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【 CASE REPORT 】

Acute Hemorrhagic Leukoencephalitis with Concurrent Retinal Vasculitis in an Elderly Japanese Patient

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Abstract:
A 68-year-old Japanese man developed a fever, headache, hiccups, and altered consciousness. Brain magnetic resonance imaging revealed a hemorrhagic lesion in the right temporal lobe and multiple high-intensity white matter lesions. A brain biopsy showed pathological findings consistent with acute disseminated encephalomyelitis (ADEM), suggesting a diagnosis of acute hemorrhagic leukoencephalitis (AHLE), an aggressive ADEM variant. The patient also developed myodesopsia and was diagnosed with retinal vasculitis, likely due to a hyperimmune state caused by AHLE. Corticosteroids enabled full recovery. Although AHLE is uncommon in elderly individuals, clinicians should be aware of its occurrence in this patient subgroup and recognize potential retinal manifestations associated with AHLE.

Key words: acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, interleukin-6, retinal vasculitis

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Introduction

Acute hemorrhagic leukoencephalitis (AHLE), also known as Hurst disease, is an uncommon and life-threatening demyelinating disorder of the central nervous system, with reported mortality rates ranging from 47% to 70% (1, 2). Although the cause remains unclear, a hyperimmune reaction triggered by an interaction between human myelin antigens and viral or bacterial antigens is suspected to induce demyelination (1). Given its shared pathology with acute disseminated encephalomyelitis (ADEM), AHLE is considered to be the most severe form, constituting about 2% of ADEM cases (3). AHLE typically affects young adults, and its occurrence in elderly individuals is exceedingly rare (1), potentially contributing to its under-recognition, underdiagnosis, or underreporting, especially in this patient population.

We herein report a case of AHLE in an elderly Japanese man featuring the uncommon complication of retinal vasculitis to raise awareness of this condition.

Case Report

A 68-year-old man was admitted with a fever, headache, and hiccups that began 4 days earlier. He had no notable medical history nor had he experienced any recent infections or vaccinations.

Brain computed tomography revealed a mass in the white matter of the right temporal lobe, exhibiting slightly high-density areas within the lesion (Fig. 1A, arrows). The lesion demonstrated isointensities internally and higher intensities in the surrounding area on fluid-attenuated inversion recovery (FLAIR) imaging, concurrently displaying reduced intensities on T2 star-weighted imaging (T2WI), indicating the presence of hemorrhaging (Fig. 1B, C, arrows). In addition, high-intensity FLAIR lesions were observed in the genu of

