Acute Hemorrhagic Leukoencephalitis

A Critical Entity for Forensic Pathologists to Recognize

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Abstract: Acute hemorrhagic leukoencephalopathy (AHLE) is a rare, acute disorder characterized by perivenular demyelination and diffuse hemorrhagic necrosis of the central nervous system. AHLE is thought to represent a hyperacute form of acute disseminated encephalomyelitis. AHLE is associated with a greater morbidity and mortality and, fortunately, is much less common than acute disseminated encephalomyelitis. Since most cases of AHLE result in patient demise, forensic pathologists should be cognizant of this entity and consider it in their differential diagnosis.

Here we describe an interesting case of a previously healthy 11-year-old boy who initially complained of vague gastroenteritis-like symptoms while visiting a mountain lake. The boy's symptoms evolved to include severe headache and dizziness, necessitating a visit to a rural emergency department. He presented with focal neurologic findings, and head computed tomography (CT) scan confirmed thalamic edema. Cerebrospinal fluid analysis was suggestive of infectious etiology, and multiple empiric therapies were initiated. He was transferred to our institution, and his clinical status continued to worsen. Given the poor prognosis, the family requested withdrawal of supportive care. On day 14 of symptoms the boy succumbed to his illness. An autopsy was requested to further characterize the proximate cause of death.

AHLE often presents with abrupt onset of fever, neck stiffness, seizure, and/or focal neurologic signs several days following a viral illness or vaccination. Thus, AHLE can clinically mimic a direct central nervous system infection or a toxic ingestion. AHLE has a very poor prognosis, with rapid deterioration and death usually occurring within days to one week after onset of symptoms. The cause for AHLE is unclear. An autoimmune pathophysiology is likely, with immune cross-reactivity between myelin basic protein moieties and various infectious agent antigens. Treatment for AHLE is not well-established; some authors describe in recent literature that a combination of immunosuppressant medications and/or therapeutic plasma exchange may be of benefit in treating AHLE.

Key Words: acute hemorrhagic leukoencephalopathy, Hurst disease, Weston Hurst syndrome, acute disseminated encephalomyelitis, demyelinating disease, infectious meningoencephalitis, amoebic encephalitis

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Acute hemorrhagic leukoencephalopathy (AHLE) is a rare, fulminant form of acute disseminated encephalomyelitis (ADEM). First described in 1941 by Dr. E. Weston Hurst, AHLE has also been referred to as Hurst disease or Weston Hurst syndrome. The disorder is thought to be a hyperacute autoimmune condition, triggered by cross reaction between antigen(s) from an infectious agent and the patient's own central nervous system (CNS) tissues. AHLE presents with abrupt onset of fever, neck stiffness, seizure, and focal neurologic signs several days after a viral illness or vaccination.[1,2] Thus, AHLE can clinically mimic a direct CNS infection or a toxic ingestion, other conditions often encountered in forensic practice. AHLE has a very poor prognosis, with rapid deterioration and death occurring usually within days to one week after symptom onset. Since most cases result in patient demise, forensic pathologists should be cognizant of this entity and consider it in their differential diagnosis.

CASE REPORT

A previously healthy 11-year-old boy complained of vague abdominal pain, nausea, and headache while on a family fishing trip at a freshwater lake. Over the following 3 days, he complained of increased malaise and presented with low-grade fever, nausea, and vomiting. Gastroenteritis was suspected, and he was treated for symptoms by a local physician. The boy continued to complain of severe headache and dizziness over the next few days, necessitating a visit to a rural emergency department 8 days after onset of illness.

He presented with left head preference and roving eyes. He was able to follow commands, but was unable to walk on his own. Head CT demonstrated bilateral patchy thalamic edema. Cerebrospinal fluid showed marked, neutrophil-predominant pleocytosis (1545 WBCs/ul, 95% PMNs) and elevated protein (191 mg/dL) suggestive of an infectious process. Empiric intravenous broad-spectrum antibiotics, acyclovir, and high-dose corticosteroids were initiated to cover the presumed infectious meningoencephalitis. There was no suspicion for toxic ingestion; admission urine or serum toxicology studies were not performed.

Neuroimaging studies obtained during the hospital admission demonstrated progressive cerebral edema involving both thalami, bilateral basal ganglia, pons, brainstem, and middle cerebral peduncles. Magnetic resonance imaging (MRI) studies revealed asymmetric, hyperintense T2-weighted lesions better visualized with FLAIR (Fig. 1A). The boy eventually developed multiorgan system failure and given his poor prognosis, the family requested DNR status and withdrawal of all supportive care. The boy expired soon thereafter, on day 14 of illness.

