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Short communication

# Fulminant hepatic failure attributed to infection with human herpesvirus 6 (HHV-6) in an immunocompetent woman: A case report and review of the literature

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ABSTRACT

Mild disease due to human herpesvirus-6 (HHV-6) has been reported in healthy children. Severe disease due to this virus can occur in immunocompromised patients but is rarely reported in previously healthy adults. We report the case of a previously healthy woman who presented with a skin rash, mild upper respiratory symptoms, and abdominal pain and succumbed to fulminant hepatic failure attributed to infection with HHV-6B.

HHV-6 may be more commonly associated with fulminant hepatitis in immunocompetent patients than previously thought and should be considered in the differential diagnosis of patients presenting with skin rash, upper respiratory symptoms, and unexplained hepatitis.



## 1. Why is this case important

Serious infection with human herpesvirus 6 (HHV-6) is rarely reported in immunocompetent adults. However, HHV-6 may be an underestimated cause of acute liver failure (ALF) with a poor prognosis. We describe the case of a previously healthy woman who succumbed to fulminant hepatitis (FH) attributed to HHV-6. We discuss similar cases from the literature and advocate the consideration of HHV-6 in the diagnostic workup of unexplained hepatitis or ALF.

## 2. Case description

A 44-year-old previously healthy woman presented to a hospital with fever, sore throat, abdominal pain, vomiting, facial and hand edema, and a diffuse, macular, initially pruritic rash (Fig. 1). She had taken acetaminophen and diphenhydramine for her symptoms. Her medical history included only long-standing hypothyroidism treated with levothyroxine. Her history was negative for recent travel, other medications, supplements, and exposures. There was no family history of liver disease.

The clinical course is shown in Fig. 1. Additional laboratory values included: white blood cells (WBC) 21,200/μL, platelets

*Abbreviations:* ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; ATN, acute tubular necrosis; AV, atrioventrivular; AZ, azithromycin; CF, ceftriaxone; CL, clindamycin; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; DIHS, drug-Induced hypersensitivity syndrome; DNA, deoxyribonucleic acid; EBV, Epstein Barr virus; EF, ejection fraction; FH, fulminant hepatitis; GC, ganciclovir; HHV-6, human herpesvirus-6; HSM, hepatosplenomegaly; HSV, herpes simplex virus; IFA, immunofluorescent assay; IF, immunofluorescence; IHC, immunohistochemistry; ILI, influenza-like illness; INR, international normalized ratio; IV, intravenous; LAN, lymphadenopathy; LDH, lactate dehydrogenase; LTx, liver transplant; lymphs, lymphocytes; EM, electron microscopy; MOF, multiorgan failure; MPR, methylprednisolone; MTR, metronidazole; N/A, not available; NABC, non-A, non-B, non-C; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PEN, penicillin; PR, prednisone; PT, prothrombin time; RUQ, right upper quadrant; SJS, Stevens–Johnson syndrome; TBSA, total body surface area; Tbil, total bilirubin; TEN, toxic epidermal necrolysis; US, ultrasound; VC, vancomycin; VGC, valganciclovir; VZV, varicella-zoster virus; VZVIg, varicella-zoster virus immune globulin; WBC, white blood cell count.

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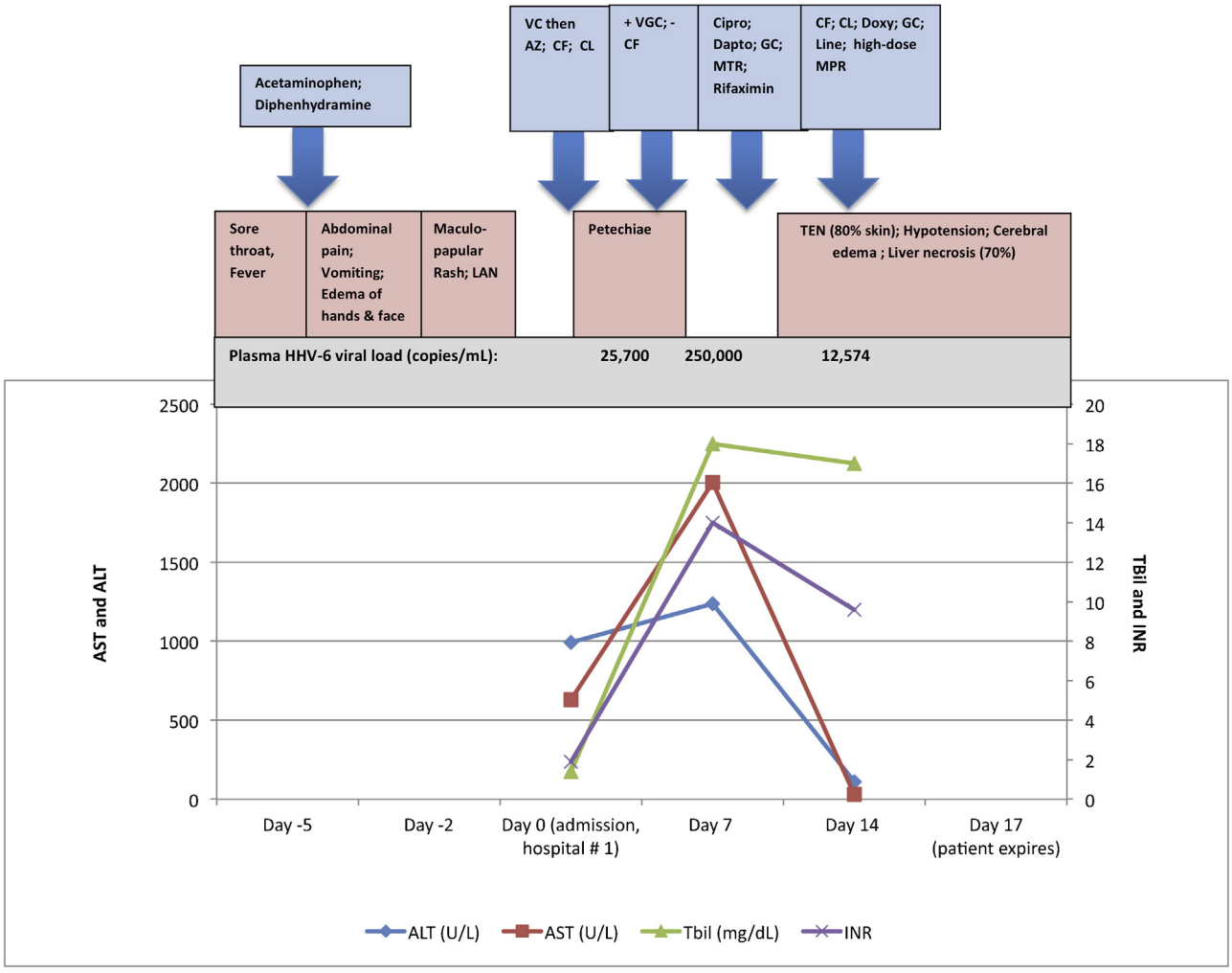