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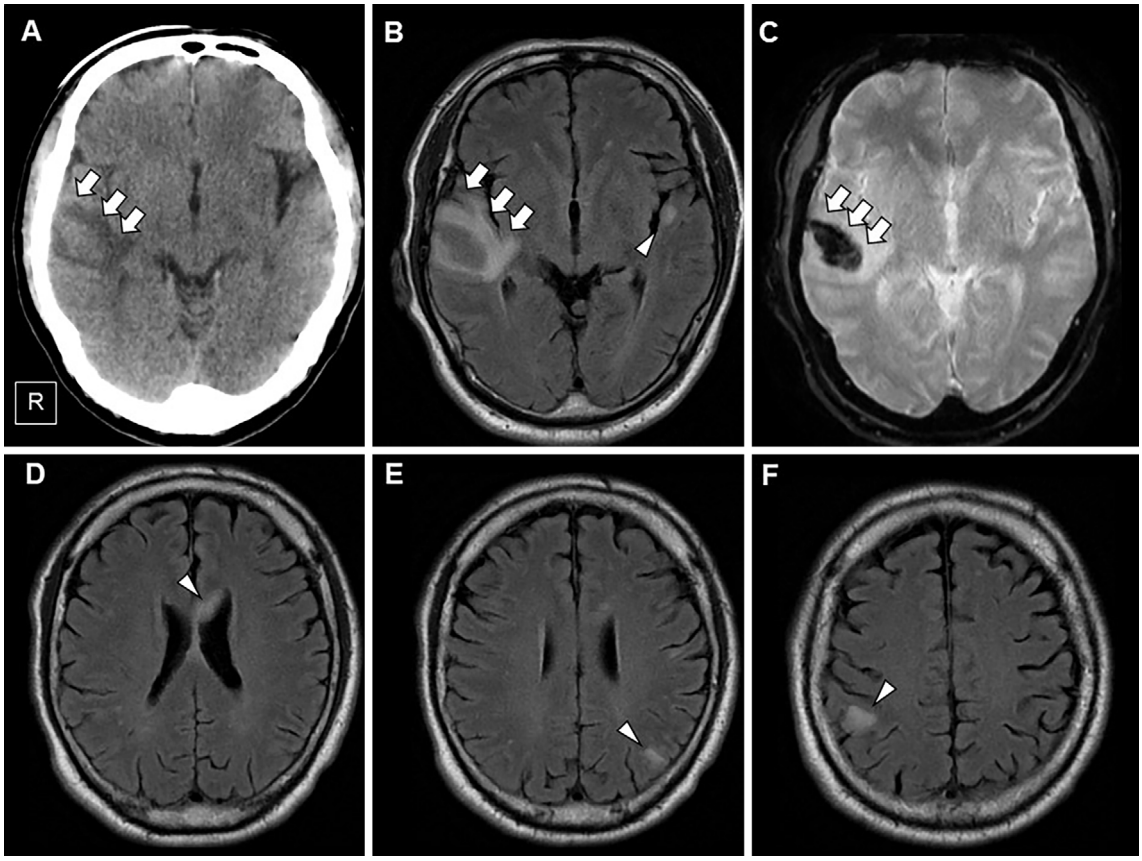

Figure 1. **Brain computed tomography (A) and magnetic resonance imaging (B-F) on admission. Brain CT revealed a mass lesion in the right temporal lobe, exhibiting a slightly higher-density area inside the lesion (A, arrows). The lesion demonstrated isointensity within the lesion and high intensity in the surrounding region [fluid-attenuated inversion recovery (FLAIR)] (B, arrows), along with low intensities on T2 star-weighted imaging (C, arrows). In addition, high-intensity FLAIR lesions were observed in the genu of the corpus callosum (D, arrowhead), white matter of the left temporal lobe (B, arrowhead), and parietal lobes bilaterally (E, F, arrowheads).**

the corpus callosum and white matter of the left temporal and parietal lobes bilaterally (Fig. 1B, D-F, arrowheads), with no corresponding low intensities on T2WI. The lesions did not exhibit gadolinium enhancement. magnetic resonance venography (MRV) did not reveal venous thrombosis.

On a laboratory evaluation, his C-reactive protein concentration was slightly elevated at 3.47 mg/dL (normal level, < 0.3 mg/dL), and his D-dimer level was slightly elevated at 3.2 μg/mL (normal level, <0.5 μg/mL). Other coagulation system findings were within the normal range. A neurological examination on admission revealed mild impairment of consciousness [Glasgow Coma Scale (GCS) score 14/15, E3 V5M6] and hiccups. No other neurological signs, including nuchal rigidity, were observed.

However, his symptoms worsened on the second day after admission, with disturbance of consciousness (GCS 10/15, E 2V3M5) and inability to communicate. A cerebrospinal fluid (CSF) analysis revealed a heightened CSF pressure of 290 mmH_2O, pleocytosis with a cell count of 148/μL (mononuclear 73%), and elevated protein levels of 331 mg/dL. In addition, the interleukin-6 (IL-6) level in the CSF markedly increased to 2,240 pg/mL (normal level <8.7 pg/mL) (4). Oligoclonal IgG bands were negative. The myelin basic protein value in the CSF was significantly elevated to >500 pg/mL (normal level <102 pg/mL). A comprehensive assessment of bacterial and viral infections, including herpes simplex, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and severe acute respiratory syndrome coronavirus (SARS-CoV2), showed negative results. Furthermore, rheumatological investigations, including anti-nuclear antibodies, anti-Ro/SS-A antibodies, anti-La/SS-B antibodies, anti-cyclic citrullinated peptide antibodies, anti-double stranded DNA antibodies, anti-Sm antibodies, anti-RNP antibodies, antiphospholipid antibodies, and myeroperoxidase (MPO) and PR3 anti-neutrophil cytoplasmic antibody (ANCA), were negative. Studies of antibodies, including anti-aquaporin 4, anti-myelin oligodendrocyte glycoprotein, and anti-N-methyl-D-aspartate antibodies, yielded negative results.

