CASE REPORT

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Human Herpesvirus-6 and Sudden Death in Infancy: Report of a Case and Review of the Literature

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ABSTRACT: Investigation of sudden death in infancy is a vital function of the medical examiner's office. Surveillance of these cases may lead to recognition of new diseases or new manifestations of previously described diseases. Human herpesvirus-6 (HHV-6) is a relatively newly described virus that has been recognized as a cause of acute febrile illness in early childhood. While most cases are apparently self-limited, seven fatal cases have been reported. We present a case of a seven-month-old Latin American male with recent otitis media and vomiting who was found dead in bed. Autopsy revealed interstitial pneumonitis with an atypical polymorphous lymphocytic infiltrate in the liver, kidney, heart, spleen, lymph nodes, and bone marrow, associated with erythrophagocytosis. Polymerase chain reaction (PCR) analysis of formalin-fixed paraffin-embedded tissue was positive for HHV-6 and negative for Epstein-Barr virus (EBV) and cytomegalovirus (CMV). HHV-6 was also detected in the atypical lymphoid infiltrate by in-situ hybridization.

KEYWORDS: forensic science, human herpesvirus 6, HHV-6, sudden death in infancy, atypical polymorphous lymphocytic infiltrate

In 1986 Salahuddin and co-workers first reported the isolation of a unique herpesvirus from peripheral blood lymphocytes of six individuals affected by various lymphoproliferative disorders (1). This herpesvirus, known as human herpesvirus-6 (HHV-6), was originally termed B-cell lymphotrophic virus though it actually has diverse cellular tropism (1). HHV-6 is a double-stranded DNA virus similar to cytomegalovirus (CMV) with in-vitro sensitivity to gancyclovir and relative resistance to acyclovir (2). HHV-6 has been identified as the etiologic agent of exanthem subitum (roseola infantum) in infants (3), and of an acute febrile illness in young children (4,5). The ubiquitous nature of the virus is evident by the seroconversion of most children by the age of three years (4). While most cases of HHV-6 infection are self-limited and follow an uncomplicated course, seven fatal cases have been reported. The cause of death in fatal HHV-6 infection has been reported as hemophagocytic lymphohistiocytosis (6,7), encephalitis (8,9), hepatitis (10,11), and disseminated infection (12). Complete autopsy examination has only been reported once (12). We report another case of fatal disseminated HHV-6 infection in a child associated with sudden death.

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Clinical History

The patient was a 6¾-months'-old Latin American male infant with a history of otitis media treated with Zithromax. He subsequently developed nausea, vomiting, and diarrhea, which were treated with Pedialite and promethazine. Shortly after returning from a follow-up visit to the pediatrician, the child was found unresponsive in bed. Though he was transported to the emergency room, he could not be resuscitated.

Autopsy and Histopathologic Findings

At necropsy, the height and weight of the child were appropriate for age. Splenomegaly (47 g, normal 23 $\pm$ 10 g) and lymphadenopathy were grossly evident. A brisk atypical lymphoid infiltrate was seen microscopically in multiple organs. This consisted of a mixed population of small mature lymphocytes, large noncleaved lymphocytes, plasma cells, and immunoblasts. The lymphoid infiltrate was accompanied by varying numbers of eosinophils and histiocytes. The character of the infiltrate as well as the distribution had a striking similarity to the pathologic findings in Epstein-Barr virus (EBV) associated with acute infectious mononucleosis.

Sections of lungs revealed interstitial pneumonitis with an atypical mononuclear infiltrate as described above within the alveolar septa, the pulmonary vasculature, and extending into the perivascular regions and surrounding the bronchioles (Fig. 1*a*). Tracheitis was evident by a prominent mucosal and submucosal atypical lymphoid infiltrate.

The lymph nodes showed an interfollicular atypical mononuclear infiltrate, reactive germinal centers, and also extensive erythrophagocytosis. The paracortical areas of the spleen were expanded by the same atypical mononuclear infiltrate with focal erythrophagocytosis and marked congestion. The bone marrow had atypical mononuclear infiltrate and histiocytes with erythrophagocytosis.

