

Neuropathology Education

A 76-year-old man who developed febrile unconsciousness with magnetic resonance imaging findings indicating encephalitis

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CLINICAL HISTORY

On 24 April 2002, a 76-year-old man who had suffered acute hepatitis during his childhood underwent a medical examination that revealed abnormal liver function. Two days later, he consulted a doctor at the Hospital of Teikyo University School of Medicine; his serum AST was 1468 IU/L, ALT 1232 IU/L, γ -GTP 316 IU/L, ALP 510 IU/L, total bilirubin 2.7 mg/dL, and direct bilirubin 1.7 mg/dL. He was admitted to the Hospital on the same day. The patient was alert, and he was jaundiced without edema. His pulse rate was 72/min. Neither his liver nor spleen were palpable. On 11 May, he developed nasal bleeding. Because the plasma prothrombin time (%) was low (32%), a pulse therapy with methyl prednisolone was started. Three days later, he developed hepatic encephalopathy, grade II, with a diagnosis of subacute fulminant hepatitis. Disseminated intravascular coagulopathy also occurred. Plasma exchange was done from 15 May to 24 May, with the patient becoming alert on 23 May.

On the evening of 10 June 2002, a high fever (39.2°C) and abnormal behavior with mild consciousness disturbance (Japan Coma Scale I-2) developed. An EEG on 10 June revealed spike-and-wave complexes in the left cerebral hemisphere, and diffusion-weighted MRI of the head demonstrated high-intensity lesions essentially confined to the bilateral insular cortex (Fig. 1). With these findings combined, a diagnosis of encephalitis was made, although the lumbar puncture could not be performed because of the bleeding tendency. In spite of immediately started acyclovir, the patient's condition deteriorated rapidly, result-

ing in deep coma on 14 June. He died on 20 June, only 10 days after the onset of symptoms of encephalitis. The laboratory examination showed that hepatitis A IgM antibody and antigen, hepatitis C virus RNA, Epstein-Barr virus antibody, and cytomegalovirus antibody were negative.

NEUROPATHOLOGICAL FINDINGS

Macroscopic findings: The fixed brain weighed 1350 g. Part of the left medial temporal lobe had been sectioned for viral PCR. Other surface areas of the brain had no abnormality. Sections of the brain exhibited mild discoloration of the bilateral insular cortex tinted by a few scattered petechiae, with the left side predominance (Fig. 2). The cortico-medullary borders underlying the affected cortex were blurred. The discolored cortex was softer than the others, similar to a fresh infarct. No other abnormality was seen.

Microscopic findings: The insular cortex had an appearance of fresh laminar infarct with many vacuolations and scattered petechiae (Fig. 3). Higher magnifications revealed that many neurons and small vessels were surrounded by vacuoles (Fig. 4) and the neuropils were obviously rarefied. Many neurons in this region had homogeneously eosinophilic cytoplasm with a pyknotic nucleus (Fig. 4 inset). Reactive astrocytes were scarcely seen. In the vicinity of or within the small hemorrhage, the vessels themselves were necrotic. In several areas of the overlying subarchnoid space, mononuclear cells, including considerable number of plasma cells, could be seen to accumulate (Fig. 5), thus indicating inflammatory processes underlying the cortical lesion. The immunohistochemistry using antibodies against HSV stained many neurons, almost exclusively their perikarya and dendrites, in the insular cortex (Fig. 6). Electron microscopic examination revealed virions ultrastructurally compatible with herpes viruses located within neuronal nuclei (Fig. 7). Obvious Cowdry

