Case report

Fulminant herpes simplex hepatitis in a patient with ulcerative colitis

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SUMMARY A 16 year old girl with ulcerative colitis developed hepatitis with a high fever, leukopenia and a marked rise in serum transaminases without jaundice. There were no skin, oral, or genital lesions. Liver biopsy was precluded by abnormalities in coagulation. Postmortem examination of the liver by light and electron microscopy, culture, immunoperoxidase and immunofluorescent staining confirmed the diagnosis of hepatitis due to type 1 herpes simplex virus. Despite the rarity, this viral aetiology should be included in the differential diagnosis of all patients with severe hepatitis. The absence of mucocutaneous lesions should not exclude the diagnosis, especially when other clinical features are compatible.

Hepatitis caused by the herpes simplex virus is quite rare in adults. We are aware of 45 patients reported in the literature.¹⁻³⁵ Our experience with a 16 year old girl with ulcerative colitis who developed fulminant herpes simplex hepatitis allows us to emphasise this occurrence and discuss its clinical features.

Case report

A 16 year old white girl had been in excellent health until nine months previously, when she developed bloody diarrhoea. A diagnosis of ulcerative colitis was made and treatment with sulphasalazine was started. After eight months her symptoms continued, and she was admitted to the Mount Sinai Hospital and treated with intravenous corticotropin, 120 U/day, for 10 days with gradual improvement. Flexible sigmoidoscopy before hospital discharge revealed moderately severe mucosal erythema, oedema, and friability from the anal line to 30 cm proximally. Biopsies showed acute and chronic inflammation on hematoxylin and eosin stain without obvious

infectious agents and were consistent with idiopathic ulcerative colitis. Stool culture and examinations for ova and parasites were repeatedly negative for pathogens. The alkaline phosphatase was 1.8 μ kat/l (76 U/l), alanine aminotransferase (ALT) 0.23 μ kat/l (14 U/l), and the bilirubin was 9 μ mol/l (0.5 mg/dl). The patient was then released from the hospital to be treated with prednisone 40 mg/day.

Two weeks later, she was readmitted because of four days of fever, malaise, anorexia, and watery diarrhoea without blood. Body temperature on admission was 39.5°C. The patient was anicteric, and the abdomen was soft, non-tender, and without hepatosplenomegaly. Sigmoidoscopy revealed a mildly active ulcerative colitis. There were no skin, oral, or genital lesions. The white blood cell count was 1.5×10^9 /l (1500/mm³) with 62% polymorphonuclear cells, 24% bands, 12% lymphocytes, and 2% monocytes. The haemoglobin was 6.76 mmol/l (10.9 g/dl), and the platelet count was 127×10^9 /l (127,000/mm³). Chest and abdominal radiographs were normal. Blood urine, and stool cultures showed no pathogens. Other laboratory results included: aspartate aminotransferase (AST) 75.35 μ kat/l (4520 IU/l), alanine aminotransferase (ALT) 120.86 μ kat/l (7250 IU/l), bilirubin 10 μ mol/l (0.6 mg/dl), alkaline

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phosphatase 1 μ kat/l (58 IU/l), prothrombin time 15.4 seconds with a control of 12.1 seconds, partial thromboplastin time 57.6 seconds with a control of 34.4 seconds, fibrinogen 1.0 g/l (100 mg/dl), and fibrin split products 10.39 μ g/ml. Immunosassay for hepatitis B surface antigen, surface antibody, core antibody, and hepatitis A (IgM) antibody were negative. The serum heterophile screen was negative, and cytomegalovirus antibody titres by complement fixation methods were less than 1:8. The patient had no previous history of liver disease, herpetic infection, drug ingestion, toxin exposure, transfusions or intravenous drug use. The patient was initially treated with intravenous hydrocortisone at a dose of 150 mg/day. This was quickly tapered to a dose of 75 mg/day as maintenance therapy, as soon as

