CASE REPORT

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Fatal Virus-Associated Hemophagocytic Syndrome in a Young Adult Producing Nontraumatic Splenic Rupture

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ABSTRACT: A 24-year-old man with no previous medical history was admitted to a local hospital with pancytopenia after a recent "viral illness." During his hospitalization, he developed sudden abdominal distension and hypotension. Surgical exploration of his abdomen revealed a ruptured spleen. The spleen was removed, but the patient did not survive the operation. We investigated this unexpected and unexplained hospital death for any traumatic or iatrogenic injury. The cause of death after review of the clinical history, autopsy, and microscopic sections was virus-associated hemophagocytic syndrome (VAHS). VAHS consists of a generalized histiocytic proliferation and marked hemophagocytosis associated with a systemic viral infection. Clinically it presents as pancytopenia and organomegaly. This recently described entity is often confused with malignant histiocytosis. This is the first case report of VAHS producing nontraumatic splenic rupture, thus adding to the differential diagnosis of spontaneous splenic rupture and sudden natural death.

KEYWORDS: pathology and biology, virus-associated hemophagocytic syndrome, splenic rupture, sudden death, hemophagocytosis, malignant histiocytosis

Natural death is the most frequently encountered cause of death in the medical examiner's office. Splenic rupture is an uncommon cause, usually due to infectious mononucleosis and often affecting young adults. We present a case involving fatal splenic rupture in a 24-year-old man who presented with a prolonged virallike illness and pancytopenia. Although no specific viral etiology was uncovered, this is most likely viral-associated hemophagocytic syndrome as described by Risdall et al. [*1*]. This is the first case of viral-associated hemophagocytic syndrome that is associated with nontraumatic splenic rupture.

Report

A 24-year-old man was in good health when he developed low-grade fever, fatigue, anorexia, and weight loss (8 lbs) over a period of 1 and one-half weeks. He did not

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improve on oral erythromycin. He was an outboard-motor technician and denied any allergies, alcohol or drug abuse, and took no other medications. He denied any risk factors for acquired immune deficiency syndrome (AIDS). He reportedly had no lymphadenopathy or skin rashes. He had hepatosplenomegaly. He denied any abdominal pain or complaints. He was admitted to a local hospital after he was found to be pancytopenic. His white blood count was 0.9 $\times$ 10^9/L, hemoglobin was 8.7 g/dL, and platelet count was 34 $\times$ 10^9/L. His red blood cells were normochromic and normocytic with rare teardrop forms. Occasional atypical plasmacytoid lymphotyces were present.

Serum total bilirubin was 1.6 mg/dL. Serum aspartate amino transferase (AST) and alanine amino transferase (ALT) were both elevated at 117 U/L and 247 U/L respectively. Serum ferritin was 2014 ng/mL (normal = 30 to 300). Prothrombin and partial thromboplastin times and fibrinogen were all within normal limits. Other immunologic and microbiologic test results are summarized in Table 1.

He was initially treated with prednisone and vancomycin. He showed no clinical or hematologic change until his seventh hospital day, when he developed sudden hypotension and abdominal swelling. A ruptured spleen was removed during emergency laparotomy. The patient did not survive this operation and he was referred to the medical examiner's office.

At postmortem examination, the skin was unremarkable, except for evidence of recent surgery. No contusions or broken ribs were seen. Bilateral pleural effusions were present. The lungs weighed 1220 and 790 g and were red, airless, and expressed abundant red fluid. The 320 g heart had normal coronary arteries and myocardium. The 2970 g liver was red-brown and swollen. The spleen was surgically absent and the lymph nodes were slightly enlarged. The remaining organs, including the brain, were normal. Postmortem blood was submitted for various serological tests summarized in Table 1.

Microscopic slides of the 530 gm spleen were available for review. The spleen was described as soft, friable, and easily fractured. No masses or nodules were seen. Microscopically, the red pulp was congested and filled with histiocytes showing erythrophagocytosis (Fig 1). The histiocytes did not have cytologic features of malignancy. The white pulp was normal. The bone marrow and lymph nodes contained similar histiocytes with marked hemophagocytosis. Both red blood cells and nucleated cells were engulfed by the ravenous scavengers (Fig. 2).

