Norovirus Gastroenteritis Accompanied by Marked Elevation of Transaminases

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ABSTRACT
A 56-year-old woman was admitted because of frequent watery diarrhea, vomiting, and abdominal cramps. An examination of the stool for norovirus antigen was positive, and a blood examination revealed a marked elevation of liver enzymes. Liver dysfunction, as well as symptoms related to gastroenteritis, was ameliorated solely by supportive treatment. Although liver injury concurrent with norovirus gastroenteritis is rarely documented and its pathogenesis remains unknown, clinicians should consider liver injury as one of the possible extra-intestinal manifestations of norovirus gastroenteritis.

Key words: Norovirus, Liver injury, Elevation of transaminases, Complications related to norovirus gastroenteritis

Norovirus is a common pathogen, accounting for more than 90% of non-bacterial or approximately 50% of epidemic gastroenteritis worldwide3-10). Primary symptoms of norovirus gastroenteritis include sudden-onset of abdominal cramps, vomiting, and watery diarrhea3-7,9), following an incubation period ranging from 10 to 72 hr3-8,9). Gastroenteritis is generally mild, has a short-duration, and is self-limited except in vulnerable individuals such as debilitated elderly individuals3,9), newborns3,16), children less than 5 years old16), or immunocompromised hosts3,5,6). The frequency of norovirus gastroenteritis has recently increased1,7), and several reports are focusing on the extra-intestinal manifestations of norovirus infection, including epilepsy1,3,7), encephalopathy3, hemolytic uremic syndrome1,2), and disseminated intravascular coagulation2). Only one report discusses liver involvement related to norovirus gastroenteritis15). Herein, we describe an adult patient with norovirus gastroenteritis accompanied by transient but significant elevation of liver enzymes. We also discuss possible mechanisms of liver injury concurrent with norovirus infection with a review of literature.

CASE REPORT
A 56-year-old woman, who had cared for her grandchild with gastroenteritis 3 days before, was admitted to our hospital because of acute onset of abdominal cramps, frequent vomiting, and watery diarrhea. She had a medical history of operations for appendicitis, myoma uteri, and gallstones, but no history of blood transfusion, habitual alcohol consumption, or drug intake. There was no obvious episode suggesting circulatory insufficiency before the hospitalization. Physical examination upon admission revealed only mild tenderness in the left lower abdomen. On the basis of a positive test for norovirus antigens in the stool specimen by using commercial kits with an immunochromatographic assay (QUICKNAVITM-NORO; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and clinical manifestations, we diagnosed the patient as having acute norovirus gastroenteritis. Laboratory tests revealed liver dysfunction and elevated alanine aminotransferase (ALT) to 458 IU/liter, aspartate aminotransferase (AST) to 1150 IU/liter, lactate dehydrogenase to 886 IU/liter, alkaline phosphatase to 318 IU/liter, and γ-glutamyl transpeptidase to 73 IU/liter, but total bilirubin was within the normal range at 1.29 mg/dl. Serum markers related to viral hepatitis, such as IgM hepatitis A antibody, surface antigen of hepatitis B, IgM hepatitis B core antibody, RNA of hepatitis C virus, IgM cytomegalovirus antibody, IgM Epstein-Barr virus antibody, and IgM herpes simplex antibody, were all negative. Abdominal sonography revealed no significant findings except a post-cholecystectomy state. Symptoms of acute...
gastroenteritis subsided simply by bowel resting and intravenous rehydration. Abnormal liver dysfunction was also promptly ameliorated, and the patient was discharged on the fourth hospital day. Two weeks later, normalization of liver enzymes was confirmed (Figure).

