CASE REPORT

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Fatal Neutropenic Enterocolitis during Pegylated Interferon and Ribavirin Combination Therapy for Chronic Hepatitis C Virus Infection

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It is known that neutropenia caused by combination pegylated interferon plus ribavirin therapy for hepatitis C virus (HCV) infection is well tolerated and carries a negligible risk of infection. Neutropenic enterocolitis is encountered most frequently in patients with hemato-oncologic diseases who are undergoing intensive chemotherapy. However, little information exists regarding this life-threatening event in the setting of HCV therapy. We present here an unusual case of fatal neutropenic enterocolitis in a cirrhotic patient receiving combination therapy for HCV infection. This is the first report of a death from neutropenic enterocolitis associated with treatment for chronic HCV infection. The present case suggests that caution should be exercised when continuing HCV therapy in neutropenic patients with advanced fibrosis, and the decision to maintain such therapy should be balanced against the potential for serious adverse events. **(Gut and Liver 2009;3:218-221)**

Key Words: Neutropenic enterocolitis; Hepatitis C; Interferons

INTRODUCTION

Hepatitis C virus (HCV) infection, the major cause of chronic liver disease, cirrhosis, and liver cancer, affects approximately 170 million individuals worldwide.[1] Combination therapy with pegylated interferon (PEG-IFN) plus ribavirin has become the current standard regimen for patients with chronic hepatitis C. Such therapy is associated with overall sustained virologic response rates of 75% to 90% among patients with HCV genotype 2 or 3 infection and 45% to 52% among those with genotype 1.[2] Recently, a new combination therapy together with thymosin alpha-1 has been investigated in difficult-to-treat patients to increase treatment response.[3] The therapy is associated with various side effects, especially hematologic abnormalities. Some studies suggest that PEG-IFN is commonly associated with a higher incidence of neutropenia compared with standard IFN therapy.[4] Nevertheless, it is known that neutropenia during PEG-IFN therapy does not appear to be associated with serious sequela and seems to be effectively managed by dose modifications.[5]

Neutropenic enterocolitis is a life-threatening complication of intensive chemotherapy, and remains a clinical syndrome characterized by abdominal pain and fever in neutropenic patients. This disease entity has been most often described in patients with hematologic malignancies such as acute leukemia, multiple myeloma, and aplastic anemia, following chemotherapy.[6] In rare cases, this complication has also been reported in the setting of solid cancer and autologous transplantation,[6] but almost never documented in patients with chronic hepatitis C. In this report, we describe a rare case of fatal neutropenic enterocolitis encountered in a patient with chronic HCV infection receiving PEG-IFN plus ribavirin combination therapy.

CASE REPORT

A 54-year-old man with known HCV infection was referred to our institution for treatment of chronic hepatitis

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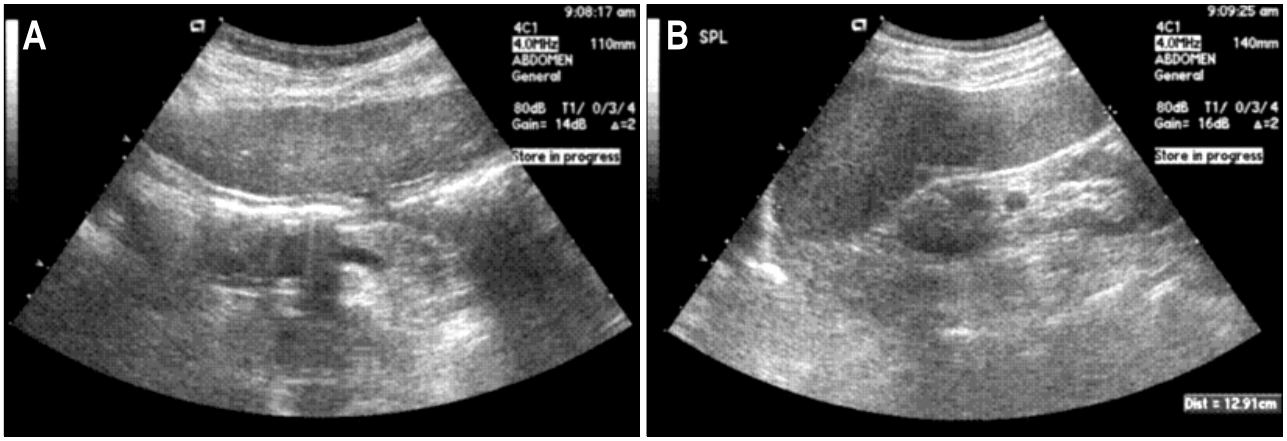

Fig. 1. Ultrasonography of the liver showing (A) a coarse echotexture of the parenchyma, an irregular nodular surface, and (B) splenomegaly (approximately 13 cm).

