Acute hepatitis induced by alpha-interferon in a patient with chronic hepatitis C

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CASE PRESENTATION

A 33-year-old man with positive anti-HCV antibodies was examined as an outpatient due to persistently high aminotransferase activity during the previous year. The initial biochemical values on September 17, 1996 were: serum alanine aminotransferase 272 IU/L (normal less than 30 IU/L), serum aspartate aminotransferase 184 IU/L (normal less than 30 IU/L), serum alkaline phosphatase 97 IU/L. The present report describes a case of acute hepatitis with a marked elevation of aminotransferase activity and jaundice during the treatment of chronic hepatitis C with alpha-interferon.

Key Words: Acute hepatitis; Alpha-interferon; Chronic hepatitis C; Therapy

Hépatite aiguë causée par l’interféron alpha chez un patient atteint d’hépatite C chronique

merase chain reaction, with 10.7×10^6 copies of HCV RNA were positive by reverse transcriptase polymerase chain reaction. The second liver biopsy showed the dates of the start and discontinuation of alpha-interferon therapy, as well as the dates of hepatitis C virus (HCV) RNA negative (–) tests. IFN Interferon therapy started on October 21, 1996, and the therapy was discontinued on January 27, 1997. At 36 months’ follow-up, the aminotransferase activity remained normal, and tests for HCV RNA were negative.

**DISCUSSION**

We believe that alpha-interferon caused acute hepatitis in this patient. No positive serology for acute hepatitis (A, B, E and G), cytomegalovirus, Epstein-Barr or herpes was found. Moreover, the patient neither abused alcohol nor took any drugs besides interferon, thus excluding these as possible causes of acute hepatitis. Antoantibodies, another possible cause, were not found, so they were excluded as a cause. Anti-interferon antibodies were also not detected. Hepatotropic viruses and some other viruses, as well as exacerbation of autoimmune hepatitis, were excluded as causes, although non-A, non-E acute hepatitis could not be ruled out.

A very important argument for interferon therapy being responsible for the acute hepatitis in this case is the rapid normalization of aminotransferase activity after treatment was stopped. The mechanism responsible for the development of acute hepatitis during interferon therapy is not easily explained. Toxic effects of interferon on hepatocytes or an immunologically mediated mechanism are possible theoretical explanations.
It is well known that high doses of interferon can cause hepatic necrosis in mice. Baglioni (10) explained that interferon could induce a marked decrease in protein synthesis, as well as inhibition of several enzymes, such as 2′,5′ oligoadenylate synthetase and protein kinase. At the same time, interferon decreases the transcription of mitochondrial DNA and impairs fatty acid beta-oxidation. All of these changes lead to hepatocyte injury.

Itoh et al (11) showed the ultrastructural change of hepatocytes in patients receiving interferon for chronic hepatitis B. A marked decrease in the number of mitochondria, as well as alterations of endoplasmic reticulum and fat vacuoles, were seen in their patients. These changes suggest decreased fatty acid oxidation.

There are many arguments against the toxic effects of interferon, including the fact that a very large number of patients are treated with interferon, and only a very small number of them developed toxic effects. Another argument is that the occurrence of hepatitis is not dose-related. Our patient had no microvesicular steatosis, which is the characteristic lesion when fatty acid beta-oxidation is inhibited, and marked lymphocytic infiltration was present (12).

We are inclined to believe that an interferon-induced, immune-mediated mechanism underlies the acute hepatitis seen in our patient. Although such a reaction is not common during the treatment of chronic hepatitis C, it may, however, be considered possible. For example, after several months of interferon therapy in patients with chronic hepatitis B, the illness is exacerbated almost regularly, ie, aminotransferase activity increases suddenly, reflecting immune-mediated lysis of hepatocytes and the elimination of B viruses due to an enhanced cellular immune response. The occasional exacerbation of autoimmune chronic hepatitis in patients with positive antismooth muscle antibodies or anti-LKM-1 antibodies supports this type of reaction (13-15). It could, therefore, be assumed that this is also possible in hepatitis C.

CONCLUSIONS
In the absence of other causes, the present report of a patient with chronic hepatitis C suggests that there is a strong relationship between acute hepatitis and alpha-interferon treatment. The most probable mechanism is an excessive immune response to HCV, but it is not clear whether this excessive immune response contributes to the elimination of HCV. Further clinical investigations of similar cases are required to clarify the mechanism involved in the development of this type of hepatitis and its role in the elimination of HCV from the body.

REFERENCES