the abnormal liver function tests were reported from the laboratory. On the fifth hospital day the patient became hypotensive and oliguric. She was lethargic but oriented. Abdominal exam now revealed ascites, and rectal bleeding was noted. The AST had risen to 166.7 μ kat/l (10000 IU/l), the ALT to 166.7 μ kat/l (10000 IU/l), and the bilirubin to 91 μ mol/l (5.3 mg/dl). Serum ammonia was 188 μ mol/l (321 μ g/dl). The white blood cell count increased to $5.6 \times 10^9/l$ (5,600/ mm^3), but the haemoglobin fell to 4.41 mmol/l (7.1 g/dl), and the platelet count to 55×10^9 (55000/ mm^3). The prothrombin time was 48.6 seconds with a control of 12.6 seconds, partial thromboplastin time 84.0 seconds with a control of 56.0 seconds, and fibrinogen .75 g/l (75 mg/dl). The blood urea nitrogen was 5.7 mmol/l (16 mg/dl) and the serum creatinine

Fig. 1

Fig. 1 Light microscopic section of liver showing margination of nuclear chromatin and loss of nuclear detail in cells parasitised by herpes simplex virus. H and E.

Fig. 2

Fig. 2 Electron micrograph showing clusters of herpes simplex virus particles near nuclear chromatin.

Fig. 3

Fig. 3 Immunoperoxidase stain of formalin fixed liver showing herpes simplex antigen in nucleus and cytoplasm (arrow).

212 µmol (2.4 mg/dl). Fresh frozen plasma and packed red blood cells were administered for continued rectal bleeding. Over the next 24 hours the patient developed progressive encephalopathy leading to hepatic coma. She also became totally anuric, and persistently hypotensive. Despite aggressive supportive measures, including lactulose, neomycin, fresh frozen plasma, and vasopressors, she died on the morning of the seventh hospital day.

AUTOPSY

Post mortem examination was performed within six hours of death. The body of a well developed girl was externally normal except for mild icterus, numerous contusions and haemorrhages around needle puncture sites, and a distended tense abdomen. There was 100 mg of clear yellow ascitic fluid in the peritoneal cavity. The autopsy was limited to the examination of the liver. This weighed 1750 g, had a slightly wrinkled capsule and showed numerous diffuse yellow areas of necrosis on a dark purple background. Sections revealed soft dark red parenchyma studded with discrete and frequently confluent yellow foci of necrosis.

Microscopic examination showed subtotal necrosis of the liver parenchyma. Only 5% of all liver cells appeared viable. Many of these cells had nuclei which were uniformly basophilic with a homogenous 'ground glass' amphophilic appearance (Fig. 1). Less commonly seen were intranuclear fully developed Cowdry type A inclusions, which were brightly eosinophilic with irregular borders surrounded by a clear 'halo' that separated the inclusions from the margined chromatin at the nuclear membrane. There was diffuse haemorrhage with little inflammation except for scattered foci of neutrophils around central veins.

Samples of fresh liver were fixed in 3% cacodylate buffered glutaraldehyde, treated with osmium tetroxide, dehydrated, and embedded in Epon. Ultrathin sections stained with uranyl acetate and lead citrate were examined by transmission electron microscopy. This revealed numerous and often clustered herpes type particles within hepatocytes (Fig. 2).

Immunoperoxidase studies on formalin fixed liver using herpes simplex virus type 1 and type 2 antibody (Lipshaw, Detroit) were strongly positive for herpes antigen in the nuclei, cytoplasm, and cell membranes (Fig. 3). Immunofluorescent studies using specific conjugate (Kallestad, Austin, Texas) were positive for herpes simplex virus type 1. The presence of herpes simplex was also shown by cytopathic effect after inoculation of fresh hepatic material into human embryonic kidney (Whittaker MA Bio-products, Walkersville, MD) and human foreskin

(Bartels, American Scientific, Mahwah, NJ) tissue culture.

