

## Herpes Simplex Virus Hepatitis: Case Report and Review

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Hepatitis is an unusual manifestation of herpesvirus infection. Herpes simplex virus hepatitis is a difficult diagnosis to establish, and the infection is often fatal. We report one case of herpes simplex virus hepatitis and review 51 cases in the literature. Impaired immunity resulting from pregnancy, malignancy, immunosuppression, or inhalational anesthetics may be predisposing factors. Fever, nausea, vomiting, abdominal pain, leukopenia, thrombocytopenia, coagulopathy, and a marked rise in serum transaminase levels are invariably present. Liver biopsy is the procedure of choice for diagnosis. The liver appears mottled and has a minimal inflammatory response. Mortality rates associated with herpes simplex virus hepatitis are high, and early diagnosis and treatment with acyclovir or vidarabine may produce a favorable outcome.

Hepatitis secondary to infection with herpes simplex virus (HSV) type 1 or 2 is a rare, frequently fulminant disease typically affecting patients with impaired immunity. The antemortem diagnosis is often difficult to establish because the clinical features are nonspecific. Signs and symptoms include fever, anorexia, nausea, vomiting, abdominal pain or tenderness, leukopenia, coagulopathy, and a marked rise in serum transaminase levels without jaundice. We present a case of fatal hepatitis secondary to HSV type 1 infection that simulated the clinical presentation of an infarcted bowel. In addition, we review the previously reported cases of HSV hepatitis and discuss the presumed mechanisms and pathology of the disease, diagnostic methods, and treatment.

### Case Report

A 66-year-old man was admitted to our institution for resection of a recurrent suprasellar tumor. The results of the preoperative physical examination were within normal limits except for decreased visual acuity. Radical excision of a meningioma on the dorsum sella was performed while the patient was under general anesthesia. Drugs utilized intraoperatively were thiopental, fentanyl citrate, vecuronium, isoflurane, pancuronium bromide, nitrous oxide, neostigmine, glycopyrrolate, methylprednisolone, and phenytoin.

On postoperative day 1, the patient's temperature increased to 102°F, and he appeared lethargic. His physical examination was notable for a clean, dry surgical site; a crusted cutaneous lesion on an erythematous base where his endotracheal tube had been taped at the corner of his mouth; meningismus; and bilateral basilar rales. Neurological examination did not reveal

a focus, but the patient was difficult to arouse. A CT of the head and evaluation of the CSF demonstrated expected postoperative changes.

The patient was treated with vancomycin (500 mg every 6 hours) and ceftazidime (2 g every 8 hours) for presumed bacterial infection. Culture of a skin lesion for HSV was performed; however, acyclovir therapy was not initiated because the clinical suspicion that this was a hepatic lesion was low. All cultures were negative, including that of the skin lesion. Therapy with phenytoin and methylprednisolone was continued. Thereafter, the patient's mental status improved, although low-grade fever persisted until postoperative day 11.

Therapy with all antibiotics was discontinued on postoperative day 13. On postoperative day 14 his temperature increased to 104°F, and empirical therapy with vancomycin and ceftazidime was started. The patient remained febrile from postoperative days 14 to 20.

On postoperative day 20, the patient's condition acutely deteriorated. He was noted to be lethargic with a systolic blood pressure of 80 mm Hg, a pulse rate of 120, a respiratory rate of 26, and a temperature of 103°F. Diffuse abdominal tenderness was present, and bowel sounds were absent. Oozing of blood was noted from the two intravenous sites. Arterial blood gas determinations while the patient was receiving a fraction of inspired O<sub>2</sub> of 0.4 revealed the following: pH, 7.40; PaCO<sub>2</sub>, 23 mm Hg; PaO<sub>2</sub>, 109 mm Hg; and HCO<sub>3</sub> concentration, 14 mmol/L.

Laboratory studies disclosed the following: WBC count, 4,800/mm<sup>3</sup>; hematocrit, 31.3%; platelet count, 20,000/mm<sup>3</sup>; prothrombin time, 15.7 seconds; partial thromboplastin time, 56 seconds; international normalized ratio, 15.7; serum amylase level, 175 mg/dL; blood urea nitrogen level, 27 mg/dL; creatinine level, 1.9 mg/dL; arterial lactate level, 13.5 mg/dL; and glucose level, 172 mg/dL.