MATERIALS AND METHODS

A full medical autopsy was performed to include external examination followed by internal macroscopic and microscopic examination of internal organs, including the brain. Hematoxylin and eosin (H&E) stained slides containing sections of vital organs were examined by light microscopy. Lesional brain tissue sections were stained with Luxol Fast Blue (LFB)/periodic acid Schiff as well as tissue Gram stain, and examined by light microscopy. Immunohistochemical (IHC) preparations for macrophage markers HAM-56 (Ventana Medical Systems, Inc., Tucson, AZ; 1:40) and CD-68 (Ventana Medical Systems, Inc., Tucson, AZ; 16 mg/mL) were performed on lesional brain sections. Paraffin-embedded sections of the brain were sent for IHC preparations for *Naegleria*,

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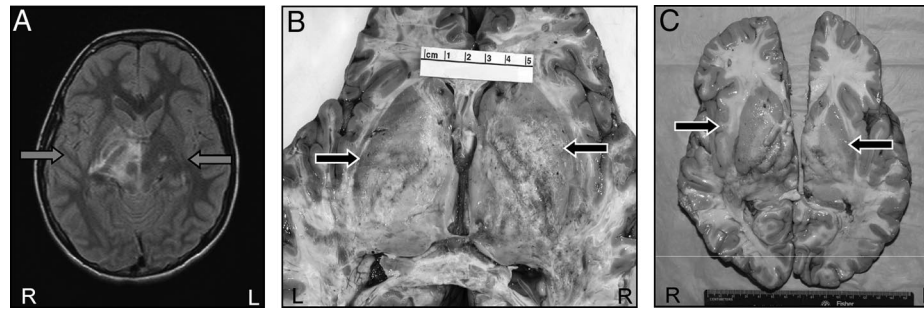

FIGURE 1. A–C, T2-weighted MRI (FLAIR) showing patchy, asymmetric edema involving bilateral thalami and adjacent white matter tracts (A). Fresh cut sections (B) and fixed cut sections (C) of brain, showing corresponding severe patchy necrosis of thalami and basal ganglia.

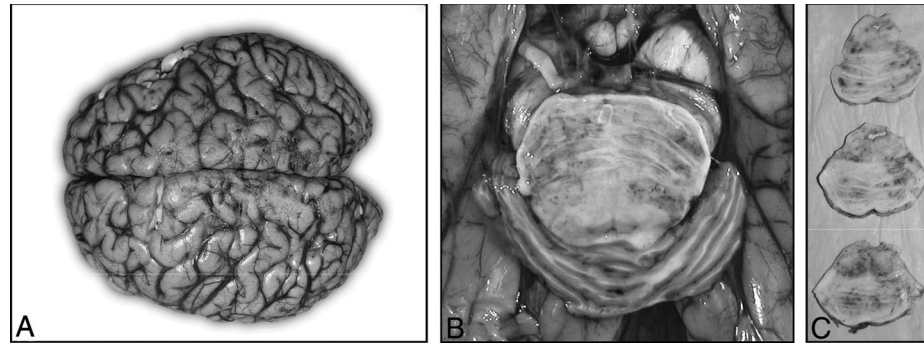

FIGURE 2. A–C, Overall the brain was markedly edematous with severe leptomeningeal vascular congestion (A). Scattered petechial hemorrhages were evident within both unfixed (B) and fixed sections (C) of pons.

Acanthamoeba, and *Balamuthia* antigens (courtesy Dr. Govinda S. Visvesvara, Centers for Disease Control and Prevention, Atlanta, GA). Postmortem blood, urine, cerebrospinal fluid CSF, and brain tissue were obtained under sterile conditions and sent for routine aerobic and anaerobic bacterial cultures, viral, fungal, and mycobacterial cultures.