**DISCUSSION**

Although norovirus gastroenteritis is generally a self-limited disease except in vulnerable individuals, relatively rare but serious extra-intestinal complications, such as epilepsy\(^1,5,7\), encephalopathy\(^4\), hemolytic uremic syndrome\(^12\) or disseminated intravascular coagulation\(^2\), have recently been reported. While approximately 20-40% of pediatric patients of rotavirus gastroenteritis are accompanied by elevation of hepatic transaminase\(^14\), the presence of norovirus infection in these patients is not well documented. Recently, Tsuge et al\(^15\) reported 4 infant cases (from 1 year 5 months to 6 years 9 months old) of norovirus gastroenteritis with elevated transaminases. In their report, they discussed 5 characteristic features: (1) patients were all pediatric cases; (2) the clinical course of norovirus gastroenteritis is accompanied by elevation of hepatic transaminase\(^14\), the presence of norovirus infection in these patients is not well documented. Recently, Tsuge et al\(^15\) reported 4 infant cases (from 1 year 5 months to 6 years 9 months old) of norovirus gastroenteritis with elevated transaminases. In their report, they discussed 5 characteristic features: (1) patients were all pediatric cases; (2) the clinical course of norovirus gastroenteritis was uneventful; (3) the degree of transaminase elevation was mild at the peak of gastroenteritis; (4) elevated transaminase peaked 2 weeks after the onset of gastroenteritis; and (5) liver injury was self-limited and did not relapse. The present case was consistent with Tsuge’s report with respect to rapid recovery from gastroenteritis and liver injury, but in our case, higher transaminase peaks of 1150 IU/liter of AST and 458 IU/liter of ALT and synchronized peaks of gastroenteritis and elevated transaminases were observed. These inconsistencies may be attributed to either the host’s background or norovirus virulence. As the histo-blood antigens (the ABO, Lewis and secretor families) are suggested to influence norovirus susceptibility\(^3,4,9\), differences in immune responses\(^6,8,13\) according to age, gender, or other unknown genetic backgrounds may determine the occurrence or severity of extra-intestinal complications related to norovirus gastroenteritis. In addition, the genetic diversity of the norovirus\(^9\) may influence its virulence, such as its ability to invade the bloodstream\(^5,7,13,14\) or cerebrospinal fluid\(^4\), or its affinity to specific organs resulting in extra-intestinal manifestations.

In the cases of liver injury associated with rotavirus gastroenteritis, extra-intestinal viral spread, i.e., the viremic state, is important in the pathogenesis\(^7,13,14\). Norovirus RNA was detected in the blood of 15% of patients with norovirus gastroenteritis\(^10\), and norovirus RNA was detected in the cerebrospinal fluid in a patient with norovirus gastroenteritis, complicating encephalopathy\(^9\). Thus, the fact that norovirus directly damages the organs cannot be ruled out. Norovirus infects the villous enterocytes of the duodenum or the proximal jejunum via carbohydrate ligands expressed on the intestinal epithelium surface and also play a role as hist-blood group antigens\(^3,5\), resulting in enteritis. Thus, it is likely that many noroviruses intrude the portal vein via the impaired mucosal integrity and subsequently reach the liver to elevate transaminase levels.

Little is known regarding the mechanism of liver damage concomitant with norovirus gastroenteritis. This may be ascribed to un-established growing systems in cell lines or experimental animal models\(^8,13\). Recently, animal models and cell culture systems of murine norovirus 1 (MNV-1) infection have been established\(^8\), although it must be confirmed whether MNV-1 behavior and its animal model are relevant to human norovirus infection. In the MNV-1 infection animal model, MNV-1 was detected in systemic organs, including the liver, lung, spleen, and lymph nodes\(^9\). Further, while pathological study of the liver showed only a few inflammatory foci in immunocompetent murine models\(^11\), various degrees of hepatitis, such as from mild focal infiltration of inflammatory mononuclear cells and neutrophils to severe loss of hepatocytes in the perportal area, have been shown in immunodeficient murine models\(^7\). These experimental observations may suggest the possibility that norovirus is rapidly eliminated from the liver with minimum damage in an immunocompetent state, but persistent norovirus infection in an immunocompromised state\(^6\) causes varying degrees of inflammatory damage to the liver, in a way similar to hepatotropic viruses such as hepatitis B or C virus.

In summary, the present case suggests that norovirus may induce liver injury as an extra-intestinal manifestation. Further studies to not only clarify the clinical characteristics of liver injury
concomitant with norovirus gastroenteritis but also define its mechanisms through establishing a viral culture system with cell lines or adequate animal infection models are indispensable.

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REFERENCES