Hepatic portal triads were expanded by the same atypical mononuclear infiltrate with focal extension past the limiting plate (Fig. 1*b*). Occasional hepatocellular necrosis, marked congestion, and a moderate amount of microvesicular steatosis were also noted. Sections of the heart showed an epicardial, interstitial, and perivas-

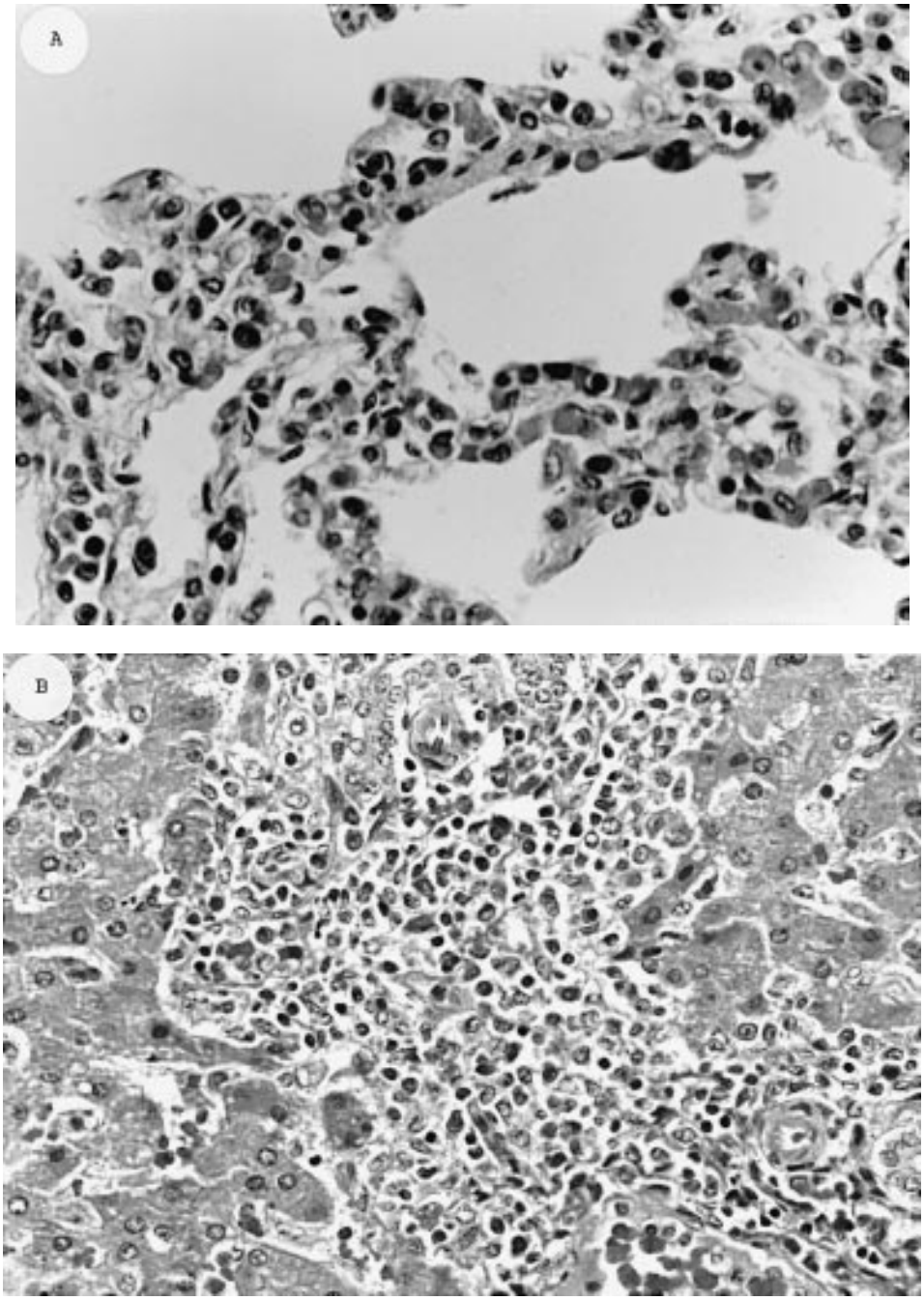


FIG. 1—*An atypical mononuclear infiltrate is seen within the pulmonary alveolar septae (Panel A, Hematoxylin and Eosin, ×150). It expands the hepatic portal tract with focal extension past the limiting plate (Panel B, Hematoxylin and Eosin, ×300), infiltrates the cardiac interstitium (Panel C, Hematoxylin and Eosin, ×300), focally invades the renal tubular epithelium (Panel D, Hematoxylin and Eosin, ×300), and fills the intravascular spaces in the brain (Panel E, Hematoxylin and Eosin, ×300). The presence of HHV-6 is demonstrated by the nuclear staining of some of these atypical cells within the pulmonary alveolar septae by in-situ hybridization (Panel F, ×300).*

