

Varicella-Zoster Virus Infection Associated with Acute Liver Failure

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Although acute liver failure due to the varicella-zoster virus is rare, it is frequently fatal. Immunologic impairment is a significant predisposing factor. Classic symptoms at presentation are rash, abdominal pain, and fever. After some days patients go on to develop full-blown liver failure. The diagnosis can be confirmed by histological examination and electron microscopy with fluorescent staining, immunohistochemistry, and in situ hybridization of the liver. In cases of high suspicion, acyclovir therapy should not be delayed.

Varicella-zoster virus (VZV) is frequently associated with mild hepatitis but rarely with acute liver failure. We report a patient with acute, fatal liver necrosis due to infection with VZV. In addition, we review previous reports of VZV-induced liver failure and discuss its manifestation as well as the associated diagnostic methods and treatment.

Case Report

A 30-year-old male was admitted to a regional hospital for evaluation of severe abdominal pain, fever, myalgia, and cutaneous vesicles on his face and scalp. He had a history of bilateral nephrectomy followed by renal transplantation in 1987 because of reflux nephropathy. The patient developed low-grade rejection necessitating a second renal transplantation in 1990. At the time of admission his daily immunosuppressive regimen included methylprednisolone, 4 mg; cyclosporine, 175 mg; and azathioprine, 100 mg; antihypertensive therapy consisted of enalapril and metoprolol. Three weeks before admission the patient's 5-year-old son had developed chickenpox. One week before admission the patient experienced myalgias and chills.

Physical examination on admission showed vesicles suggestive of VZV infection on the face as well as marked epigastric tenderness; there were no other abnormal findings. Results of the laboratory evaluation were as follows: hemoglobin level, 13.3 mg/dL; WBC count 7,700/ μ L; platelet count, 268,000/ μ L; blood urea nitrogen level, 92 mg/dL (normal, 20–45 mg/dL); creatinine level, 3.1 mg/dL (normal, 0.7–1.35 mg/dL); bilirubin level, 0.82 mg/dL (normal, 0.2–1 mg/dL); alkaline phosphatase level, 150 U/mL (normal, 90–260 u/mL); aspartate aminotransferase (AST) level, 33 U/L (normal, 5–37 U/L); alanine aminotransferase (ALT) level, 27 U/L (normal, 5–40 U/L); lactate dehydrogenase

(LDH) level, 400 U/L (normal, 240–480 U/L); and prothrombin time, 1.02 INR (international normalized ratio). A chest radiograph, abdominal ultrasonography, esophagogastroduodenoscopy, and an abdominal CT scan revealed no relevant lesions.

Treatment with acyclovir was started on the fourth day after admission. The immunosuppressive regimen was continued with standard dosages. The patient was transferred to our hospital on the fifth day. During transportation he developed respiratory distress and increasing mental obtundation, necessitating intubation and mechanical ventilation upon arrival at our facility. Arterial blood gas values obtained at that time were compatible with severe metabolic acidosis. Findings on the chest radiograph obtained after intubation were normal. Four hours later the patient developed deep coma, massive upper gastrointestinal bleeding, and severe hypotension. Laboratory studies disclosed acute liver failure: AST level, 4,520 U/L; ALT level, 1,650 U/L; LDH level, 21,040 U/L; prothrombin time, 10.44 INR; and activated partial thromboplastin time, 180 seconds. An electroencephalogram showed only sporadic cerebral activity. The patient died despite massive transfusion of packed cells and fresh frozen plasma and administration of vasopressors, antibiotics, and cardiopulmonary resuscitation.

Cultures of blood obtained on admission yielded *Staphylococcus aureus*. The serum IgM and IgG antibody levels were negative, but a serum VZV PCR assay was positive. Histopathologic examination of the liver showed diffuse zones of acidophilic necrosis surrounded by hepatocytes with typical eosinophilic nuclear inclusions. A PCR assay of the liver biopsy specimen for VZV, obtained immediately postmortem, was positive. Other than the right lung, no organs showed viral involvement at autopsy.

Discussion

VZV hepatitis with acute liver failure appears to be an uncommon, yet frequently fatal condition. We searched MEDLINE (1966–1996) with the key words *varicella* and *liver* for additional cases.

Most of the patients described were immunocompromised for one or several reasons such as splenectomy, renal transplantation, bone-marrow transplantation, use of corticosteroids,

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and AIDS. The most frequent presenting symptoms were cutaneous varicella lesions, acute abdominal or back pain, and fever. The typical papulovesicular rash may precede [1–5], be concomitant with [6], or appear delayed relative to [7, 8] the abdominal complaints. However, Rogers et al. [9] and Ross et al. [10] described patients with severe varicella hepatitis without any skin lesions. Patients with disseminated varicella appear to remain moderately ill for some days and then go on to develop full-scale liver failure with coagulation disturbances and shock. The mechanisms involved in this fulminant visceral dissemination in the patients described remains unclear but are most likely related more to the impaired immune function than to the virulence of the VZV strain. Infection usually appears to be a de novo or primary infection. Our patient had a negative history for VZV as a child. He was infected by his son 3 weeks before admission.

The standard treatment for organ VZV infection is acyclovir, 10 mg/kg t.i.d., and this should be started immediately upon suspicion of the diagnosis. Our patient received acyclovir ~10 days after the first prodromes (i.e., the day before referral to our hospital), and he died the day after starting therapy. Varicella-zoster immunoglobulins (VZIG) may modify the natural history of VZV infection but only when administered within 72 hours after exposure [4]. Unfortunately, VZIG was not administered to our patient by his general practitioner.

The mortality associated with VZV-induced hepatic failure is very high. The few patients who survived received acyclovir and/or underwent liver transplantation [2, 11]. The causal link between VZV and hepatic failure is not always straightforward. The clinical picture, combined with positive VZV serology and a positive skin biopsy specimen, may be highly suggestive [5, 7]. Histopathologic examination of the liver contributes to the diagnosis [1, 3, 4, 8–11]. In typical cases there are areas of limited hemorrhagic necrosis, multinucleation, ground-glass nuclear staining, and eosinophilic Cawdry type A intranuclear inclusions. Electron microscopy shows intracellular virions characteristic of herpesviridae [8–10]. Herpes simplex virus and VZV can be differentiated by fluorescent staining [4–6, 9], immunohistochemistry [3], in situ hybridization [3], or PCR [9].

The diagnosis of VZV-induced hepatic failure in our patient was based on the history of contact with his child with chick-

enpox, suggestive cutaneous vesicles, typical histological study of the liver, and a positive PCR for VZV on liver biopsy and serum. It is remarkable that our patient remained negative for antibodies to VZV. Two mechanisms may explain this finding. Either he was unable to produce antiviral antibodies due to his immunosuppressive medication, or the production of antibodies was low and consumed immediately by immune complex formation.

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