The liver showed alternating areas of congested and anemic parenchyma microscopically. Large collections of cytologically benign histiocytes filled the portal triads often spilling out into the surrounding parenchyma. This was accompanied by individual hepatocyte necrosis (Figs. 3 and 4). These histiocytes, as well as the kuppfer cells, showed marked hemophagocytosis.

TABLE 1—*Summary of premortem and postmortem testing.*

Premortem Tests	Postmortem Tests
HCV—negative	Heterophile, mono screen—negative
CMV antibodies—negative	EBV VCA[a] IgG—1:40
HIV—negative	EBV EBNA[b]—1:10
ANA—negative	EBV early Ag R + D[c]—1:20
HBsAg—negative	CMV (IgG)—negative
HBsAb-negative	HSV I (IgG)—negative
HBcAb—negative	HSV II (IgG)—negative
HAV (IgM)—negative	Adenovirus Ab—Less than 1:8
Blood cultures—negative	
Stool cultures—no pathogens	

[a]VCA—Viral capsid antigen.
[b]EBNA—Epstein-Barr nuclear antigen.
[c]R + D—restricted and diffuse types of early antigens.

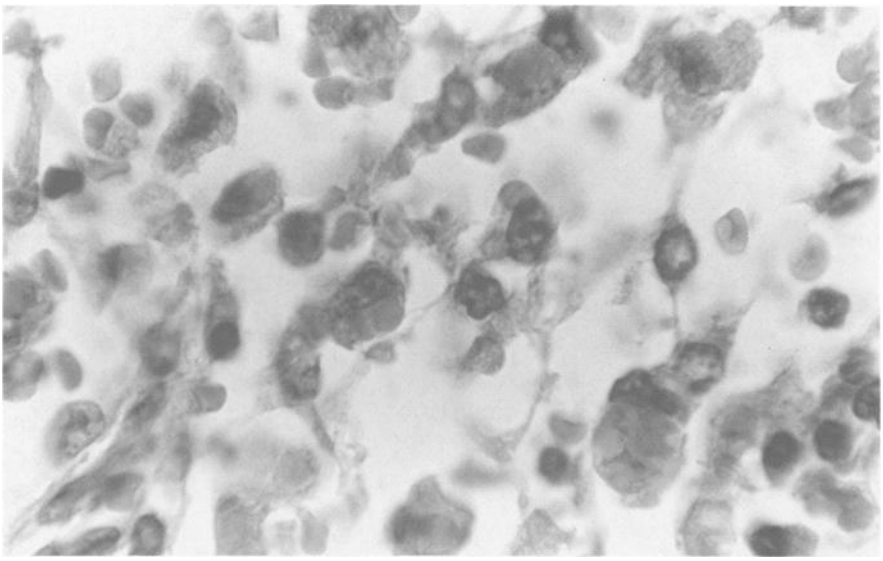

FIG. 1—*Histiocytes with erythrophagocytosis within the splenic sinuses* [*Hematoxylin and eosin, 150x*].

Examination of the lung revealed focal exudation containing fluid, red blood cells, and histiocytes. Lymphocytes and polymorphonuclear leukocytes were sparse. Lymphocytes and histiocytes were seen concentrated around bronchioles (Fig. 5), muscular vessels, and within the interstium. No viral cytopathic effect was seen in any cells. Immunohistochemistry failed to detect cytomegalovirus (CMV) and the herpes simplex viruses (I and II).