RESULTS

At autopsy, external examination revealed no evidence of trauma. Evidence of medical intervention was present and included a secure endotracheal tube, a ventriculostomy catheter affixed over the left parietal region, and a Foley catheter. Examination of the brain revealed marked, diffuse cerebral edema (brain weight 1561 g, normal for age 1395 g) and severe leptomeningeal congestion (Fig. 2A). The ventricles were markedly shrunken, and the tip of the intraventricular catheter was near the third ventricle. The unfixed, horizontally sectioned brain contained poorly-demarcated edematous and necrotic lesions in bilateral thalami and basal ganglia (Fig. 1B) and pons (Fig. 2B), as well as within the cerebral peduncles and cerebellar white matter. Petechial hemorrhages were scattered throughout the deep white matter of the cerebral hemispheres and cerebellum, and were best seen in the fresh pons (Fig. 2B). The ventricles were markedly compressed by the edema; herniation was not identified. Examination of the remaining internal organs revealed moderately edematous lungs (combined lung weight 904 g; normal for age 633 g). The kidneys were heavy (combined kidney weight 431 g; normal 258 g) and boggy with poor demarcation of the cortices. The lining of the bladder was mildly hemorrhagic. The remaining internal organs were unremarkable.

Light microscopic examination of lesional brain tissue revealed thin sleeves of pallor surrounding small-caliber parenchymal blood vessels, distributed especially within the white matter (Fig. 3A). This patchy perivenular pallor was found to represent demyelination on myelin stain (Fig. 3B). The perivascular inflammatory infiltrate mostly consisted of activated macrophages (Fig. 3C) containing engulfed chunks of myelin, however, neutrophils and occasional monocytes were also scattered within the lesional brain tissue. Of note, many intraparenchymal venules in the lesions were obliterated by vascular necrosis, fibrin exudates, and neutrophilic debris (Fig. 4A). Many of the damaged small blood vessels were encircled by red blood cells, the so-called "ring and ball hemorrhages" which corresponded to the petechial hemorrhages seen grossly (Fig. 4B).

Light microscopic examination of sections of the lungs revealed patchy moderate pulmonary edema with acute lung injury, and sections of the kidneys were consistent with acute tubular necrosis. The bladder sections showed patchy submucosal chronic inflammation and occasional poorly-formed granulomas. Special stains failed to reveal organisms in sections of brain and bladder. Furthermore, all premortem and postmortem microbiologic, serologic, and molecular studies for infectious agents such as aerobic and anaerobic bacteria, fungus, mycobacteria, as well as a multitude of viruses such as respiratory viral agents, herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and West Nile Virus, were negative. All IHC analyses for ameba antigens performed at the CDC were negative.

DISCUSSION

AHLE is a rare, acute demyelinating disorder characterized by diffuse, hemorrhagic necrosis and perivenular sleeves of tissue damage and myelin loss surrounding small parenchymal vessels, usually venules, of the CNS. It is thought to represent a fulminant, hyperacute form of ADEM, but is considerably less common and associated with far greater morbidity and mortality. The few patients that do survive usually suffer serious, permanent neurologic sequelae. Fortunately, less than 2% of all cases of ADEM are this hyperacute, hemorrhagic type.[3]

Patients with AHLE present with abrupt onset of fever, headache, neck stiffness, seizure, and/or focal neurologic deficit. Symptoms often arise within 2 to 12 days of experiencing a nonspecific upper respiratory illness or vaccination.[2] Neuroimaging and CSF analysis usually show significant abnormalities, but cultures for organisms are negative and, ultimately, direct examination of brain

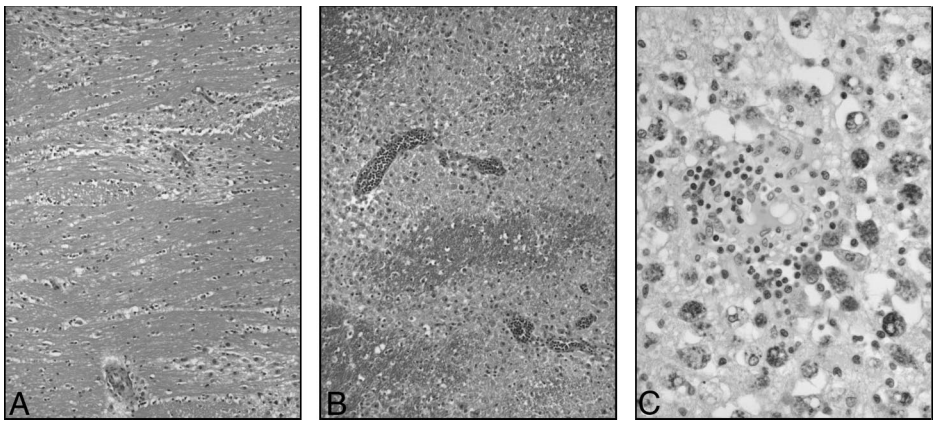

FIGURE 3. A (H&E, 100×), B (LFB/PAS, 100×), and C (HAM-56 IHC, 400×). Light microscopic studies revealed thin sleeves of pallor surrounding small-caliber parenchymal blood vessels (A) which correspond to areas of demyelination on special stain (B). Macrophages stain strongly positive for macrophage marker HAM-56 (C).