Discussion

Infection with herpes simplex virus usually occurs through mucocutaneous areas. Host factors then determine whether dissemination will occur. In mice, the presence of mature macrophages at the infection site correlates with prevention of dissemination. Protective antibodies, production of interferon, and natural killer cells also play a role in preventing spread.³⁶ In man, severe herpes simplex virus infection has most often been associated with defects in cell mediated immunity.³⁷

Thirty six previously reported cases had possible causes for immunosuppression. These included therapy for corticosteroids alone in six patients^{2 6 25 30 33} or combined with azathioprine in 11,^{7 11 13 14 19 21 22 26 27} the third trimester of pregnancy in nine,^{1 9 15 18 20 24 28 31} cancer in four,^{5 35} severe burns in two,³ general anaesthesia in two,^{16 32} chronic neutropenia in one,²³ and thymic dysplasia in one.⁸ Nine patients had no apparent predisposing factor.^{4 10 12 17 29 34 35}

Our patient was a previously healthy girl who developed type 1 herpes simplex viral hepatitis. Her situation was unusual compared with other patients treated with corticosteroids alone who suffered from herpes hepatitis. Three of these received therapy for one month or longer to control disorders which have themselves been associated with immunologic abnormalities.^{2 6 30} The other three patients, similar to our case, received corticosteroids for less than one month, but had other factors which may have contributed to their potential immunosuppressive action, including a very high dose (dexamethasone intravenously, 16 mg daily), older age, or general anaesthesia.^{25 33} As depression in cell mediated immunity caused by corticosteroids has been shown in laboratory animals, as given to our patient they may have potentially predisposed to her disseminated herpes simplex virus infection.³⁸ There is little clinical evidence however, that they alone commonly produce an increased infection rate of any type in man.^{39 42} Perhaps immunologic changes related to the ulcerative colitis may have contributed in some way to our patient's illness.^{43 44} This seemed unlikely, as even with severe or fulminant disease and therapy with corticosteroids and/or immunosuppressant drugs, herpes simplex virus hepatitis has not been previously noted among patients with inflammatory bowel disease.

The antemortem diagnosis of herpes simplex hepatitis may be difficult. The clinical features are not specific, including the presence of high fever, leukopenia, and marked rise in serum transaminases

(100 fold) without jaundice. Furthermore, liver biopsy is often precluded by abnormalities in coagulation. Even with recognisable external evidence of herpetic infection among 24 previously reported patients^{1-6 8-10 13-15 18-25 28 34} in only 10 was the clinical diagnosis of herpes hepatitis considered.^{1 8 13 15 19-21 24 25 34} Seven of these patients were treated with adenine arabinoside,^{13 15 19 21 24 34} but only one survived.¹⁵ She was the only patient of the 45 reported who did not have fulminant hepatitis. Two patients who did not receive antiviral therapy survived with supportive care alone.^{1 25} There were no obvious factors that would have predicted the favourable outcome of these two survivors.

Twenty one patients, (including our patient), had no skin, mouth or genital lesions, and all died.^{7 11 12 16 17 25-27 29 33 35} The premortem diagnosis was made in only one patient, who underwent a liver biopsy during a laparotomy for an incorrect presumptive diagnosis of peritonitis.¹⁷ The diagnosis was suspected in a renal transplant recipient who died despite the initiation of specific therapy with adenine arabinoside.²⁶

Thus, the correct diagnosis was made before death in only 11 of 45 patients (24%), and in only one patient who presented without external evidence of herpetic infection. The mortality was over 90%, including seven of the eight patients who received antiviral therapy. The results of therapy with acyclovir, which may have greater activity against the herpes simplex virus than adenine arabinoside,³⁵ has not yet been reported among patients with documented hepatitis.

Our patient emphasises that herpes simplex virus should be included in the differential diagnosis of all patients with fulminant hepatitis despite the absence of typical mucocutaneous lesions, and obvious predisposing factors. A liver biopsy may be confirmatory, but is often not feasible. Unfortunately, there is currently no evidence to suggest that diagnosis and treatment will improve the outcome.

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