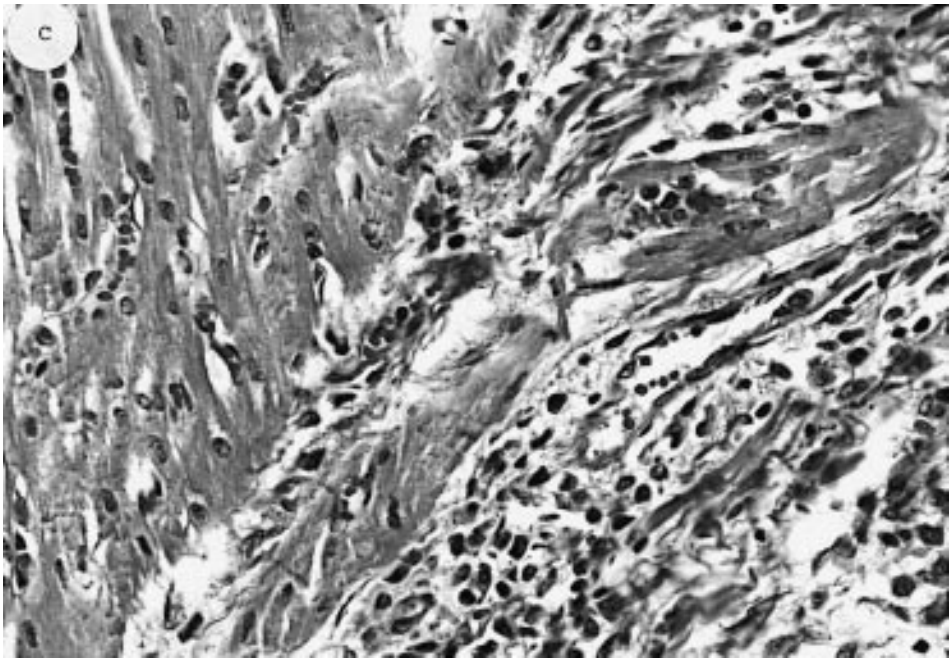
cular atypical mononuclear infiltrate with focal myocyte necrosis (Fig. 1*c*). The intravascular spaces in the heart and other organs showed large numbers of these atypical mononuclear cells. Interstitial atypical mononuclear infiltrate was seen within the renal cortex, which focally invaded the tubular epithelium (Fig. 1*d*).

Sections of brain showed similar atypical mononuclear cells within the blood vessels and in the perivascular spaces (Fig. 1*e*). There was also cerebral and cerebellar white matter gliosis with rarefaction consistent with edema, and medullary white matter gliosis with olivary gliosis.

The thymus showed acute stress involution. Sections of intestine showed a submucosal atypical mononuclear infiltrate focally extending into the mucosa and into the muscularis propria. Marked congestion was seen within both adrenals. Section of the thyroid revealed no histopathologic abnormalities.

Ancillary Studies

Immunohistochemistry—Formalin-fixed and paraffin-embedded sections from liver, lung, lymph nodes, and spleen were stained