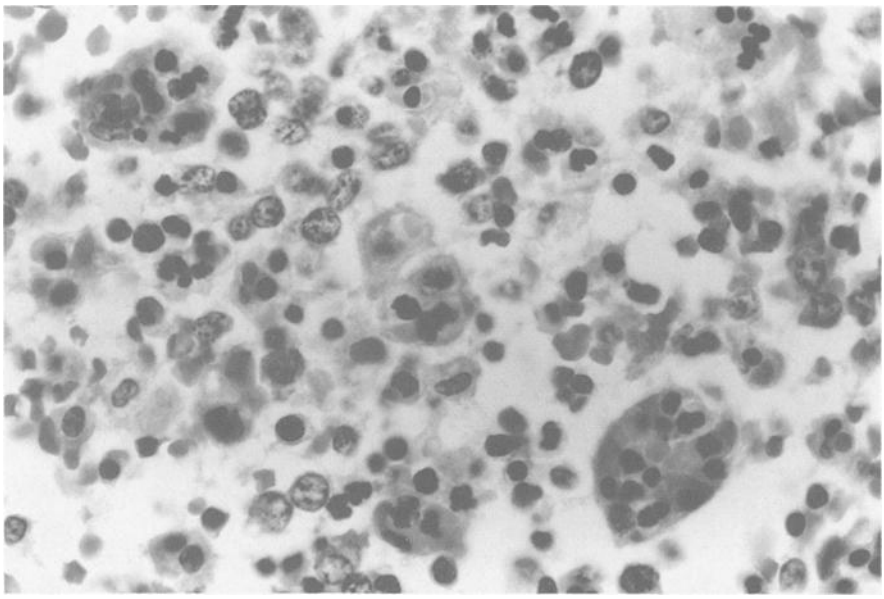

FIG. 2—*Cytologically benign histiocytes engulf red blood cells and nucleated cells within the bone marrow* [*Hematoxylin and eosin, 80x*].

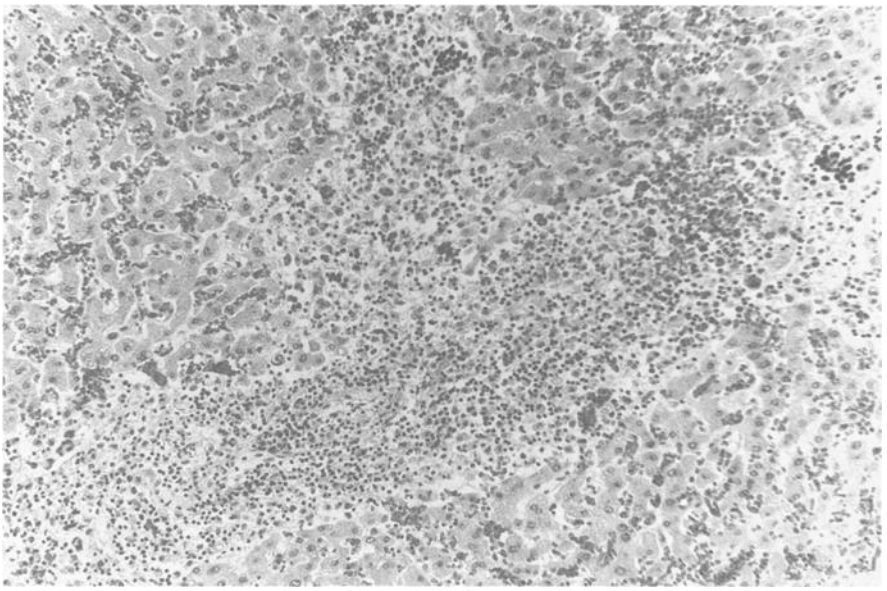

FIG. 3—*The portal regions are filled with lymphocytes and histiocytes. There are also foci of extramedullary hematopoeisis and hepatocyte necrosis [Hematoxylin and eosin, 25x].*

Discussion

Sudden death due to nontraumatic or spontaneous splenic rupture has many causes (Table 2) and is often seen by medical examiners. We investigated this death because traumatic or iatrogenic injury may have caused the splenic rupture and hemoperitoneum in this previously healthy young man.