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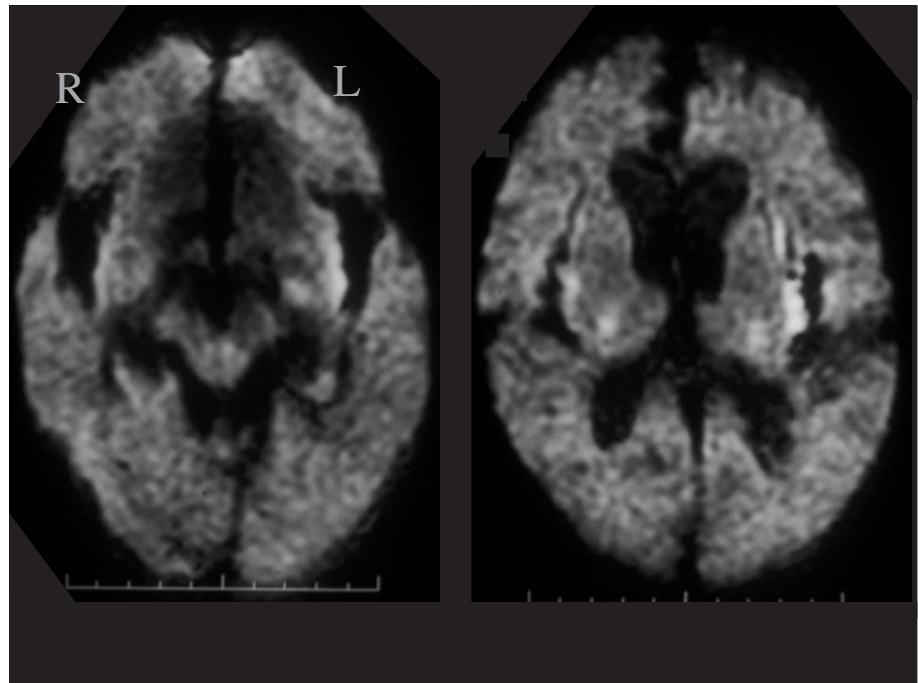


Fig. 1 Magnetic resonance diffusion-weighted imaging shows high signals in the bilateral insular cortex, with the left side predominancy.

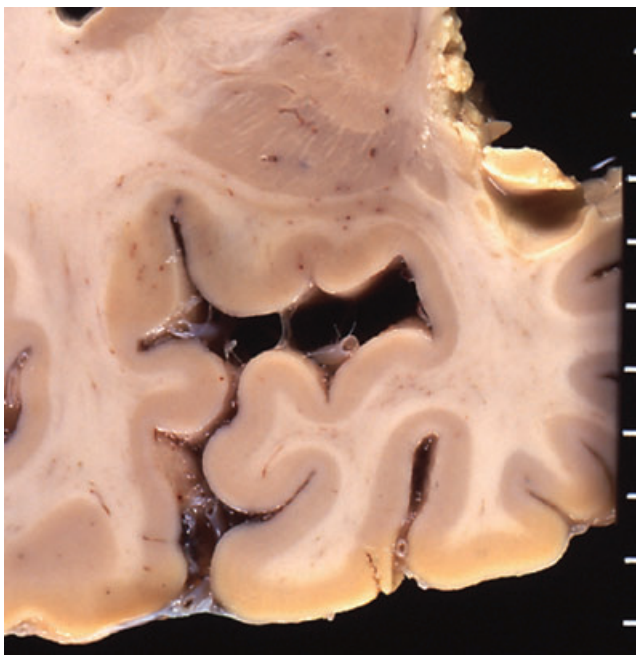


Fig. 2 A section of the brain shows slightly brownish discoloration of the insular cortex and blurring of the underlying corticomedullary junction.

A-type intranuclear inclusions, however, could not be seen in HE sections.

A PCR method applied to the frozen specimen from the left temporal lobe demonstrated HSV DNA.

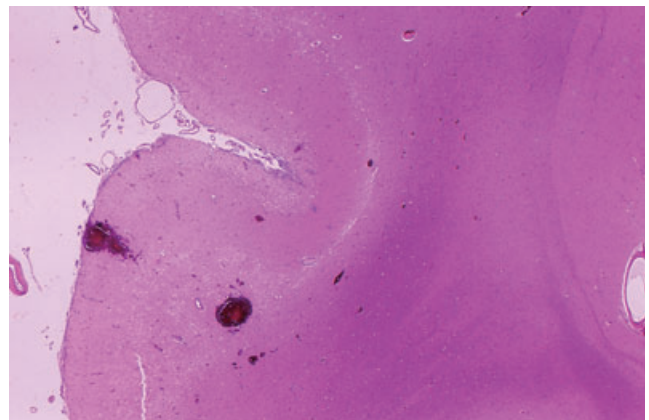


Fig. 3 The insular cortex has roughly laminar distribution of spongy state and several petechiae. HE (magnification: $\times 2.5$).

DIAGNOSIS

HSV encephalitis.