From the second day of admission, he received empirical intravenous acyclovir and steroid pulse therapy with intravenous methylprednisolone at a dose of 1,000 mg daily for three days, followed by oral prednisolone at 70 mg (1 mg/kg), which was gradually tapered. To establish an accurate diagnosis, a biopsy of the right temporal lobe lesion was

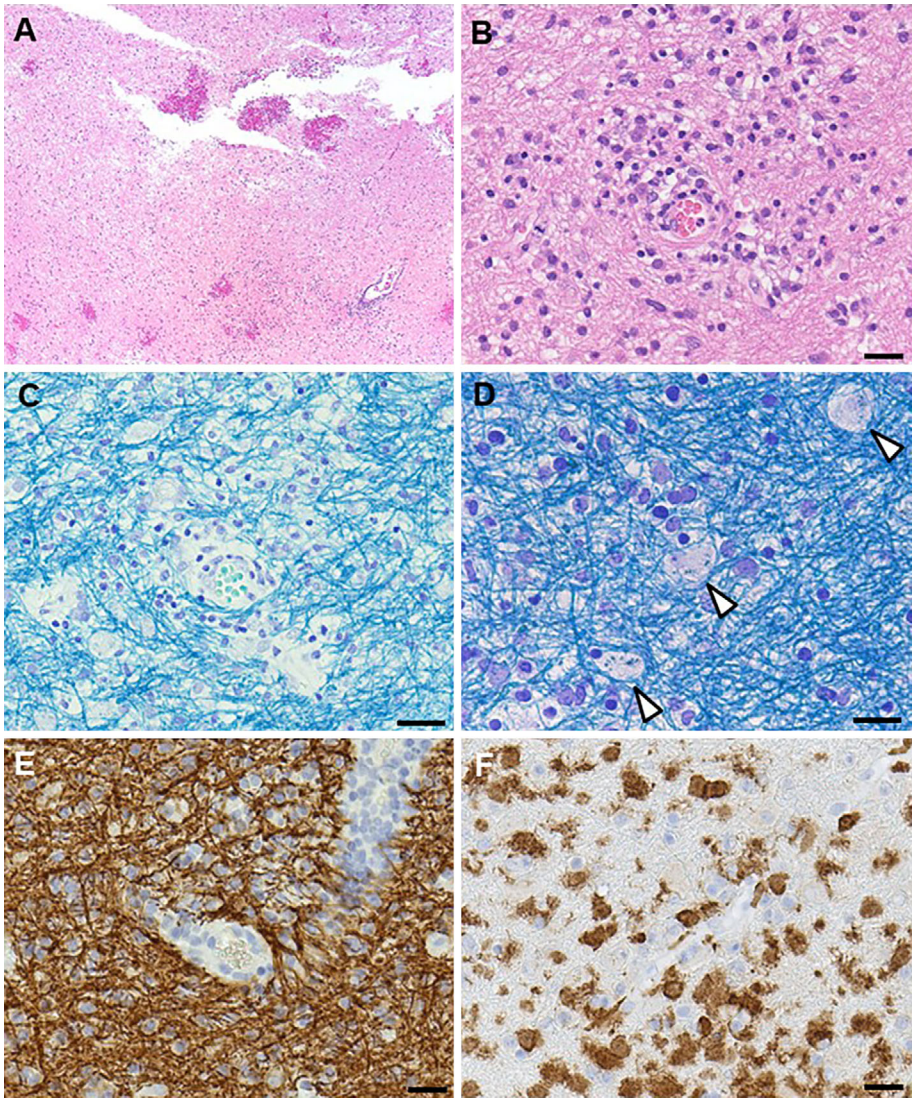

Figure 2. **Pathological findings from the lesion in the right temporal lobe. Hematoxylin and Eosin staining revealed multiple petechial hemorrhaging (A) and perivascular infiltration of lymphocytes and macrophages (B) in the white matter. Klüver-Barrera staining revealed a mild reduction in myelin sheath stainability in the perivascular area (C) and myelin phagocytosis by foamy macrophages (D, arrowheads). Whereas, the axonal staining was preserved on immunohistochemical staining of the neurofilament (E), indicating the presence of demyelination. Immunostaining using anti-Iba1 antibodies showed activated microglia/macrophage infiltration in the white matter (F). Scale bar=200 μm (A), 50 μm (B, C, E, F), 20 μm (D).**

performed on the eighth day of admission. A pathological evaluation demonstrated multiple petechial hemorrhaging, infiltration of perivascular lymphocytes, activated macroglia/macrophages, and demyelination in the white matter (Fig. 2A-F), consistent with ADEM. Based on pathological and radiological findings, a diagnosis of AHLE was established.