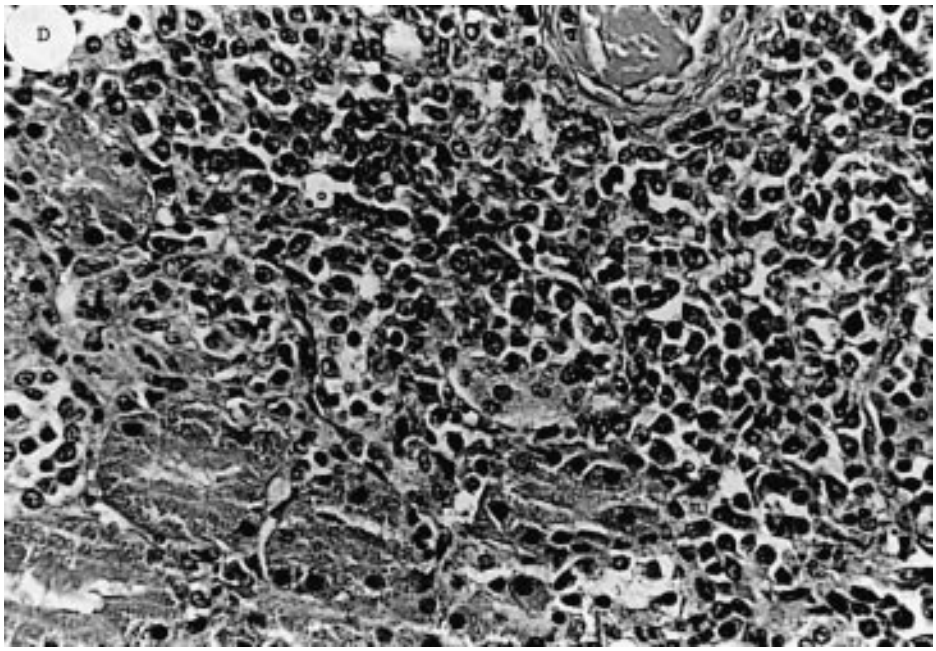


FIG. 1—*(Continued)*

immunohistochemically for pan B-cell (L26) and pan T-cell (UCHL-1, CD3) markers. The majority of the lymphoid cells (70%) were marked with UCHL-1, with a smaller population positive for CD3. Approximately 30% of the lymphoid infiltrate was stained with L26. The immunophenotype of the lymphoid cell did not correlate with morphology (i.e., degree of activation) by light microscopy.

Polymerase chain reaction (PCR)—DNA was extracted from a formalin-fixed and paraffin-embedded section of lung, and PCR amplification for EBV, CMV, and HHV-6 genomic DNA was performed as previously described (13,14). Prior to amplification for viral DNA, the integrity of the extracted DNA was assessed using primers to the human medium-chain acyl-CoA dehydrogenase gene. PCR analysis was positive for HHV-6 and negative for EBV and CMV. RT-PCR for HIV-RNA was not performed due to the unavailability of fresh tissue.

In-situ hybridization—HHV-6 in-situ hybridization (ISH) was performed on formalin-fixed and paraffin embedded sections from lung, kidney, lymph node, and spleen. HHV-6 was detected in the atypical lymphoid infiltrate in all four sections (Fig. 1*f*).

Serology—An HIV-1 antibody screen was performed which was nonreactive; however, in this age group an antibody screen may not be accurate. Antigen testing was not performed.

