

CORRESPONDENCE

Disseminated Herpes Simplex Type 2 and Systemic *Candida* Infection in a Patient with Previous Asymptomatic Human Immunodeficiency Virus Infection

COLLEAGUES—Fulminant hepatitis and disseminated infection caused by herpes simplex virus (HSV) is rare and usually found only in patients with impaired cellular immunity [1]. No case of fulminant hepatic failure due to HSV infection has been reported, however, in patients with AIDS [1, 2]. We recently observed such a patient with previously unrevealed human immunodeficiency virus (HIV) infection.

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A 21-y-old woman left Switzerland for a vacation in Kenya on 4 April 1985. During the next several days she suffered from painful ulcers at the external genitalia, vaginal discharges, high fever, chills, severe abdominal cramps, anorexia, and fatigue. On 15 April, episodes with watery diarrhea began; two days later she became anuric. On 18 April she returned to Switzerland and was hospitalized. A medical history revealed that the patient had used marijuana occasionally since 1980 but no intravenous drugs; she had had sexual intercourse with several men. Physical examination on admission revealed an afebrile, fatigued woman in acute distress who had generalized dehydration, jaundice, and hypotension (90/60 mm Hg). The liver was increased to 18 cm; the abdomen was distended, with diffuse peritonitis. The vulva was covered with vesicles and ulcers. Laboratory data revealed leukopenia (1900/ μ L with 19% lymphocytes), thrombopenia (31 000/ μ L), renal failure (creatinine 634 μ M), hypoglycemia (2.2 mM), aci-

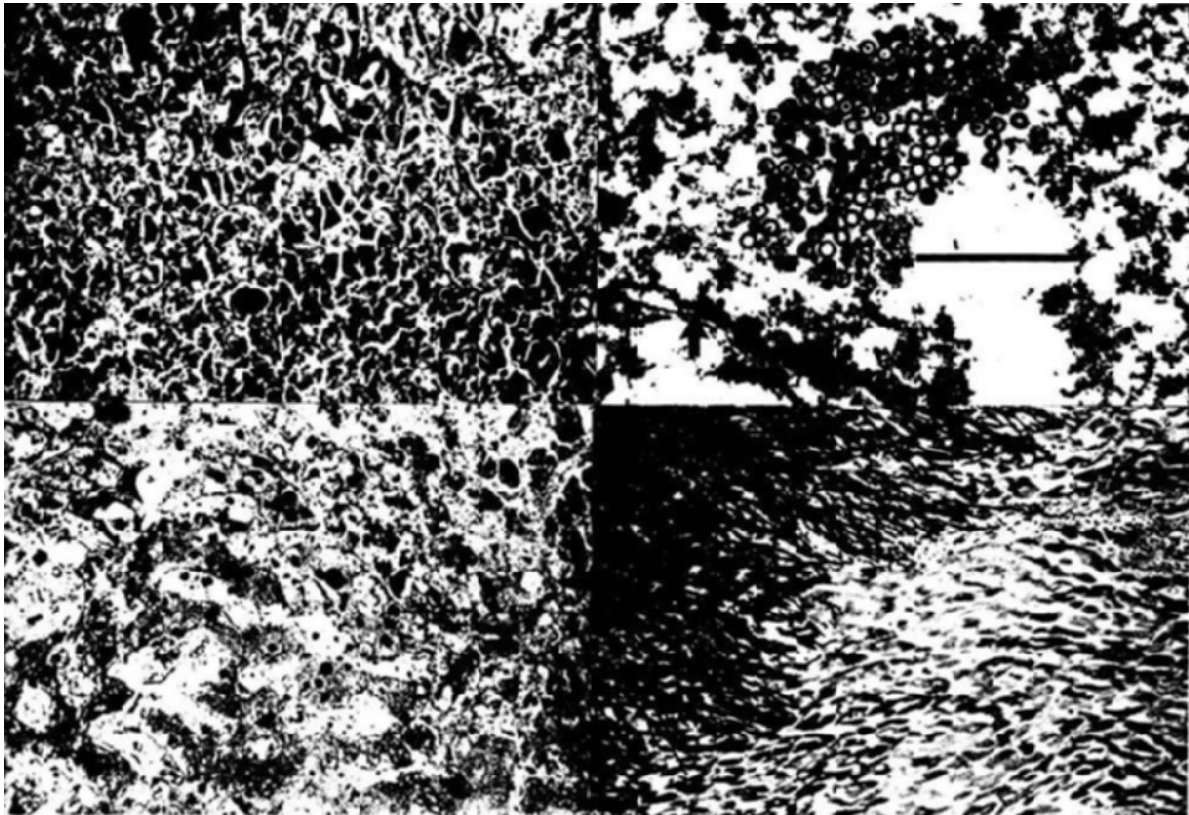


Figure 1. *Top left*, massive hemorrhagic liver necrosis (bottom of panel). Most hepatocytic nuclei contain inclusion bodies, a factor giving the nucleus a ground glass-like appearance (*arrow*). Multinucleated giant cells are shown by the *arrowhead* (magnification, $\times 86.25$; stained with hematoxylin and eosin). *Top right*, transmission electron micrograph of intranuclear viral particles in a hepatocyte (nuclear membrane shown by *arrow*; *bar*, 1 μ m). *Bottom left*, hepatocytic nuclei expressing HSV DNA sequences (*black dots*) evidenced by in situ hybridization of liver tissue with an HSV-1/HSV-2 DNA probe (magnification, $\times 86.25$; counter-stain, light green). *Bottom right*, massive invasion of *Candida*, with necrosis of myocardium (magnification, $\times 86.25$; stained with Methenamine silver).

dosis (lactate, 14.5 mM), liver failure (serum aspartate aminotransferase, 5820 units/L), and disseminated intravascular coagulation (prothrombin, 21% of control; fibrinogen, 0.86 g/L; factor V, 11% of control; fibrinogen split products, >40 µg/mL). Serological studies excluded acute infections with hepatitis A, hepatitis B, varicella-zoster virus, HSV (IgG, 1:1000; IgM, negative), Epstein-Barr virus, cytomegalovirus, salmonellosis, listeriosis, amebiasis, malaria, leishmaniasis, and toxoplasmosis.