The patient's symptoms gradually improved after steroid treatment. However, upon alleviation of his consciousness disorder by the 10th day of admission, myodesopsia was observed in his right eye. Although his visual acuity was not impaired, a fundus examination on the 14th day of admission revealed vitreous opacification, soft exudates, retinal arteriolar sheathing, and dot-blot intraretinal hemorrhaging adjacent to the retinal arterioles in his right eye (Fig. 3A), indicating the possible occurrence of retinal vasculitis (5). No abnormalities were observed in the left fundus. Given that retinal vasculitis emerged during the acute phase of AHLE and that no potential causes were identified despite an extensive microbiologic and rheumatologic investigation, we assumed that retinal vasculitis was a complication of AHLE.

By day 20 after admission, the patient was completely asymptomatic. His CSF findings, including IL-6 levels, normalized by day 27. Brain magnetic resonance imaging (MRI) on day 27 after admission indicated a decrease in the size of the right temporal lesion and the absence of other brain lesions (Fig. 4). A fundus examination on day 32 showed improvement in the other abnormal retinal findings,

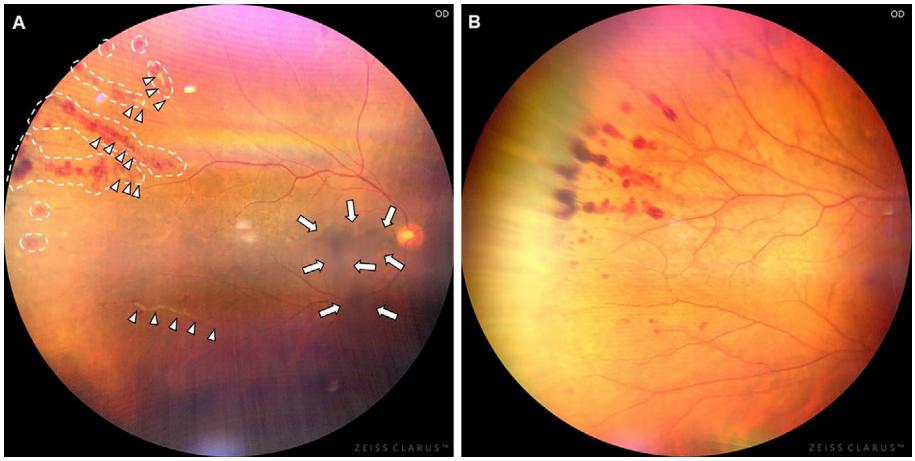

Figure 3. **Fundus examinations on day 14 (A) and day 32 (B) of admission. The fundus examination on day 14 of admission (A) revealed vitreous opacification (arrows), retinal arteriole sheathing (arrowheads), and dot-blot intraretinal hemorrhaging (dashed lines) bordering the retinal arterioles in the right eye. Compared to the initial examination, the fundus examination on day 32 of admission showed persistence of the retinal hemorrhaging, with improvement in the other retinal abnormalities (B).**