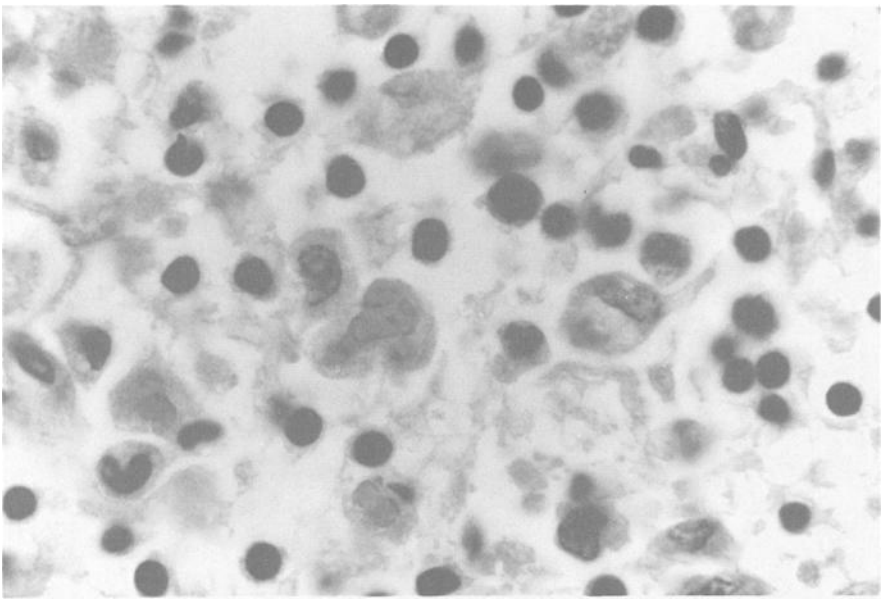

FIG. 4—*Erythrophagocytosis is a dominant feature of the histiocytes infiltrating the liver [Hematoxylin and eosin, 100x].*

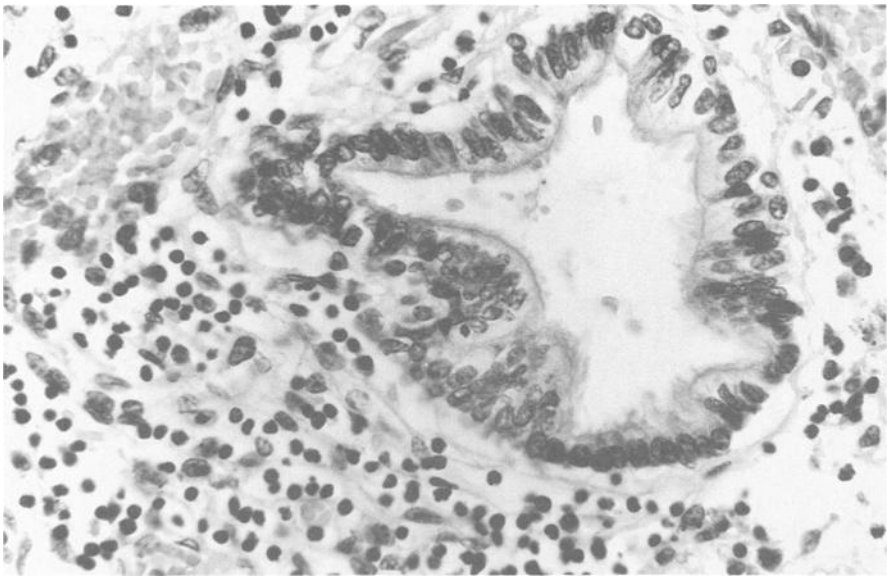

FIG. 5—*This bronchiole shows a lymphocytic and histiocytic infiltrate without necrosis of the respiratory epithelium [Hematoxylin and eosin, 100x].*

Viral-associated hemophagocytic syndrome (VAHS), also known as histiocytic medullary reticulosis, is an imperfectly defined constellation of signs, symptoms, and laboratory findings. There is a history of a virallike illness 2 to 6 weeks prior to the onset of symptoms. The syndrome begins with increased fever, severe constitutional symptoms, hepatosplenomegaly, lymphadenopathy, pancytopenia, elevated liver function tests, and occasionally macular skin rash or pulmonary infiltrates on chest x-ray [*2*]. The peripheral smear is usually unremarkable. Hyperferritinemia is a frequent laboratory finding [*3,4*]. The decedent had all these findings except for the skin rash or pulmonary infiltrates. There is usually a viral infection (Table 3), however, nonviral agents and various diseases have been implicated in this syndrome (Table 3). There was no evidence of CMV, Ebstein-Barr virus, herpes simplex virus, hepatitis A, B, or C, human immunodeficiency virus, adenovirus, bacterial, mycobacterial, or fungal infection in this patient.

The organs most often affected in VAHS are the bone marrow, lymph nodes, spleen, and liver. Mature histiocytes with benign cytologic features are prominent in each of these organs. In the liver, they overrun the portal areas spilling into the sinusoids producing focal hepatocellular necrosis. Striking hemophagocytosis by these histiocytes account for the syndrome's name. Phagocytosis of red blood cells, platelets, and white cells results in pancytopenia. The leptomeninges are rarely involved [*2*]. Except for the meninges, all of the above organs were affected in the decedent. The infiltration of the splenic capsule by these cells, as in infectious mononucleosis, accounted for the spontaneous rupture of the spleen.