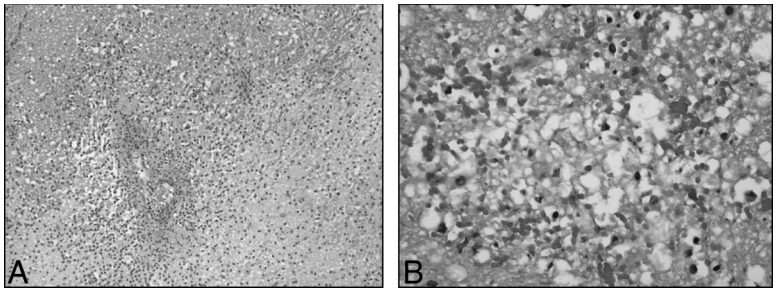

FIGURE 4. A (H&E, 100×) and B (H&E, 400×). Many intraparenchymal venules were obliterated by vascular necrosis and contained fibrin exudates and neutrophilic debris (A), and several of these vessels were encircled by extravasated red blood cells characteristic of so-called "ring and ball hemorrhage," (B) which corresponded to the petechial hemorrhages seen grossly.

tissue may be necessary for definitive diagnosis. Premortem biopsies are often not undertaken since most patients succumb within a one week after onset of symptoms, making it a disorder that often falls within the realm of forensic pathology.

The etiology of AHLE is unclear. An autoimmune pathophysiology has been postulated, and some propose likely cross-reactivity between various infectious agents and human myelin basic protein moieties[4]; in which case, exposure to the agent may lead to development of a T-cell clone and thus propagation of the inflammatory cascade and subsequent myelin destruction. Alternatively, it is possible that activation of preexisting myelin-reactive T-cell clones occurs through stimulation by a nonspecific inflammatory process, resulting in myelin loss.[3] Numerous case reports and small case series implicate various triggering agents such as influenza A virus, HSV, VZV, EBV, and human herpesvirus type 6.[3,5–7] Interestingly, certain individuals may have increased genetic susceptibility to developing AHLE based on certain MHC haplotypes involved in modulation of the immune response.[3]

AHLE is not only a diagnostic but therapeutic challenge, as treatment guidelines for AHLE are not well established. The rarity of cases and rapid clinical decline of these patients has precluded successful completion of randomized controlled therapeutic trials. Surgical decompression by craniectomy and/or ventriculostomy, as well as immunosuppressive agents such as intravenous corticosteroid, immunoglobulins, and cyclophosphamide are frequently employed, with variable success.[4,8] More recently, authors describe the potential benefits of therapeutic plasmapheresis in these patients.[3,9]

Neuroimaging may help direct one towards the correct diagnosis, but the findings in AHLE are nonspecific. CT scans may be normal, or show widespread hypodensities in white matter or gray matter structures. The cerebral hemisphere, brainstem, cerebellum, and/or spinal cord may be involved. MRI studies often show irregular, hyperintense T2-weighted lesions which are better visualized with FLAIR.[4,10] The lesions often take on a vascular distribution and may mimic vasculitis, thrombotic thrombocytopenic purpura, or other microangiopathies. In severe cases, the edema may result in considerable mass effect.

A definitive diagnosis of AHLE requires direct examination of brain tissue, either by brain biopsy or during postmortem examination. The gross autopsy findings of diffuse cerebral edema, brain parenchymal necrosis, and white matter petechial hemorrhages are quite nonspecific. It is important to realize that the lesions of AHLE may be subtle, presenting as a few scattered petechial hemorrhages which may be easily missed, to the development of frank hematomas in some cases. In the current case, the microscopic presentation of the lesional brain tissue from autopsy was most helpful, as it revealed the characteristic histopathologic features of AHLE: extensive perivascular demyelination, fibrinoid vascular necrosis, widespread perivascular mixed inflammatory infiltrates, and "ring and ball hemorrhages." Myelin stains and specific macrophage markers were employed in this case, to further determine the nature of the inflammatory process. These features may be seen in part in other disorders, however with the constellation of all 3 features in combination with the clinical presentation, the distribution of the findings, and pertinent negative findings of this case, one may conclude the diagnosis of AHLE.