The patient was intubated and monitored invasively in the intensive care unit. Initial hemodynamic parameters were as follows: cardiac output, 5 L/min; cardiac index, 2.6 L/(min · m<sup>2</sup>); wedge pressure, 11 mm Hg; systemic vascular resistance, 944 dyne/(s · cm<sup>5</sup>); and mixed venous oxygen satu-

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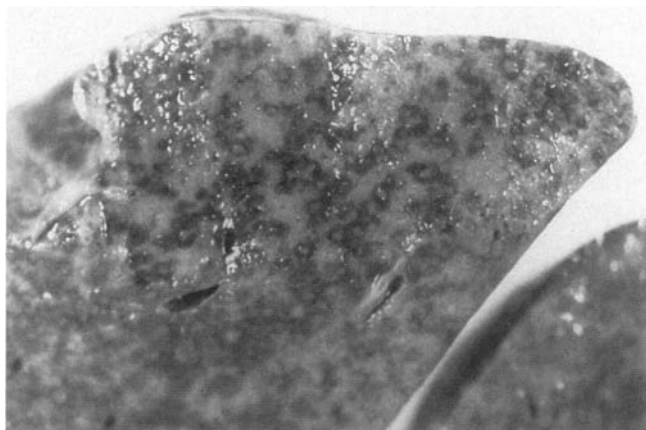
ration, 76%. Assist/control mode ventilation was started. Arterial blood gas determinations while the patient was receiving a fraction of inspired O<sub>2</sub> of 0.5 revealed the following: pH, 7.15; PaCO<sub>2</sub>, 22 mm Hg; and Pao<sub>2</sub>, 117 mm Hg. He was resuscitated with a transfusion of fresh frozen plasma, platelets, and 5% albumin. Dobutamine and dopamine infusions were started in an attempt to increase cardiac and urinary outputs.

Because of abdominal tenderness, a surgical consultant recommended abdominal CT; this scan revealed small bowel edema and ascites, findings consistent with the diagnosis of bowel ischemia. The liver was normal. Exploratory laparotomy demonstrated findings consistent with diffuse hepatic necrosis and ascites. The bowel was not obstructed or infarcted. The patient was returned to the intensive care unit where he died the following day. Results of liver function tests that became available while the patient was still in the operating room were consistent with acute hepatic necrosis (serum aspartate amino transferase level, 10,340 U; lactate dehydrogenase level, 13,360 U; and total bilirubin level, 1.9 mg/dL).

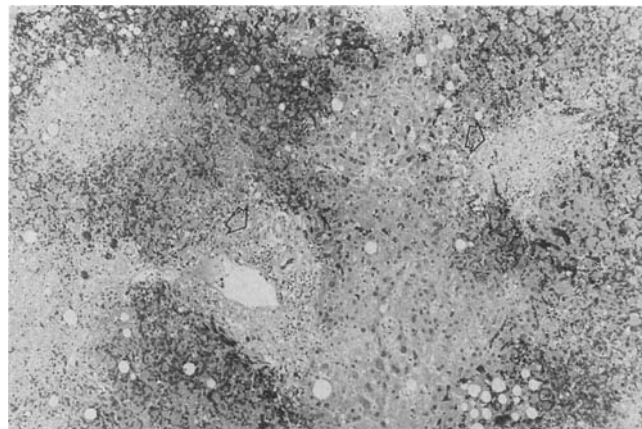
At autopsy, the most striking findings were in the liver. Macroscopically, the liver was dark red and congested with serpiginous yellow necrotic zones (figure 1). Histologically, there were zonal areas of necrosis and hemorrhage involving ~80% of the liver parenchyma. Within these zones, residual hepatocytes had enlarged "ground glass" nuclei with margination of chromatin, which is diagnostic of HSV hepatitis (figures 2 and 3). The diagnosis was further verified by positive results of an immunohistochemical study with antibodies to HSV type 1 (Dako, Carpinteria, CA). In addition, electron microscopy revealed viral particles. Pathological examination of other organs (such as the lungs, adrenal glands, oropharynx, esophagus, and rectum) also revealed findings consistent with HSV infection.

## Discussion

Hepatitis secondary to HSV infection occurs primarily in neonates and malnourished children and is usually fatal [1–4].



**Figure 1.** The liver of a patient with herpes simplex virus hepatitis. Note the confluent zonal areas of hemorrhagic necrosis.