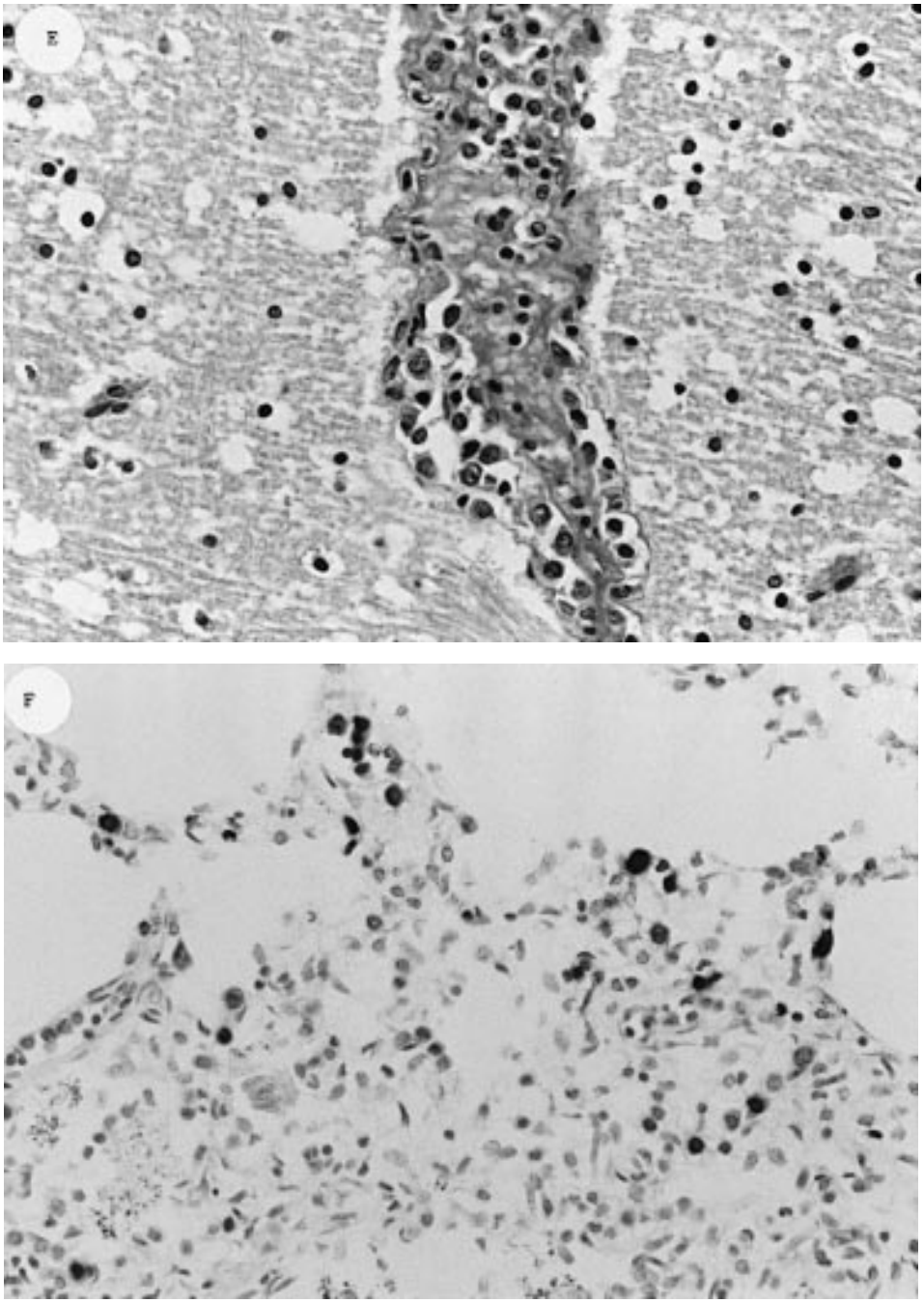


FIG. 1—*(Continued)*

Discussion

HHV-6 has been reported as a possible etiologic agent in a number of childhood illnesses, with exanthem subitum (roseola infantum) and acute febrile illness definitively associated with HHV-6 infection. Yamanishi et al. (3) found that HHV-6 could be cultured during the febrile phase of exanthem subitum and, further, that the children demonstrated seroconversion within weeks of the acute illness. Illness associated with primary HHV-6 infection accounted for 10 to 40% of febrile admissions of young children to the pediatric emergency department in two studies (4,5). Otitis media with fever was a common diagnosis in these cases. HHV-6 has been linked to a variety of disorders by studies in which the presence of HHV-6 was demonstrated through a wide range of methodologies such as serologic study, polymerase chain reaction, and in-situ hybridization. These disorders include infectious mononucleosis-like illness (15), virus-associated hemophagocytic syndrome (6,7,16,17), fatal disseminated infection (12), febrile seizures (4,23,24), and others (Table 1).

Seven cases of fatal HHV-6 associated illness have been reported in the literature (6–12); however, complete histopathologic description was documented solely in one publication (12) (Table 2). Only bone marrow examination revealing hemophagocytosis was described for the two cases of fatal hemophagocytic lymphohistiocytosis (6,7). Due to limitation of the autopsy permit, nonrevealing findings of the brain biopsies were reported in the

TABLE 1—*Spectrum of HHV-6 infections.*

Clinical Manifestations	References
Exanthem subitum (roseola infantum)	Yamanishi et al. (3)
Acute febrile illness	Hall et al. (4), Pruksanonda et al. (5)
Infectious mononucleosis-like illness	Steeper et al. (15)
Virus-associated hemophagocytic syndrome	Portolani et al. (6), Huang et al. (7), Liu et al. (16), Sugita et al. (17)
Fatal disseminated infection	Prezioso et al. (12)
Meningitis or encephalitis	Knox et al. (8), Asano et al. (9), Ishiguro et al. (18), Yoshikawa et al. (19), Patnaik et al. (20), Huang et al. (21), Suga et al. (22)
Febrile seizure	Hall et al. (4), Barone et al. (23), Kondo et al. (24)
Hepatitis	Mendel et al. (10)
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)	Levine et al. (25)