C. Pretreatment laboratory tests were as follows: elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, 97 and 202 IU/L, respectively; total bilirubin level, 1.9 mg/dL; white blood cell (WBC) count, 5,400/mm^3; platelet count, 149,000/mm^3; prothrombin time (INR), 1.21; genotype 2a; and HCV viral load, 371,000 IU/mL. There was no history of alcohol abuse, gastrointestinal diseases, other co-infectious diseases, and metabolic diseases. Although a liver biopsy was not performed, an ultrasound examination of the liver revealed a coarse echotexture of the parenchyma, an irregular nodular surface, and splenomegaly (13 cm), together highly suggestive of cirrhosis (Fig. 1). A 24-week course of standard combination therapy with PEG-IFN alpha 2a 180 μg weekly and ribavirin 800 mg daily was planned. At week 12 of treatment, serum HCV RNA was negative, but AST and ALT levels remained elevated at approximately 2 times the upper limits of normal. The therapy was continued until week 22 without serious side effects, except a sustained weight loss of 15 kg, anorexia, and general weakness. Through 20 weeks of treatment, WBC counts of the patient were maintained between 2,000 and 2,600/mm^3, with absolute neutrophil counts (ANC) ranging from 760 to 945/mm^3 (Fig. 2). After 22 weeks of antiviral treatment, however, he complained of the sudden onset of diarrhea and abdominal pain with severe tenderness over the right side of the abdomen. On admission to the hospital, his temperature was 39.1°C, the pulse was 113/min and regular, the respiratory rate was 28/min, and the blood pressure was 90/50 mmHg. The laboratory findings included total WBC count, 1,000/mm^3; ANC, 611/mm^3; platelet count, 41,000/mm^3; hemoglobin, 9.8 g/dL; and elevated liver enzymes (AST, 217 IU/L and ALT, 117 IU/L). A computed tomography

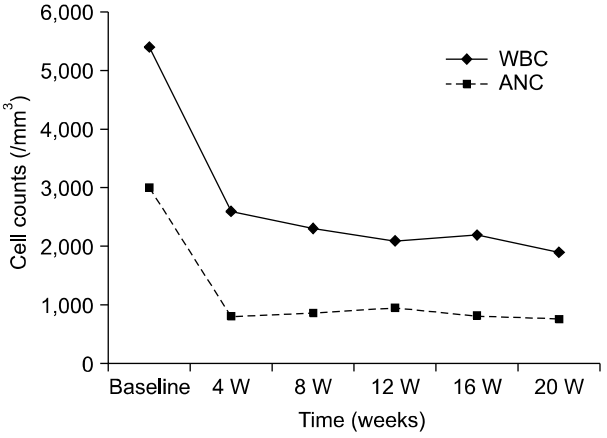

Fig. 2. Serial changes in the white blood cell count (WBC) and absolute neutrophil counts (ANCs) after pegylated interferon and ribavirin combination therapy.

(CT) scan with contrast of the patient's abdomen was obtained and demonstrated marked edematous wall thickening of the ascending and proximal transverse colons, with pericolic strands (Fig. 3). Stool specimens were non-specific and negative for Clostridium difficile toxin. The diagnosis of neutropenic enterocolitis was made based on the presence of fever, abdominal pain, and bowel wall thickening. Broad spectrum antibiotics, inotropic support, and granulocyte colony-stimulating factor were administered immediately. Despite intensive antibiotic therapy and best supportive treatment, he continued to deteriorate and ultimately died from multiorgan failure on hospital day 9. The blood cultures were positive for Escherichia coli.