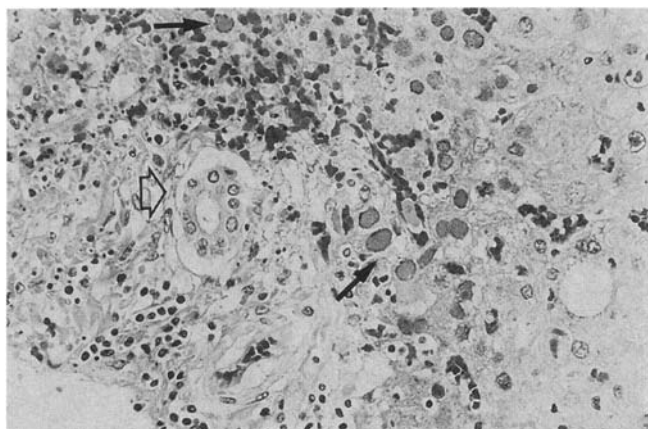
**Figure 2.** Postmortem liver specimen from a patient with herpes simplex virus hepatitis. The portal tracts (*open arrows*) are surrounded by hemorrhagic (dark) and necrotic (light) areas. The parenchyma between the marked portal tracts is relatively well preserved (stain, hematoxylin-eosin; original magnification,  $\times 40$ ).

Fulminant hepatitis due to HSV is rare in adults. It can occur in apparently immunocompetent adults; however, it is primarily a disease of patients with impaired immunity [5, 6]. The first reported case of HSV hepatitis was in 1969 [7]; it occurred in a pregnant patient.

Severe HSV infection is most commonly associated with defects in cell-mediated immunity that may occur after renal transplantation as a result of administration of azathioprine and steroids [8–15]; during steroid administration for other reasons, such as head trauma [16], chronic obstructive pulmonary disease [16], and asthma [17]; or in association with celiac disease [18], pemphigus vulgaris [19, 20], systemic lupus erythematosus [21], myelodysplastic syndrome [21], burns [22], thymic dysplasia [23], AIDS [24], ulcerative colitis [25], inhalational anesthetics [26–28], pregnancy in the late second or third trimester [7, 29–36], cancer [36–38], and vulvovaginitis [39]. Cases have also been described in patients without any underlying conditions [36, 40–46] (table 1).

Four mechanisms for HSV dissemination and resultant hepatitis have been hypothesized [46]: (1) a large HSV inoculum at the time of the initial infection may overwhelm the defense system and result in visceral dissemination; (2) fulminant hepatitis may occur as a result of dissemination from mucosal herpetic lesions because of an impairment in macrophages, cytotoxic T lymphocytes, and delayed-type hypersensitivity reactions; (3) the virulence of HSV may be enhanced by activation of a latent virus possibly in association with reinfection by a second strain of HSV; and (4) there may be some strains of HSV that are hepatovirulent.

HSV hepatitis has been associated with pregnancy in the late second or third trimester [7, 29–36]. A decrease in the IgG level has been described from the 27th to the 33rd week of pregnancy. This decreased level correlates with the 20% to 30% hemodilution that occurs in pregnancy at this time [47,



**Figure 3.** Postmortem liver specimen from a patient with herpes simplex virus hepatitis. The bile duct has intact epithelium (*open arrow*) and is surrounded by hemorrhagic necrosis and a mild portal lymphocytic infiltrate. Numerous hepatocytes with enlarged "ground glass" nuclei and margination of chromatin (*solid arrows*), which are characteristic of herpes simplex virus infection, are present in the preserved parenchyma (stain, hematoxylin-eosin; original magnification,  $\times 400$ ).

48]. In addition, there is a significant reduction in the maternal lymphocyte response to phytohemagglutinin in most pregnant women [48–50]. There is also a decrease in the number of T cells during pregnancy, and the T cell count is lowest during the third trimester [51].

Administration of inhalant anesthetics, such as enflurane, isoflurane, desflurane, and nitrous oxide, has been associated with subsequent fulminant hepatitis due to massive HSV infection [26–28]. Nitrous oxide can diminish the immune response and predispose patients to a decreased capacity to resist a viral infection. In vitro studies have demonstrated that patients with cancer who receive nitrous oxide have a mitigated ability to kill tumor cells [52, 53]. However, HSV hepatitis may develop in association with administration of anesthetic agents merely by chance.

### Pathology

Gross examination of the liver reveals a mottled appearance riddled with multiple red-yellow lesions. Histologically, these are irregular zones of confluent hemorrhagic necrosis, scattered acidophilic bodies, destruction of the reticulin network, and intranuclear "ground glass" inclusions with margination of chromatin and a minimal inflammatory response. This coagulation necrosis is predominantly centrilobular with minimal portal involvement.

