Acute Hepatitis Caused by Genotype 4 HCV Presenting with Microangiopathic Hemolytic Anemia

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ABSTRACT

Many cases have been reported about the role of chronic hepatitis C and interferon therapy in the development and recurrence of thrombotic thrombocytopenic purpura (TTP), but to our knowledge there is no previous report about the association between acute hepatitis C and any microangiopathic hemolytic anemia (MAHA) including TTP. We report a case of acute hepatitis C that presented with MAHA resembling TTP, which resolved with spontaneous clearance of viral infection.

INTRODUCTION

The diagnosis of thrombotic thrombocytopenic purpura (TTP) is often considered in patients with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia.1,2 Classically, it presents with a pentad of hemolytic anemia, thrombocytopenic purpura, fever, and renal and neurologic symptoms.2 Many cases have been reported about the role of chronic hepatitis C and interferon therapy in the development and recurrence of TTP.3-6 To our knowledge there is no previous report about the association between acute hepatitis C and MAHA including TTP.

CASE REPORT

A 45-year-old nonalcoholic man presented 14 days after appendectomy with fever, confusion, persistent vomiting, bleeding gums, and paresthesia of extremities. There was no history of recent diarrhea or recent drug exposure except for amoxicillin/clavulanic acid given for 7 days after his appendectomy. On examination there were generalized petechiae and purpura, but no palpable organomegaly or lymphadenopathy, no acute abdomen, and the surgical wound was clean. Ultrasound and computed tomography of the abdomen and pelvis were free from any localized infection and causes of acute abdomen.

The patient’s hemoglobin level was 9 g/dL, platelet count 21 × 10⁹/L, whole blood count 8,000 cell/µL, creatinine 7.6 mg/dL, urea 365 mg/dL, alanine aminotransferase was 1,100 U/L, and aspartate aminotransferase 550 U/L. Total serum bilirubin was 1.2 mg/dL, and direct bilirubin 0.3 mg/dL. Prothrombin time and partial thromboplastin time were normal. Lactate dehydrogenase was 987 U/L; D-dimer level was normal. The peripheral smear revealed severe schistocytosis, and the reticulocyte production index was 7 (Figure 1).

Hepatitis C virus (HCV) antibody was positive, while surface antigen of the hepatitis B virus (HBsAg), immunoglobulin M (IgM), total hepatitis B core antibody (HBcAb), human immunodeficiency virus (HIV) antibody, cytomegalovirus (CMV) IgM, Epstein-Barr virus (EBV) IgM, Varicella zoster virus (VZV) IgM antibodies, antinuclear antibodies, anti-dsDNA, anti-cardiolipin (IgM and IgG), lupus anticoagulant, anti-ß glycoprotein I (IgM and IgG), ASMA, and anti-liver kidney microsome antibodies were negative.

ACG Case Rep J 2018;5:e73. doi:10.14309/crj.2018.73. Published online: October 17, 2018.
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Due to the presence of its classic clinical pentad of hemolytic anemia, thrombocytopenic purpura, fever, and renal and neurologic symptoms, a diagnosis of TTP was suggested; however, ADAMTS13 assay is unavailable in our institute. Plasmapheresis plus steroids were started.

On revisiting the patient’s medical records, HCV antibodies were negative twice; the last test was 44 days before appendectomy. The patient denied any other possible risk factor for acquiring HCV infection. Polymerase chain reaction (PCR) for HCV RNA was 507,000 IU/mL of genotype 4. After only 2 sessions of plasmapheresis, hemoglobin level, liver enzymes, and liver and renal function tests returned to normal without renal dialysis. Platelets were $81 \times 10^9/L$ (and continued to rise thereafter until reaching normal levels on day 12 after admission), and all of the patient’s symptoms disappeared, including his neurological symptoms. Plasmapheresis and prednisone were discontinued. All laboratory results remained normal. PCR at 4 weeks after appendectomy was negative without using antiviral therapy. Repeat PCR at 3, 6, and 12 months were negative.