VAHS can be confused with malignant histiocytosis [*5*]. The histiocytes in malignant histiocytosis are immature with malignant cytologic features. The cells are large, 20 to 40μ, with reticular nuclear chromatin, variably prominent nucleoli, a high nuclear:cytoplasmic ratio, and deeply basophilic cytoplasm containing a few sharply defined clear 1 to 2μ vacuoles. There is usually no hemophagocytosis in these malignant histiocytes. The bone marrow is usually not involved at the time of diagnosis in malignant histiocytosis [*1,2*]. These negative findings are helpful in the differential diagnosis. The

TABLE 2—*Causes of non-traumatic splenic rupture.*

Viral
Epstein-Barr virus [*7–16*]
Infectious hepatitis [*17,18*]
Mumps [*19*]
Viral-Associated Hemophagocytic syndrome
HIV infection [*20*]
Varicella-zoster [*21*]
Bacterial
Infectious endocarditis [*22–24*]
Typhoid fever [*25*]
Parasitic
Malaria [*26–28*]
Hematologic Malignancies/Disorders
Hairy cell leukemia [*29*]
Lymphoma [*30,31*]
Mycosis fungoides [*32*]
Acute and chronic granulocytic leukemia [*11,33–37*]
Myelodysplastic syndrome [*38*]
Waldenstrom's macroglobulinemia [*33*]
Hemophilia [*39*]
Other Malignancies and Tumors
Angiosarcoma [*40,41*]
Metastatic carcinoma [*42–45*]
Metastatic melanoma [*33*]
Capillary hemangioma [*46*]
Connective Tissue Disorders/Vasculitis
Periarteritis nodosa [*47,48*]
Rheumatoid arthritis [*49–51*]
Amyloidosis [*52*]
Miscellaneous
Peliosis [*53*]
Abdominal ectopic pregnancy [*54,55*]
Chronic pancreatitis/pseudocyst [*56,57*]
Crohn's disease [*58*]
Sarcoidosis [*59,60*]
Splenic artery aneurysm [*61,62*]
Uremia [*63*]

use of immunohistochemistry has shown that the majority of cells in malignant histiocytosis contain T-cell antigens. These authors now favor replacing the term malignant histiocytosis with sinusoidal large cell lymphoma [*6*]. The malignant features were not present in the decedent.

Risdall's original article had two different clinical groups. One group (14 patients) were immunosuppressed, predominantly renal transplant patients. The other group (5 patients) developed VAHS in the absence of an underlying disease [*1*]. In those patients without an underlying disease or immunosuppression, only two had conclusively diagnosed viral infections (EBV and adenovirus). The lymphocytic bronchiolitis in the de-

TABLE 3—*Disorders and pathogens associated with viral-associated hemophagocytic syndrome.*

Epstein-Barr virus (EBV) [*1,64–69*]
Cytomegalovirus (CMV) [*1,70,71*]
Measles [*72*]
Parvovirus B19 [*73,74*]
Herpes zoster [*75*]
Echovirus [*1*]
Coxsackie A9 [*76*]
Leismaniasis [*77*]
Brucellosis [*78*]
Tuberculosis [*79–82*]
Trichosporon beigelii [*83*]
Gram negative bacteria [*82–85*]
Unknown [*82,86*]
Peripheral T-cell lymphoma [*82,87–89*]
Acute and chronic lymphocytic leukemia [*90,91*]
X-linked lymphoproliferative syndrome [*66,67*]
Hodgkin's and non-Hodgkin's lymphoma [*92,93*]
Germ cell tumor [*94*]
Gastric carcinoma [*95*]
Ovarian carcinoma [*82*]

cedent suggests a viral agent, however, viral antibody titers and immunohistochemistry failed to detect a specific agent. We did not test for every possible virus known.

In summary, we presented a case of nontraumatic splenic rupture in a 24-year-old man who had the clinical course and autopsy findings seen in viral-associated hemophagocytic syndrome. Although a viral etiology is suspected, it could not be confirmed in this case. VAHS should be included in the differential diagnosis of spontaneous or nontraumatic rupture of the spleen.

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