In contrast, hepatitis in association with halogenated anesthetic agents appears more discrete and has clearly defined centrilobular necrosis with mitochondrial membrane disruption [54]. The intranuclear inclusions are the most distinctive feature of HSV hepatitis, but contrary to other organs, nuclear

molding and formation of multinucleated giant cells are not seen. Immunohistochemical analysis with antibody specific to HSV or electron microscopy can be used for diagnostic confirmation.

### Clinical Features

The clinical picture of HSV hepatitis is usually fulminant, resembling septic shock more than hepatic failure. The clinical picture can also be reminiscent of halothane hepatitis with postoperative fever, impaired liver function, fulminant hepatic necrosis, and death within 3 to 11 days. Patients with disseminated HSV hepatitis usually remain moderately ill for a period of 3 to 10 days, and then suddenly their conditions deteriorate with hepatic necrosis, disseminated intravascular coagulation (DIC), hypotension, and death usually within 1 week.

### Literature Review

Fever was described in 82% of the 52 patients within 30 days of the diagnosis of HSV hepatitis. Patients can have severe abdominal pain and peritoneal signs: 33% of the 52 patients had right upper quadrant pain or tenderness, and 18% had nausea and/or vomiting. Skin, mouth, and/or genital lesions were present in 57% of the patients whose cases were reviewed. Of the 52 patients, 14 (27%) had oral mucocutaneous lesions, 16 (31%) had genital lesions, and only 2 (4%) had both oral and genital lesions.

Forty-three percent of the patients had a WBC count of  $<5,000/\text{mm}^3$ . Forty-five percent of the patients had a platelet count of  $<150,000/\text{mm}^3$ . DIC was described in 35% of the patients. Coagulopathy not associated with DIC was noted in

**Table 1.** Underlying conditions in 52 patients with herpes simplex virus hepatitis.

Underlying condition	No. of patients
Renal transplant	9
Use of steroids (other than those for renal transplant)	10
CNS edema	3
Pemphigus vulgaris	2
Chronic obstructive pulmonary disease	1
Asthma	2
Celiac disease	1
Myelodysplastic syndrome	1
Ulcerative colitis	1
Systemic lupus erythematosus	1
Polio	1
Pregnancy	9
Burns	2
Cancer	7
Thymic dysplasia	1
AIDS	1
Inhalational anesthetics	4
None	8

20% of the cases. Hepatomegaly was found in 45% of the patients during hospitalization or at the time of autopsy. In 71% of the cases, the results of liver function tests were abnormal.

The correct diagnosis was made before death in only 12 (23%) of the 52 reported cases. The mortality rate among this group of patients was >80%; five of nine of these patients who received antiviral treatment died. The difficulty in establishing the diagnosis of HSV hepatitis is that clinical features are nonspecific, including the presence of high-grade fever, leukopenia, and a marked rise in serum transaminase levels without jaundice.

HSV infection should be included in the differential diagnosis for all patients with fulminant hepatitis despite the absence of typical mucocutaneous lesions and obvious predisposing factors. The simultaneous occurrence of three events (a rise in temperature, a marked elevation of serum transaminase levels, and a severe decrease in the WBC count) should suggest HSV hepatitis. A liver biopsy should be done in suspected cases if the coagulation profile shows that the procedure can be performed safely. Fulminant hepatitis may not be accompanied by jaundice especially if clinical deterioration is rapid.

### Treatment

With the advent of effective chemotherapy, diagnosing disseminated HSV infection has therapeutic relevance. The fulminant nature of HSV hepatitis emphasizes the need for an aggressive approach if an antiviral agent is to be beneficial. If results of liver biopsy are consistent with HSV hepatitis, then treatment with acyclovir should be considered without waiting for culture results [21, 55].

The treatment of HSV hepatitis has not been established. Before 1983, acyclovir was not available as treatment for HSV infection, and subsequent data on the usefulness of this agent as therapy for disseminated HSV infection are scarce. However, acyclovir is probably the safest and most effective therapy for HSV infection. Antiviral agents have been used in only nine cases of HSV hepatitis, and only four of these patients survived. None of the antiviral agents have been demonstrated to be effective as therapy for HSV hepatitis in controlled trials. Furthermore, there is at least one reported case [16] of spontaneous recovery from HSV hepatitis, which suggests that not all cases run the fulminant course that is typical in patients who die.

### Conclusion

HSV hepatitis is a difficult diagnosis to establish. It should be considered in the differential diagnosis of any case of severe hepatitis with concomitant fever, abdominal pain, elevated values of liver function tests with or without jaundice. If HSV hepatitis is suspected, then therapy with acyclovir or vidarabine must be rapidly initiated for a better chance of a favorable outcome.

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