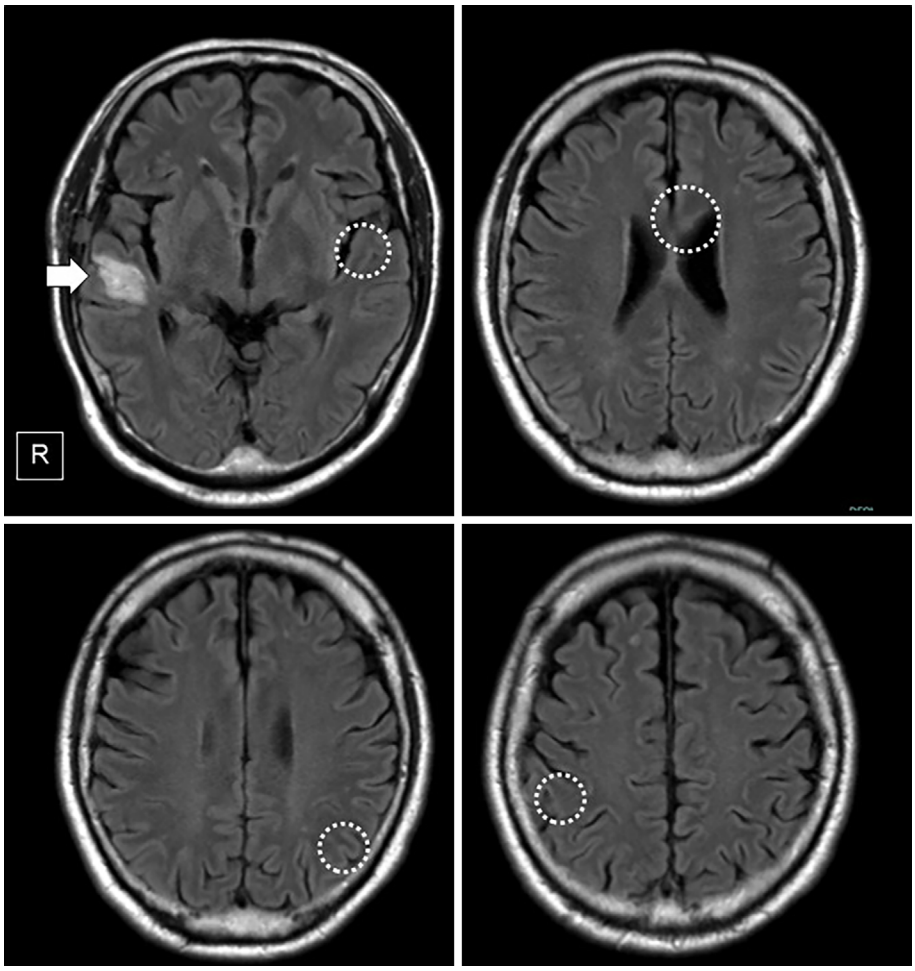

Figure 4. **Brain magnetic resonance imaging on day 27 of admission. Fluid-attenuated inversion recovery imaging indicates a reduction in the size of the right temporal lesion (arrow) and complete disappearance of the other previously observed white matter lesions (dashed circles).**

while retinal hemorrhaging remained (Fig. 3B). He was discharged on day 38 without any neurological complications and was continued on prednisolone 15 mg. The prednisolone dose was gradually tapered over the following three months

after discharge.

Discussion

We herein report a rare case of AHLE in an elderly Japanese man that was successfully treated with corticosteroids. While specific triggering factors, such as prior infections or vaccinations, were not identified in this case, the brain lesions with hemorrhaging observed on MRI and the corresponding pathological findings were in line with the typical presentations of AHLE. Perivenous demyelination (6), a pathological characteristic of ADEM or AHLE, was not apparent in this case. Given that perivenous demyelination typically manifests in the later stages of AHLE (7), a brain biopsy performed during the acute phase in this instance might have failed to detect it. Furthermore, it has been reported that perivenous demyelination is typically indistinct within the hemorrhagic foci in AHLE (8). Therefore, the brain biopsy performed within the hemorrhagic lesion in the right temporal lobe may have failed to identify typical perivenous demyelination. In addition, the early initiation of steroid pulse therapy might have obscured the perivenous demyelination.

