Acute Hepatitis as a Manifestation of Parvovirus B19 Infection

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There are few reports in the literature of hepatitis as a manifestation of parvovirus B19 infection. We describe a case of parvovirus B19-associated acute hepatitis diagnosed based on a positive serologic test (IgM) and molecular detection of parvovirus B19 DNA in a liver biopsy specimen. Parvovirus B19 infection should be considered in the differential diagnosis of patients presenting with acute hepatitis.

CASE REPORT

A 30-year-old female with no significant past medical history was admitted to a tertiary-care hospital in Winnipeg, Manitoba, Canada, with a new onset of fever and jaundice. The patient had become unwell approximately 5 days prior to presentation. Over this time, she reported a low-grade fever, diffuse arthralgias, myalgias, sore throat, anorexia, and abdomen. Approximately 24 h prior to admission, she developed clinical jaundice. The patient denied any sick contacts. She had traveled to Las Vegas 1 week before becoming ill. There was no history of intravenous drug use, nor was there any history of heavy alcohol consumption. The patient had recently been using valacyclovir for an episode of genital herpes. She denied the use of other medications.

On physical examination, the patient was visibly jaundiced and a faint, erythematous, macular rash was present on her legs, arms, and abdomen. Her maximum temperature was 38.2°C. A gynecological examination did not demonstrate any lesions consistent with active herpes simplex virus (HSV) infection. Initial laboratory investigations revealed an aspartate aminotransferase level of 67 U/liter (normal value, 10 to 32 U/liter), an alanine aminotransferase level of 367 U/liter (normal value, 0 to 30 U/liter), an alkaline phosphatase level of 171 U/liter (normal value, 0.9 to 1.1), a lactate dehydrogenase level of 179 U/liter (normal value, 0 to 30 U/liter), and a direct bilirubin level of 96 μmol/liter (normal value, 0 to 7 μmol/liter), an international normalized ratio of 1.4 (normal value, 0.9 to 1.1), a lactate dehydrogenase level of 179 U/liter (normal value, 63 to 200 U/liter), and a peripheral white cell count of 7.1 × 10^9/liter (normal value, 4.5 × 10^9 to 11 × 10^9/liter). The patient was admitted to the hospital with a diagnosis of acute hepatitis. Serologic testing for hepatitis A, B, and C viruses, serologic testing for HIV, HIV viral load testing (RNA), hepatitis C viral RNA testing, a venereal disease research laboratory test, serological tests for Epstein-Barr virus IgM and cytomegalovirus IgM, and a monospot test were all negative. Additional tests for antinuclear antibody, rheumatoid factor, antimitochondrial antibody, and anti-neutrophilic cytoplasmic antibodies, as well as blood cultures, a urine culture, and a throat swab for bacterial and viral cultures were also negative. Immunoglobulin and complement levels were normal. An anti-smooth-muscle antibody was detected at a low titer of 1:40. Ultrasound of the liver did not demonstrate evidence of biliary obstruction or hepatic vein occlusion. A liver biopsy specimen (Fig. 1) performed 6 days postadmission demonstrated mild acute lobular hepatitis. The findings on the biopsy specimen did not support autoimmune hepatitis as the etiology of the patient’s liver disease. Specifically, there was no portal inflammation, interface activity, or perivenulitis. No features to suggest HSV infection were identified.

Given the history of rash, fever, and arthralgias, serologic testing for parvovirus B19 infection was ordered for completeness. Serologic testing was performed using a kit from Biotrin International Ltd. (Dublin, Ireland). The patient was positive for parvovirus B19 IgM, with an optical density value of 11.5 (reference values: <0.9, negative; 0.9 to 1.1, equivocal; >1.1, positive). The patient was also positive for parvovirus IgG, with an optical density value of 7.0 (reference values: <0.9, negative; 0.9 to 1.1, equivocal; >1.1, positive). The residual formalin-fixed tissue block from the liver biopsy specimen was subsequently forwarded to the Canadian National Microbiology Laboratory (Winnipeg, Manitoba, Canada) for molecular detection of parvovirus B19 DNA. Briefly, viral DNA was extracted using the QIAamp DNA Mini kit (Qiagen, Mississauga, Ontario, Canada). An in-house-made positive control consisting of parvovirus B19 DNA in a plasmid added to human serum (Invitrogen, Burlington, Ontario, Canada) was used as an extraction control. The extracted DNA was subjected to a nested PCR using in-house-designed primers as follows: outer PCR, sense primer TTA GAG ATG GAG AGC AGT TTA TAG AAA A and antisense primer CCG ACA AAT GAT TCT CCT GAA CTG; inner PCR, sense primer TTG GTG GTC TGG GAT GAA GG and antisense primer CAG AGC TTT CAC CAC CAC TGC TG. The iProof PCR
Parvovirus B19 is a nonenveloped, single-stranded DNA virus belonging to the family Parvoviridae (5). It is included in the Erythovirus genus, a group of viruses that use erythroid progenitor cells for optimal propagation (5, 13). Parvovirus B19 is most often transmitted between human hosts via respiratory droplets. However, vertical transmission and transmission via blood products also occur (5, 12). By the time old age is reached, most individuals demonstrate seropositivity for this virus (5, 13). Parvovirus B19 infection is asymptomatic in the majority of cases, but there are several well-known clinical manifestations. These include erythema infectiosum (the classic fifth disease of childhood), arthropathy, transient aplastic crisis, and hydrops fetalis (13). Meningitis, encephalitis, and myocarditis have also been described (13).