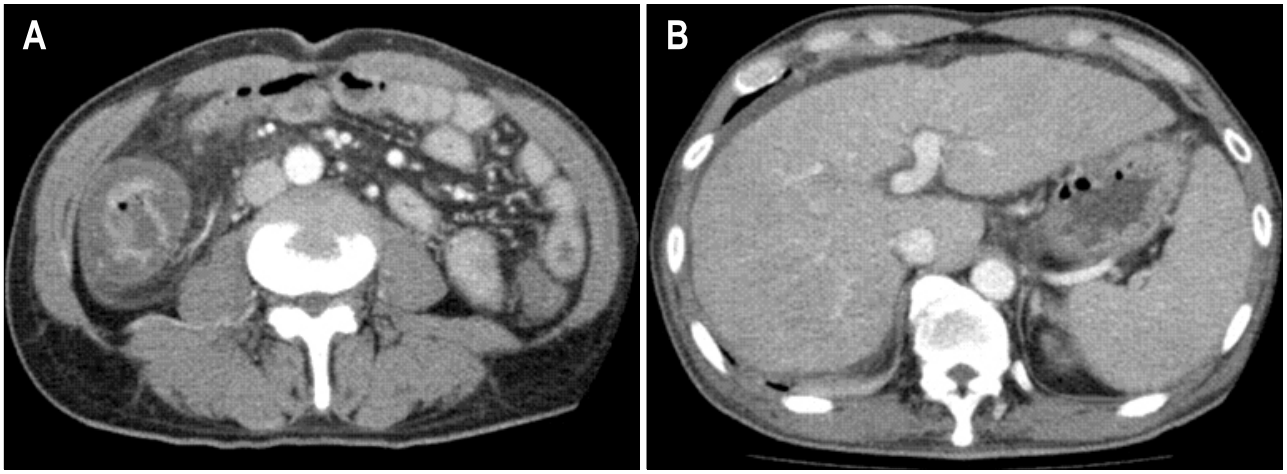

Fig. 3. CT scan on admission of a patient who presented with symptoms of neutropenic enterocolitis. (A) Edematous wall thickening of the ascending colon with pericolic strands. (B) Cirrhotic liver with minimal ascites in the perihepatic space, and splenomegaly.

DISCUSSION

Neutropenic enterocolitis occurs most often following treatment of hematologic malignancies and high-dose chemotherapy in solid tumors, and has a 5.3% pooled incidence rate, with high mortality rates ranging from 50% to 100%.[7] Neutropenia is often observed in patients with chronic hepatitis C receiving PEG-IFN and ribavirin combination therapy, but is generally well-tolerated without serious morbidities.[5] Moreover, intestinal complications associated with the combination therapy are rare, with only a few case reports of exacerbation of ulcerative colitis and ischemic colitis.[8-10] With regard to other intestinal events relevant to HCV therapy, a literature search found only one case of neutropenic enterocolitis which improved with empirical antibiotics and supportive care.[11] Thus, to the best of the authors' knowledge, our patient is the second reported case to date and the first reported death from neutropenic enterocolitis while on HCV therapy.

Neutropenic enterocolitis is highly suspected in neutropenic patients presenting with fever and abdominal pain, especially in the right lower quadrant.[6] Abdominal imaging is useful in supporting a diagnosis of this disease. Some have suggested the criteria for the diagnosis of neutropenic enterocolitis to be fever, abdominal pain, and demonstration of the bowel wall thickening of more than 4 mm in any segment by ultrasound or CT scanning in a neutropenic state.[6] Our patient met all of these criteria, and the diagnosis of netropenic enterocolitis in this case was therefore definite.

Although the mechanism for the pathogenesis of neutropenic enterocolitis is not completely understood, it is postulated that a combination of factors, including mucosal injury by cytotoxic drugs, neutropenia, and impaired host defense to intestinal organisms progressing to bacteremia and sepsis, is responsible for the development of neutropenic enterocolitis.[6,12] Particularly, cirrhotic patients are at increased risk of bacterial infection because of intrinsic neutropenia, liver dysfunction, and reduced reticuloendothelial function. Thus, neutropenia during therapy of HCV infection can intensify the risk of infection in patients with HCV-related cirrhosis.

Recently, it has been shown that a shorter course of PEG-IFN and ribavirin therapy over 12 weeks is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a virologic response at 4 weeks.[13] It is unfortunate that in our case, HCV RNA at 4 weeks was not tested and the patient with HCV genotype 2a adhered so closely to a strict schedule of antiviral therapy. In retrospect, the therapy could have been discontinued earlier if serum HCV RNA was undetectable at week 4 of therapy, taking into consideration the significant weight loss and anorexia in our patient.

In conclusion, we believe this case report contains a worthwhile clinical lesson for practitioners who manage patients with chronic hepatitis C, especially those patients with advanced fibrosis or cirrhosis. Although some studies have indicated a negligible risk of infection associated with HCV treatment-related neutropenia,[5] caution should be exercised against serious infections when treating cirrhotic patients who are potentially immunocompromised. Although anorexia, weight loss and general weakness are non-specific adverse events of HCV combination therapy, if sustained and uncorrectable, clinicians should be aware of the potential development of neutropenic enterocolitis.

Furthermore, a shorter course of therapy could be considered in an effort to avoid possible severe life-threatening side effects for those with cirrhosis who have had a rapid virologic response to therapy.

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