DISCUSSION

Presently, it is almost always the brains of autopsied cases with HSV encephalitis that we have the opportunity to examine. Such specimens show the burned-out brain pathology of encephalitis with cystic lesions of the limbic, especially medial temporal regions, without immunohistochemically recognizable antigens or ultrastructurally detectable virions of HSV.¹

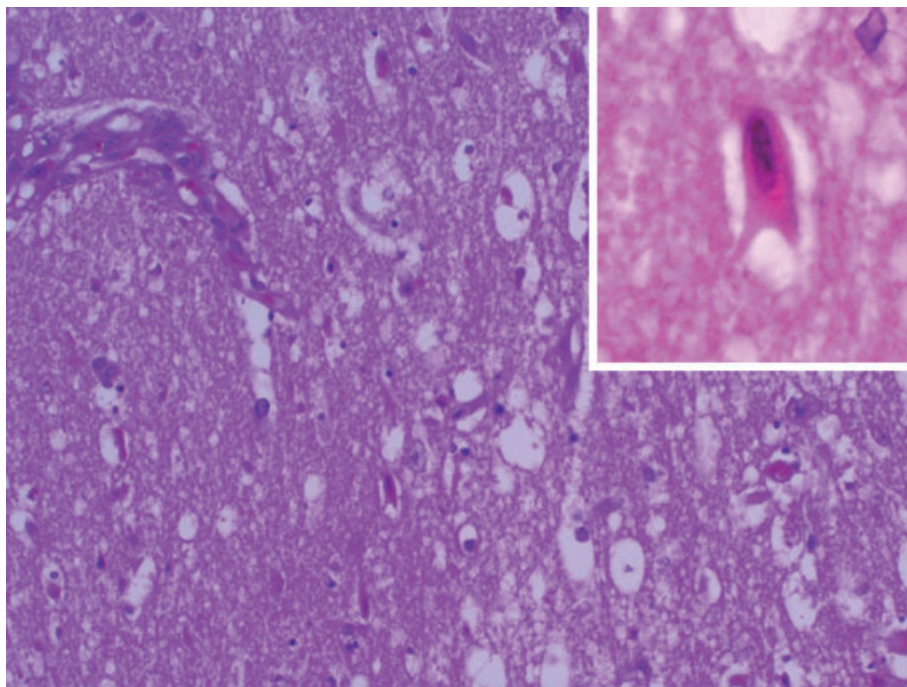


Fig. 4 The insular cortex exhibits shrunken red neurons with perineuronal and perivascular vacuoles and rarefied neuropil. HE (magnification: $\times 10$). Inset: The affected neurons have homogeneous cytoplasm and pyknotic nuclei, like neurons undergoing ischemia. HE (magnification: $\times 40$).

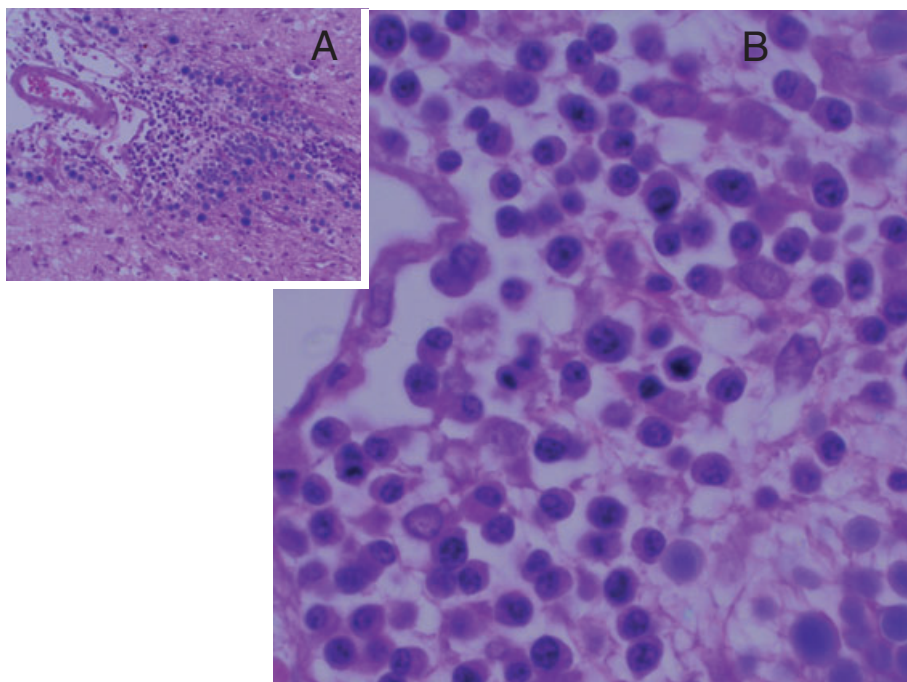


Fig. 5 (A) Infiltrations of inflammatory mononuclear cells are occasionally seen in the subarachnoid space. (B) Higher magnification of (A) reveals numerous plasma cells. (A,B): HE (magnification: (A) $\times 4$, (B) $\times 20$).