**Fig. 1.** The patient's clinical course.
This figure summarizes the patient's clinical course including symptoms, select laboratory values, and medication regimens. Notably, the peak values for AST, ALT, Tbil, and INR occurred at the same time as the peak in HHV-6 viral load.
AZ: azithromycin; CF: ceftriaxone; Cipro: ciprofloxacin; CL: clindamycin; Dapto: daptomycin; Doxy: doxycycline; GC: ganciclovir; LAN: lymphadenopathy; MPR: methylprednisolone; MTR: metronidazole; Rifaximin; TEN: toxic epidermal necrolysis; VC: vancomycin; VGC: valganciclovir.
"+" indicates a drug was added to the existing regimen; "−" indicates the drug was withdrawn. Boxes of antimicrobials without an "+" or "−" indicate a new drug regimen altogether.

223,000/mm$^3$, and alkaline phosphatase (ALP) 320 units/L. An ultrasound demonstrated minimal gallbladder wall thickening and scant pericholecystic fluid.

The following were negative: HIDA scan; rapid streptococcal antigen; blood and throat cultures; monospot; acetaminophen levels; antinuclear, antimitochondrial, anti-smooth muscle, and liver-kidney microsome antibodies; immunoglobulins and PCR for hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), and herpes simplex viruses (HSV) types1 (IgM) and 2 (IgM and IgG); Epstein–Barr virus (EBV) IgM and IgG; HBV surface antigen; PCR for respiratory viruses, cytomegalovirus (CMV), adenovirus, human herpesviruses (HHV) 7 and 8, and *Clostridium difficile* toxin B; urine toxicology. The following were positive: qualitative PCR for EBV from the blood; IgM for CMV (lowest titer); stool culture for *Campylobacter* species; plasma PCR for human herpesvirus-6, type B (HHV-6B).

The patient was transferred to another hospital, where computed tomography (CT) of the head demonstrated cerebral edema. Her ammonia level was 264 μmol/L, requiring continuous veno-venous hyperfiltration. The following were negative: blood cultures; tests for alpha-1 antitrypsin and ceruloplasmin; serologies for *Mycoplasma pneumoniae*, parvovirus B19, HHV-6 (IgM), HHV-7, and HHV-8. A tuberculosis quantiferon test was indeterminate. IgG for HSV-1, rubeola, and varicella zoster were positive. HHV-6 IgG titer was 1:80, just at the <1:80 cut-off for positivity. Lactate dehydrogenase (LDH) was 2768 units/mL. Haptoglobin was undetectable with no evidence of microangiopathic hemolysis. Cold agglutinins were present. By day 6, the D-dimer peaked at 15,672 D–D U ng/mL. HHV-6 viral load increased to 250,000 copies/mL. An ultrasound demonstrated ascites and hepatosplenomegaly. Transjugular liver biopsy showed massive (70%) necrosis with a plasma cell infiltrate in the portal areas, and no viral inclusions. The patient developed skin sloughing and hypotension requiring pressors. A skin biopsy was consistent with toxic epidermal necrolysis (TEN); antimicrobials were changed, in the event that previous antibiotics contributed to TEN (Fig. 1).

The patient was transferred to our institution on the 14th day after her original admission for burn unit care of 80% skin involvement by TEN. A head CT showed bilateral acute frontal lobe ischemic infarctions, worsening cerebral edema and diffuse anoxic brain injury. Serologies for *Brucella*, *Bartonella*, rickettsial organisms, and Q Fever IgM were negative. A Q fever IgG screen