE include high fever followed by altered mental status, seizures, and abnormal behavior [2]. Severe systemic inflammation response syndrome due to hypercytokinemia often progresses to disseminated intravascular coagulation and multiple organ failure [3]. Brain CT shows diffuse brain edema with LDAs in the periventricular white matter and thalamus bilaterally [1]. Pathological studies show massive edema and perivascular plasma exudation in the white matter, and petechial hemorrhage in the thalamus [4].

In our elderly patient, his symptoms and findings are consistent with infant IAE–ANE reported in a previous study [2]. In the elderly, IAE was previously reported only in a 76-year-old man diagnosed based on pathological examination, which revealed hemorrhagic shock and encephalopathy (HSE) [5]. To the best of our knowledge, cases of IAE–ANE in elderly patients with confirmed histological findings have never been reported. We report that the pathological findings of IAE–ANE in our elderly patient are identical to those in infants. In addition, both the patient with IAE–HSE mentioned above [5] and our patient had vascular risk factors; the former had diabetes and hypertension, and the latter had diabetes, prior stroke and long-term smoking history. The mechanism of IAE–ANE in infants is posited as destruction of the blood–brain barrier secondary to cytokine storm [6]. Weakness of

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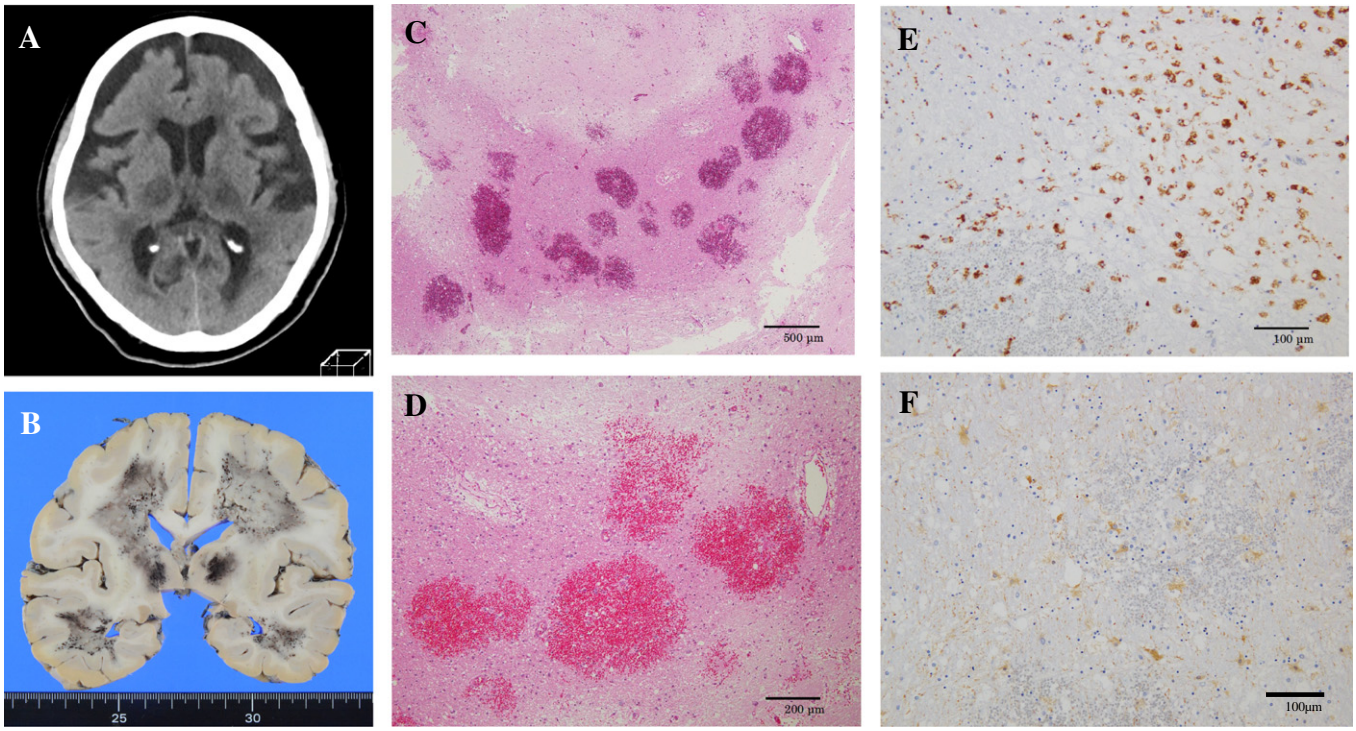

Fig. 1. A: Brain CT on hospital day 2. Bilateral low-density areas were found in the thalamus bilaterally. B: Coronal slice of brain. There was widespread necrosis in the cerebrum with multiple petechiae in the white matter and thalamus bilaterally. C & D: Hematoxylin and eosin staining reveals coagulation necrosis with ring hemorrhages around the small vessels. Edematous changes are seen mainly in the border regions between necrotic and non-necrotic lesions. E: PG-M1 immunohistochemical staining shows numerous PG-M1-positive macrophages. F: Glial fibrillary acidic protein (GFAP) staining reveals only a mild gliosis.

blood–brain barrier may play a role in the etiology of IAE–ANE. On the other hand, vascular risk factor is one of the causes of blood–brain barrier destruction [7]. We should keep in mind that elderly patients with vascular risk factors may develop IAE when they have influenza.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Nobuyuki Ishii
Hitoshi Mochizuki*
Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, Miyazaki, Japan
*Corresponding author at: Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan. Tel.: +81 985 85 2965; fax: +81 985 85 1869.
E-mail address: mochizuki-h@umin.net.

Sayaka Moriguchi-Goto
Department of Pathology, University of Miyazaki, Miyazaki, Japan

Masayuki Shintaku
Department of Pathology, Kyoto Medical Center, Kyoto, Japan

Yujiro Asada
Department of Pathology, University of Miyazaki, Miyazaki, Japan

Akitoshi Taniguchi
Kazutaka Shiomi
Masamitsu Nakazato
Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, Miyazaki, Japan

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