In a systematic review of 43 AHLE cases (1), 19% (8/43) did not report specific antecedent infectious or noninfectious conditions associated with AHLE, similar to our case. While the prognostic factors for AHLE have not been clarified, the favorable outcome in the present case could be attributed to the relatively small size of the brain lesions, which did not cause a significant mass effect, and their location away from the eloquent areas. In addition, the prompt initiation of immunosuppressive treatment may have contributed to favorable outcomes. AHLE predominantly affects young adults, whereas ADEM is commonly observed in children (9). Consequently, cases of AHLE in elderly patients are scarce. To date, only 4 documented case reports of AHLE in individuals over 65 years old have been published (10-13). It is noteworthy that three of the four elderly cases died due to the disease. This highlights the importance of clinicians recognizing that AHLE can affect elderly patients and has a high probability of being fatal regardless of the patient's age at the onset.

A unique aspect of this case is the simultaneous occurrence of autoimmune retinal vasculitis during the acute phase, despite mild symptoms that did not affect the visual acuity. Fundus findings of soft exudates, retinal arteriolar sheathing, and dot-blot intraretinal hemorrhaging adjacent to the retinal arterioles in the right eye are consistent with retinal vasculitis (5). Unfortunately, we did not perform a fundus examination at the peak of the disease. Typically, retinal manifestations associated with increased intracranial pressure involve dilation or thrombosis of retinal venules. Because fundus abnormalities in our case were observed adjacent to the retinal arterioles, it was assumed that the retinal manifestations were not related to increased intracranial pressure. It is uncommon for AHLE or ADEM to affect any organ other than the brain or the spinal cord. To our knowledge, there have been no documented case reports of AHLE or ADEM coinciding with retinal vasculitis. In the present case, the level of IL-6 in the CSF was extremely high during the acute phase of AHLE but decreased following the commencement of steroid treatment. IL-6 is a multifunctional cytokine primarily associated with inflammation. It plays a crucial role in immune response regulation and is often heightened in various conditions, such as infections, trauma, and autoimmune disorders. Elevated levels of IL-6 can trigger and perpetuate systemic inflammatory responses, potentially leading to severe outcomes, including 'cytokine storms' and widespread tissue damage in multiple organs (14, 15). For example, individuals with SARS-CoV-2 infections, who exhibit heightened IL-6 levels and hyperimmune responses, have shown susceptibility to various retinal manifestations (16, 17). In the present case, an exaggerated hyperimmune state with elevated IL-6 levels in the central nervous system associated with AHLE may have induced retinal vascular inflammation, leading to retinal hemorrhaging and vascular leakage.

Owing to the rarity of AHLE, there are no established treatment guidelines for AHLE. In previous case reports, the most commonly administered treatments included glucocorticoids, either alone or in combination with intravenous immunoglobulins or plasmapheresis (1). However, due to the high severity or fatality of the disease, establishing a clear temporal relationship between treatment and the prognosis is challenging in most cases. Since a significant elevation of CSF IL-6, as observed in this case, has been reported as a characteristic cytokine profile among AHLE patients, the potential efficacy of tocilizumab, a humanized monoclonal antibody that targets the IL-6 receptor, has been proposed for treating AHLE (18). Tocilizumab has been approved for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman disease. Furthermore, it has been used to manage cytokine storms caused by chimeric antigen receptor T-cell therapy and severe SARS-CoV-2 pneumonia (14). Further investigation is necessary to ascertain the potential benefits of tocilizumab, an IL-6 receptor signaling blocker, as a therapeutic approach for managing life-threatening AHLE.

In conclusion, we encountered a case of AHLE concomitant with retinal vasculitis in an elderly Japanese patient. Despite its rarity, clinicians should be aware of the possibility of AHLE in elderly individuals and remain vigilant about potential retinal manifestations in patients with AHLE.

The authors state that they have no Conflict of Interest (COI).

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