The present case, in contrast, exhibits 10-day-old brain pathology of HSV encephalitis. It mimics a fresh infarct: grossly with brownish discoloration of the affected cortex and softening and blurring of the corticomедullary borders of the involved areas, and microscopically with neurons carrying a shrunken reddish perikaryon and pyknotic nucleus, perivascular and perineuronal vacuolations, rar-

efied neuropils, and scarce appearance of reactive astrocytes. Without occasional infiltrations of mononuclear cells containing plasma cells, it would be misdiagnosed as a fresh ischemic lesion. In addition, the vessels themselves are necrotic in the lesions, especially in the proximity of the hemorrhages. Such histopathology of fresh HSV encephalitis makes us recognize that the process in this condition is

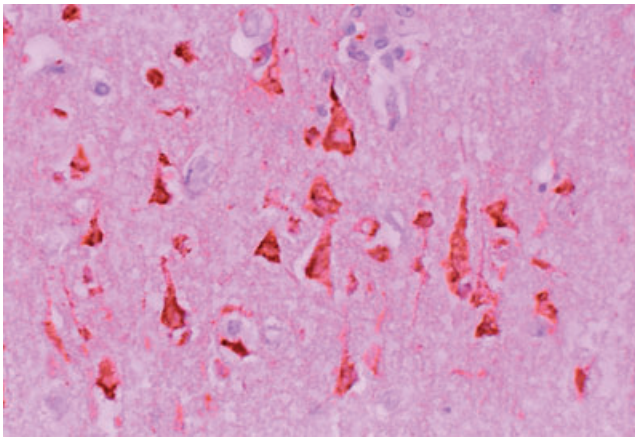


Fig. 6 Many neurons are immunopositive against anti-HSV 1 antibody (magnification: $\times 20$).

such a necrotizing one that the lesion, in the early stage, masquerades as an ischemic change, and, in the later stage, becomes cystic as a consequence of tissue necrosis.

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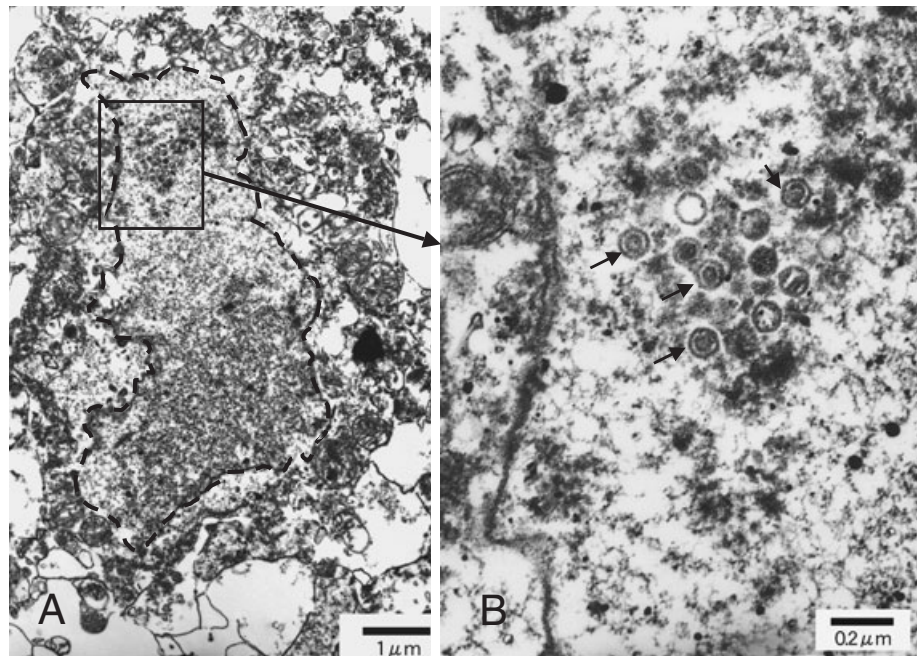


Fig. 7 (A) Electron microscopic examination demonstrates virus particles in the neuronal nucleus. The nuclear membrane is traced with a broken line. (B) Higher magnification of the blocked area in (A) shows that the virus particles are compatible with herpes viruses. Bar (A) 1.0 μm ; (B) 0.2 μm .