Acute hepatitis in association with parvovirus B19 infection has only rarely been reported in the literature (1, 3, 4, 6, 8). Diaz et al. described 2 patients with acute hepatitis in whom testing for commonly implicated infectious agents was negative (1). Both patients were positive for parvovirus B19 IgM. Molecular testing for parvovirus B19 DNA was not performed in either case (1). Ho et al. reported a case of a 34-year-old woman presenting with 6 weeks of polyarthritis, sore throat, anorexia, and fever and 4 weeks of right upper quadrant abdominal pain and jaundice (4). Laboratory testing was consistent with acute hepatitis. Testing for routine viral causes of hepatitis was unrevealing. An IgM test for parvovirus B19 was positive (4). Molecular testing (PCR) of serum and bone marrow in this case toward the end of the illness was negative (4). Two additional cases of parvovirus B19-associated hepatitis were reported by Hillingsø et al. (3). One case was diagnosed based on a positive IgM test, while the second had both a positive IgM test and parvovirus B19 DNA detected in the serum by PCR (3). An alternate explanation for the acute hepatitis of either patient was not found. Finally, Krygier et al. described a patient who presented with acute hepatitis which progressed to hepatic failure requiring liver transplantation (6). In this case, serologic testing for parvovirus B19 was positive and parvovirus DNA was detected in the explanted liver (6). These cases, in addition to the case presented here, support an association between parvovirus B19 infection and the development of acute hepatitis. The current case is unique in that it is one of the few cases where a presumptive diagnosis of parvovirus B19-associated acute hepatitis was made on the basis of both a positive serologic test and detection of parvovirus DNA in a liver biopsy specimen.

It should be noted that parvovirus B19 has also been implicated as a cause of liver failure due to fulminant hepatitis, although studies to support this association have demonstrated conflicting results. Sokal et al. detected the presence of parvovirus B19 DNA in serum from 4 of 21 patients with fulminant hepatitis of unexplained etiology (11). One of these four patients also showed IgM seropositivity. PCR for viral detection was negative in cases of fulminant hepatitis of known etiology and in matched controls with biliary atresia (11). In contrast, Lee et al. examined the sera of 78 patients from the Acute Liver Failure Study Group bank and were unable to demonstrate evidence of parvovirus B19 infection by DNA dot blot hybridization, PCR, or serum immunoglobulin testing in any of them (7). A second small study by Wong et al. also found no significant difference in the prevalence of parvovirus B19 DNA in livers from patients with fulminant hepatitis compared with liver tissue samples from patients with hepatitis B or hepatitis C virus infection (12). The reason for these discordant findings is uncertain.

The mechanism by which parvovirus B19 infection may result in hepatic injury is not clear. Hepatic cell damage related to direct viral invasion is one possibility (1, 9). Alternatively, injury may result as an indirect consequence of the immune response directed against the virus (1).

There are several limitations to the current case report which deserve attention. Testing for hepatitis E virus was not performed. While hepatitis E virus infection is considered unlikely in this case due to the absence of recent travel to areas where hepatitis E virus infection is endemic, it would have been useful to test for this virus for completeness. Follow-up serologic testing to document a rise in parvovirus B19 IgG was not done. Definitive proof that parvovirus B19 infection was the etiology of this case of hepatitis would have required seroconversion of parvovirus B19 IgG from negative to positive and detection of a high titer of parvovirus B19 DNA in peripheral blood (also not performed here). Detection of parvovirus B19 DNA in a liver biopsy specimen does not, on its own, necessarily indicate that the patient had an acute infection with...
this virus. In a study by Eis-Hübinger et al., parvovirus B19 DNA was detected by PCR in 15 of 35 explanted livers from parvovirus B19 IgG-seropositive adults undergoing orthotopic liver transplantation for various reasons (mostly not acute hepatitis) (2). Finally, the patient described in the present report had also recently received valacyclovir. Acute hepatitis in association with valacyclovir use has been very rarely reported in the literature (10). While we cannot entirely exclude a drug reaction as the cause of hepatitis in our patient, the history of a presumed recent exposure to parvovirus B19, positive parvovirus B19 serologic testing (IgM), and demonstration of parvovirus DNA in a liver biopsy specimen all argue in favor of parvovirus B19 infection as the etiology in this case.

In summary, the case described here, along with other cases in the literature, suggests that parvovirus B19 infection may be associated with the development of acute hepatitis. Infection with parvovirus B19 should be considered in the differential diagnosis of patients presenting with acute hepatitis of unknown etiology.

REFERENCES