**DISCUSSION**

TTP is a rare, life-threatening microangiopathy characterized by microcirculation thrombosis, tissue ischemia, and thrombocytopenia. Classically, it presents with a pentad of hemolytic anemia, thrombocytopenic purpura, fever, and renal and neurologic symptoms. It is related to decreased ADAMTS13 activity, the protease that is responsible for cleavage of the large multimers of von Willebrand factor (vWF). Autoantibodies against ADAMTS13 are responsible for most sporadic TTP cases.

Classically, diagnosis of TTP is based on the clinical presentation; however, $<10\%$ of patients present with the classic pentad of TTP. Although documentation of a severe decrease in ADAMTS13 activity supports TTP diagnosis, early diagnosis and management doesn’t require measurement of ADAMTS13; moreover, severe deficiency of ADAMTS13 is not specific for TTP.

Conditions that can mimic TTP include malignant hypertension, systemic lupus erythematosus, systemic sclerosis, catastrophic antiphospholipid syndrome, systemic malignancies, and systemic infections. Infections also can trigger TTP onset. One report that discussed systemic infections mimicking or triggering TTP listed many bacteria, fungi, and viruses. Viral hepatitis was included, but the type of hepatitis was not described. Severe ADAMTS13 deficiency was present in $16\%$ of patients who had ADAMTS13 measurements, so documentation of a severe decrease in ADAMTS13 activity is not sufficient to exclude systemic infections as the cause of thrombotic microangiopathy (TMA). TTP cases with systemic infections more frequently presented with the classic pentad of clinical features ($52\%$ of cases). The Oklahoma Registry experience suggests that infections mimic TTP. Another interpretation is that infections trigger TTP onset via production of anti-ADAMTS13 antibodies. Still another explanation is that viral infection can cause endothelial injury resulting in TMA that mimics TTP. There are reports about the occurrence of TTP upon treatment with interferon for HCV infection and upon recurrent TTP in patients with chronic HCV infection. Also, there are reports of the occurrence of TTP upon treatment of chronic myelogenous leukemia, multiple sclerosis, hairy cell leukemia, and Sezary syndrome using interferon.

In our patient, the presence of anemia, reticulocytosis, severe schistocytosis, and increased lactate dehydrogenase confirm MAHA. Normal prothrombin time, partial thromboplastin time, and D-dimer level exclude disseminated intravascular coagulation. The presence of the classic pentad and the absence of other alternative diagnoses make the diagnosis of TTP appropriate. No drug is suspected in our case, and there was no malignant hypertension or scleroderma. Negative antibodies make viral infection other than HCV less likely and exclude systemic lupus erythematosus and catastrophic antiphospholipid syndrome. No malignancy was present on first presentation or on follow up. There were no signs of systemic bacterial or fungal infections, and rapid improvement without antibiotics or antifungals excludes these possibilities.

Seroconversion to positive HCV antibodies plus the disappearance of HCV RNA support the diagnosis of acute hepatitis C infection. However, rapid appearance of HCV antibodies...
just 2 weeks after appendectomy made the diagnosis of acute hepatitis C questionable until the detection and then disappearance of HCV RNA became clear. Plasmapheresis had been initiated before the results of the PCR for HCV RNA were available. When these results became available, the patient was already improving and plasmapheresis was discontinued. PCR for HCV RNA 11 days later (4 weeks after appendectomy) was negative. Therefore this was a case of acute hepatitis C presenting with MAHA that mimicked TTP, which resolved with spontaneous clearance of viremia. The appearance of HCV antibodies was more rapid than usual. This may indicate a severe immune response that might have resulted in the formation of antibodies against ADAMTS13 or a severe systemic response that led to MAHA mimicking TTP.

DISCLOSURES

Author contributions: A. Kamal wrote the manuscript and is the article guarantor. AH Youssef edited the manuscript. AR Mansour provided the image.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Previous Presentation: This case was presented at the 25th United Europe Gastroenterology Week; October 28 to November 1, 2017; Barcelona, Spain.

Received January 20, 2018; Accepted June 25, 2018

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