The course of disease in the intensive care unit was characterized by increasing clouding of consciousness, hypothermia (minimum body temperature, 32.5 C; maximum, 35.6 C), seizures, generalized bleeding from the upper and lower gastrointestinal tracts and puncture sites, hypotension requiring adrenergic support, and respiratory failure requiring ventilation. During the five days of hospitalization the patient was treated with broad-spectrum antibiotics but with no antifungal or antiviral drugs, because of inappropriate diagnosis. The final course of illness was characterized by signs of decerebration (dilated and unreactive pupils, bradycardia), persistent acidosis and disseminated intravascular coagulation, and terminal liver and renal failure. On 23 April the patient died of a brain edema that was not responsive to mannitol and of irreversible heart failure (shock, increasing central venous pressure, asystolia not responsive to intracardiac pacing). After death the diagnosis of HIV infection was established by detecting serum antibodies to viral structural proteins by using the western immunoblotting technique.

An autopsy revealed generalized HSV infection with necrotic-hemorrhagic foci in the vulva, liver, spleen, pancreas, intestine, and brain. In the liver, hemorrhagic necrosis affected >70% of the parenchyma (figure 1, top left). Electron microscopy showed viral inclusion bodies (figure 1, top right). DNA-DNA in situ hybridization for HSV DNA was performed with appropriate controls by using a biotinylated DNA probe [3]. It revealed DNA sequences of HSV (combined HSV type 1/HSV type 2 [HSV-1/HSV-2] probe) in the liver (figure 1, bottom left), pancreas, and vulva. HSV-2 was isolated postmortem from the liver and grown in Vero (monkey-kidney) and MCR (human fibroblast) cells. Specific (HSV-1 or HSV-2) virus typing was done by immunofluorescence using monoclonal antibodies to HSV. As manifestations of candida septicemia, necrotic foci were detected in multiple organs, including myocardium (figure 1, bottom right). The pathology of the lymph nodes was compatible with the atrophic stage of HIV lymphadenopathy.

The patient we describe here was, by medical history, a healthy young woman who suffered from acute liver failure and local genital herpes. In postmortem studies, we detected disseminated HSV-

2 infections with three different techniques. First, HSV was isolated and grown from liver tissue and identified as HSV-2 by immunofluorescence using monoclonal antibodies to HSV-1 and HSV-2. Second, electron microscopy revealed intranuclear viral particles in liver tissue. Third, the identity of these intrahepatic viral particles was further defined by in situ hybridization. The clinical manifestation, the virus type (HSV-2), and the presence of HSV DNA sequences in vulva tissue indicated that genital herpes was the primary focus. Dissemination of a nonprimary HSV-2 infection is extremely rare and not yet described in patients with HIV infection [1, 2]. In this patient, genital herpes was not a primary infection because she had no IgM antibodies to HSV, whereas she did have IgG antibodies to HSV.

A second particular feature in this patient was the disseminated fungal infection. In patients with AIDS, although mucocutaneous *Candida* infection is very common, dissemination of such infections is rare [2]. This case illustrates, however, that congestive cardiomyopathy in association with AIDS is not limited to myocardial Kaposi's sarcoma [4] or HIV myocarditis [5] but may also be a fatal complication of an opportunistic fungal infection. The condition of this patient indicates that in the differential diagnosis of fulminant hepatitis, the possibility of HSV dissemination complicating previously unrevealed HIV infection should be considered. Because acyclovir may offer a better survival, liver biopsy and analysis using a hybridization technique should be performed in cases such as ours.

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References

1. Chase RA, Pottage JC Jr, Haber MH, Kistler G, Jensen D, Levin S. Herpes simplex viral hepatitis in adults: two case reports and review of the literature. *Rev Infect Dis* 1987;9:329-33
2. Masur H, Lane HC. The acquired immunodeficiency syndrome. In: Remington JS, Swartz MN, eds. *Current clinical topics in infectious diseases*. Vol 6. New York: McGraw-Hill, 1985:1-39
3. Singer RH, Ward DC. Actin gene expression visualized in chicken muscle tissue culture by using in situ hybridization with a biotinylated nucleotide analog. *Proc Natl Acad Sci USA* 1982;79:7331-5
4. Silver MA, Macher AM, Reichert CM, Levens DL, Parillo JE, Longo DL, Roberts WC. Cardiac involvement by Kaposi's sarcoma in acquired immune deficiency syndrome (AIDS). *Am J Cardiol* 1984;53:983-5
5. Cohen IS, Anderson DW, Virmani R, Reen BW, Macher AM, Sennesh J, Di Lorenzo P, Redfield RR. Congestive cardiomyopathy in association with the acquired immunodeficiency syndrome. *N Engl J Med* 1986;315:628-30