The differential diagnosis includes demyelinating disorders such as classic ADEM, acute multiple sclerosis (MS) of Marburg type, acute necrotizing encephalitis of childhood, Leigh syndrome, or "vanishing white matter disease," as well as infectious and toxic meningoencephalitides.[2] These cases may require special expert consultation, but usually can be distinguished based on clinicopathological correlations.

Of the demyelinating disorders, the strongest diagnostic consideration should be ADEM. AHLE is a close cousin of classic ADEM, as they are similar in both presentation and pathophysiology. ADEM similarly shows abrupt onset of fever and various neurologic signs, and is usually precipitated by a viral infection or vaccination.[1–3] Viruses implicated in ADEM include influenza virus, enterovirus, measles, mumps, rubella, VZV, EBV, CMV, HSV,

hepatitis A, and coxsackievirus. In addition, bacterial triggers include *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, *Leptospira*, and beta-hemolytic *Streptococcus*. Vaccinations which have been reported to be associated with ADEM include hepatitis B vaccine, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, VZV, influenza, Japanese encephalitis, and polio vaccines. However, according to one author, the only epidemiologically and pathologically proven association of ADEM with vaccinations is the Semple form of the rabies virus vaccine.[3]

The outcomes of ADEM versus AHLE are very different. In the acute phase of ADEM the mortality is much lower than that of AHLE, at approximately 10% to 30% within one week after onset of symptoms.[4] One review describes gradual clinical improvement in most cases over the following few weeks, with complete recovery in approximately 50% to 70% of patients with ADEM.[3] CSF studies in ADEM may reveal nonspecific findings of lymphocytic pleocytosis, elevated protein and transient elevated oligoclonal bands.[4] Active perivascular mononuclear cell infiltrates, but not necrotizing angiitis with perivascular hemorrhage, are seen on light microscopic studies of lesional brain tissue. Of note, treatment for ADEM and AHLE is somewhat similar, consisting primarily of immunomodulation therapy.

Acute MS of Marburg type is a rare idiopathic inflammatory demyelinating disease that is typically seen in young adults, and should also be considered in the differential as it can resemble AHLE clinically. However, imaging studies and microscopic findings are distinctly different. MRI studies in acute MS show large confluent lesions of the cerebral white matter which may enhance with contrast. This form of MS is relatively unresponsive to corticosteroids and carries a very poor prognosis; death may result as soon as 1 to 6 months after onset of symptoms. At autopsy, the brain shows acute stage demyelinative plaques with abundant LFB-positive macrophages similar to those seen in this case. Unlike AHLE, however perivascular hemorrhage and fibrinoid necrosis of the vessels are not present in acute MS.[1,2]

Acute necrotizing encephalopathy of childhood is a disorder seen primarily in east Asia and has been associated with influenza A infection, however other triggering viruses have also been implicated.[11] These individuals suffer brain death within 2 to 4 days of onset of symptoms. Examination of the brain shows bilateral and severe necrosis of the deep gray and subcortical white matter structures. The majority of cases demonstrate transaminitis or altered liver function, and some theorize that a hypercytokinemia may lead to a leaky blood-brain barrier and ultimately, to acute necrotizing encephalopathy.[12]

Leigh syndrome is a mitochondrial encephalopathy that leads to necrosis primarily in the brain stem and basal ganglia. These patients present with hypotonia, ophthalmoplegia, ataxia, and respiratory abnormalities in infancy or early childhood. Steatosis of the liver and hypertrophic cardiomyopathy have also been described. Most cases are due to autosomal recessively transmitted mutations, although mutations within mitochondrial DNA or coexistent pyruvate dehydrogenase deficiency have been implicated as well.[2]

"Vanishing white matter disease," also known as eIF2B-related leukodystrophy, may look similar to AHLE on neuroimaging studies. The presentation is quite different than AHLE as these patients present only with mild psychomotor development abnormalities, followed by episodic or chronic neurologic deterioration and/or seizure.[13] This disease results from a defect in one of the 5 known genes which encode various subunits of the eukaryotic initiation factor, 2B. Histopathological features also differ from AHLE in that perivenular sleeves of demyelination are not found.