TABLE 2—*Fatal cases of HHV-6 associated illness.*

Age	Sex	Clinical Presentation	Histopathologic Findings	References
3 mo	F	fatal hemophagocytic lymphohistiocytosis. Fever, pharyngitis, rash, hepatosplenomegaly, heart failure, death on hospital day 10	bone marrow hemophagocytosis	Portolani et al. (6)
8 mo	F	fatal hemophagocytic lymphohistiocytosis. Fever, rash, hepatomegaly, pancytopenia, death on hospital day 13	bone marrow hemophagocytosis	Huang et al. (7)
14 mo	F	fatal fulminant encephalitis. HIV-infected. Fever, seizures, lymphadenopathy, hepatosplenomegaly, PB-atypical lymphocytes, death on hospital day 5	frontal cerebral cortex-diffuse edema, few glial nodules in the white matter	Knox et al. (8)
9 mo	F	fatal encephalitis/encephalopathy. Fever, seizures, death on hospital day 21	no inflammatory infiltrate seen in needle biopsy of brain	Asano et al. (9)
5 day	M	fatal fulminant hepatitis. Impaired liver function, respiratory difficulty, heart failure, PB-thrombocytopenia, CSF-pleocytosis, death on hospital day 15	premortem liver biopsy-lysis of hepatocytes	Mendel et al. (10)
3 mo	M	fatal fulminant hepatitis. Fever, jaundice, convulsions, coma, impaired liver function, elevated ammonia level	none described	Asano et al. (11)
13 mo	F	fatal disseminated infection. Immunocompetent. Fever, otitis media, rash, multisystem disease, PB-atypical lymphocytes, death on hospital day 5	atypical lymphoid cells with intracellular viral inclusions infiltrating multiple organs	Prezioso et al. (12)

HIV = Human immunodeficiency virus.
PB = Peripheral blood.
CSF = Cerebrospinal fluid.

cases of presumed fulminant encephalitis (8,9). Lysis of hepatocytes in an antemortem liver biopsy was mentioned in one of the fulminant hepatitis cases (10), and no histopathologic description was documented in the other (11).

In our patient, similar to the report by Prezioso et al. (12), an atypical mononuclear infiltrate was seen in multiple organs including the lymph nodes, spleen, lungs, liver, renal cortex, heart, intestine, and brain. Our patient, however, lacked the intranuclear viral inclusions described in that case. In addition, we observed erythrophagocytosis within the spleen, lymph node, and bone marrow. Knox et al. (8) described diffuse edema and occasional glial nodules in the white matter of the frontal cerebral cortex, which were also present in our case.

The distribution of the atypical lymphoid infiltrate within the organs of this patient mimicked that described in fatal infectious mononucleosis (26). The architecture of the lymph nodes was distorted, but not obliterated, with interfollicular expansion by a polymorphous atypical infiltrate. Reed-Sternberg-like cells, sheets of immunoblasts, and necrosis, sometimes described in acute infectious mononucleosis, were not present. In addition, brisk lymphoid infiltrates were seen in the spleen, liver, and lung, which are also characteristically affected in EBV infections (26). The presence of erythrophagocytosis as seen in this case can also occur with other herpesviruses including EBV infection. Because of these histologic findings, EBV was suspected to be the etiologic agent in this case. Included in the differential was CMV-associated infectious mononucleosis-like illness. EBV as well as CMV infection, however, were ruled out by PCR analysis of the postmortem tissues. HHV-6 was confirmed to be present within the infiltrate by both PCR and in-situ hybridization.

In summary, HHV-6 can rarely be associated with fatal dissemination and death. This case represents only the second report describing a complete autopsy. The diagnosis was based on positive results for HHV-6 by PCR and in-situ hybridization with negative results for EBV and CMV. The presence of myocardial involvement with associated necrosis suggests a cardiac arrhythmia as the likely mechanism of sudden death. This case reinforces the key role that the forensic pathologist can play in the characterization of newly recognized infectious diseases. We suggest that HHV-6 be considered as the etiologic agent in cases of disseminated viral infection with an atypical polymorphous lymphocytic infiltrate that are negative for EBV and CMV.

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