Certain types of cases commonly seen in the forensic setting may appear similar to AHLE upon initial examination. The forensic pathologist should be aware of the similarities to avoid these pitfalls. Petechial brain hemorrhages occur in several unrelated conditions, as indexed in standard neuropathology reference texts, such as "Greenfield's Neuropathology."[1] The widespread petechial hemorrhage of AHLE could possibly be mistaken for other entities such as diffuse axonal injury. Diffuse axonal injury-induced petechial hemorrhages are more common in adults than children,[14] and usually are associated with a history and/or other physical evidence of trauma. In addition, petechial hemorrhages can be seen with fat embolization syndrome. Intravascular fat can be highlighted by oil red O stain on fresh/frozen brain tissue in the latter, and other systemic organs are often similarly involved with fat emboli and petechiae.[15] Furthermore, air embolism and carbon monoxide intoxication may also show petechial hemorrhages.[16] Malignant hypertension can yield petechial or larger hemorrhages in brain, but is usually associated with other disorders such as glomerulonephritis, toxemia of pregnancy, systemic vasculitis, scleroderma, pheochromocytomas. Typical histologic changes in other organs, especially the kidneys, are seen.[17] Moreover, several infections can result in petechial brain hemorrhages. Cerebral malaria can cause petechial hemorrhages,[18] but a history of travel to an endemic area and the finding of microvascular sequestration of parasitized red cells in the brain cinch that diagnosis and exclude AHLE. Finally, other rare infections of the brain, such as leptospirosis and rickettsial disease, cause petechial brain hemorrhages and microscopic examination is necessary to exclude these diagnoses. In summary, the clinical history, findings in other systemic organs, and microscopic neuropathological findings direct the pathologist to the correct diagnosis and away from these other causes of CNS petechial hemorrhages.

AHLE should not be confused with infectious meningoencephalitis. Both entities may be associated with an abrupt neurologic deficit, accompanied by CSF neutrophilic pleocytosis with elevated protein. The treatment for infectious meningoencephalitis is of course directed towards the suspected causative agent, in combination with aggressive corticosteroid therapy if brain edema is present. HSV and VZV are the most common causes of acute encephalitis, however one should note that the specific etiologic agent remains unknown in the majority (up to 60%) of cases.[4] HSV also may lead to development of scattered petechial hemorrhage in the brain which may appear similar to AHLE, however the distribution of petechiae within the medial temporal and inferior lobes and the histologic features are quite different. Antiviral agents significantly reduce morbidity and mortality in cases of HSV encephalitis; however, this therapy alone is reportedly not efficacious for AHLE. EBV, CMV, mumps, measles, and enterovirus, and purported "newly-emerging viruses" such as West Nile virus have been implicated as possible triggers for the subsequent tissue damage seen in AHLE. In our case, premortem serologic studies to detect HSV, EBV, and CMV infection (IgG/IgM) were negative, and moreover viral DNA was not detected with real-time PCR. Of interest, the direct CNS infection that is most likely to be considered by the forensic pathologist is a form of amebic encephalomyelitis, since the numerous perivascular macrophages are easily mistaken for ameba by the unwary. Indeed, the original pathologist was convinced of that diagnosis in this case and had ordered extensive staining for ameba that proved negative. In contrast, macrophages can be identified by their LFB-positive contents, their immunoreactivity for CD68, and especially immunoreactivity for HAM-56. All were used successfully in this case to confirm the diagnosis of AHLE.

In summary, the workup for AHLE often requires extensive microbiologic, serologic, and molecular studies, as ruling out an infectious etiology is key. In this case, all routine viral, bacterial, fungal, and mycobacterial cultures on pre- and postmortem specimens were negative and ultimately no infectious agents could be confirmed. It is important to understand that AHLE is a postinfectious entity, as the

tissue damage usually takes place after the triggering infectious agent has been cleared. Given the distinctive microscopic findings in the brain, as well as the negative cultures and serologies, we were able to arrive at the correct diagnosis of AHLE.

Forensic pathologists should be cognizant of AHLE as a possible diagnosis for individuals who succumb soon after onset of encephalopathic symptomatology. The forensic pathologist should be able to differentiate this disorder from other more common entities that cause petechial hemorrhage in the brain as described above. Furthermore, if infection is suspected, one should especially work to identify the specific etiology, given the obvious public health implications and possible need for close contacts to undergo further studies or treatment.

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