CASE REPORT

Severe chronic active hepatitis (autoimmune type) mimicked by coinfection of hepatitis C and human immunodeficiency viruses

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Abstract

Severe chronic active hepatitis, defined as the presence of a fivefold increase in serum aminotransferases and a twofold rise in γ globulin for at least 10 weeks, is considered a progressive immunological liver disease requiring corticosteroid treatment, particularly when serum autoantibodies and a severe lymphoplasmacellular periportal infiltrate are found in the liver biopsy specimen. A 38 year old man who fulfilled the criteria for severe chronic active hepatitis is described. His sex, his homosexuality, and the presence of antibodies against HIV, however, led to the suspicion of a coinfection with hepatitis C virus (HCV) rather than autoimmune disease. The rapid and complete response to α interferon treatment and a recently available positive antibody test for HCV supported this view. These findings indicate that a HCV related chronic active hepatitis can present as the severe auto-

immune type of chronic active hepatitis. Moreover, as in HBV infection, the response to treatment differs from that of autoimmune severe chronic active hepatitis.

In 1968, severe chronic active hepatitis was defined as a disorder characterised by at least a 10 fold increase in the serum aminotransferase activities for 10 weeks or a twofold rise in γ globulin together with a fivefold increase in serum aminotransferase activities.¹ The disease, thought to be of autoimmune origin, usually progresses rapidly, with a mortality rate of 50% in two years. Corticosteroid treatment has been shown to increase life expectancy considerably.²⁻⁴

The features of severe chronic active hepatitis were subsequently encountered in liver diseases of other aetiologies, such as primary biliary cirrhosis, primary sclerosing cholangitis, and

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Figure 1: Liver biopsy specimen showing (A) disturbed architecture and fibrosis compatible with probable cirrhosis (original magnification $\times 75$) and (B) dense periportal lymphoplasmacellular infiltrate and piecemeal necrosis (original magnification $\times 185$).

Figure 2: Serological findings before, during, and after α interferon treatment in a 38 year old man with severe chronic active hepatitis (CAH) due to hepatitis C virus (HCV) and HIV coinfection. The dose of α interferon was increased at months 11 and 20 because of active HIV infection (see text). Note the rapid return to normal of aspartate aminotransferase (AST) after beginning treatment and the absence of relapse in the six months since stopping α interferon treatment.

chronic hepatitis B virus (HBV) infection⁵⁻⁷ and metabolic disorders requiring treatments other than corticosteroids. The diagnosis of autoimmune severe chronic active hepatitis is based on the presence of this disorder plus auto-antibodies in serum and portal and periportal lymphoplasmacellular infiltrates as well as piecemeal necrosis seen on liver biopsy specimen.

The following case suggests that chronic HCV infection can mimic autoimmune severe chronic active hepatitis and that treatment with α interferon⁸ may induce clinical and biochemical remission in these patients.

Case report

HISTORY

A 38 year old man, born in the Netherlands Antilles, was admitted to hospital for treatment of syphilis with intravenous penicillin. He had had an HBV infection in the past as well as repeated gonococcal and *Treponema pallidum* infections. One year before admission he was found to be anti-HIV positive. Apart from a tonsillectomy at age 17 years and a perianal abscess and lobar pneumonia at age 37, he had not been admitted to hospital or undergone any surgical procedures. His serum transaminase activities were found to be raised. Fatigue was his only symptom. There were no signs of alcohol abuse or intravenous drug abuse. He had never had a blood transfusion or undergone earpiercing or tattooing and there was no hepatitis in the family history. The patient was not taking any medication. He was, however, a promiscuous homosexual. Physical examination showed lymph node enlargement; the liver and spleen were normal and apart from palmar

erythema, there were no signs of chronic liver disease. Over a period of 26 weeks the hepatitis progressed. His bilirubin concentration rose to 42 $\mu\text{mol/l}$ (normal less than 17), serum aspartate aminotransferase to 405 IU/l (normal less than 30), and alanine aminotransferase to 300 IU/l (normal less than 30). The patient's serum albumin decreased from 34 to 28 g/l. Blood clotting tests remained normal: normotest 83%, fibrinogen 2.0 g/l, and antithrombin III 86%. His α fetoprotein value was below 3 $\mu\text{g/l}$. Immunoglobulin (Ig) G was 72.5 g/l (normal 8-18), IgM 4.8 g/l (normal 0.6-2.8), and IgA 2.4 g/l (normal 0.9-4.5). Anti-nuclear antibodies were positive (titre 1:160) and smooth muscle antibodies were negative (liver-kidney microsomal antibodies were not tested). Virus serological tests showed the following: anti-HBc positive, HBsAg negative, anti-HBs positive, anti-hepatitis delta virus negative, anti-cytomegalovirus IgM negative, anti-Epstein-Barr virus-CA IgM negative, and anti-HIV positive. The CD4 cell count was $0.6 \times 10^9/\text{l}$ ($600/\text{mm}^3$) and in vitro lymphocyte stimulation tests were normal. Ultrasound examination of the abdomen showed a slightly enlarged liver and spleen. A liver biopsy specimen showed probable cirrhosis (Fig 1A and B) with chronic active hepatitis. The enlarged portal tracts and fibrous septa contained an extensive infiltrate consisting of lymphocytes, plasma cells, and some neutrophilic granulocytes. Piecemeal necrosis with severe degeneration of liver parenchyma and many Councilman bodies was seen (Fig 1B).

DIAGNOSIS AND TREATMENT

According to the Mayo Clinic criteria,¹⁹ this

patient had severe chronic active hepatitis with immunological features and so immunosuppressive treatment seemed to be indicated. Because of the HIV infection and a suspected non-A, non-B hepatitis, corticosteroid therapy was postponed and a course of 5 MU α interferon daily (Wellcome Laboratories, Beckenham, UK) given subcutaneously was started.⁸

Results

Serum transaminase activities returned to normal in two weeks and serum IgG values fell to less than 50% of the initial concentration (Fig 2). When the dose of interferon was tapered to 2 MU every other day, the serum transaminase activities remained normal. Interferon was well tolerated and the patient reported the gradual disappearance of fatigue during treatment. The dose of interferon was increased to 2 MU daily at month 11 in an attempt to suppress HIV replication, since HIV associated p24 antigen had become detectable in the serum. HIV p24 antigen became negative at month 13, only to reappear two months later. The patient rejected treatment with zidovudine and the dose of interferon was increased to 3 MU daily at month 20. At 22 months the patient withdrew from treatment. He felt physically well, and apart from a raised serum IgG concentration, his liver disease was in biochemical remission. His bilirubin was 0.4 $\times$ the upper limit of normal, serum aminotransferase activities were 0.5 $\times$ the upper limits of normal, albumin was 39 g/l, and IgG 37.6 g/l. Anti-nuclear antibodies became negative. Clotting factors were 100%. No reactivation of his liver disease has been observed over six months of follow up. Serological testing for HCV (ELISA, Ortho HCV, Ortho Diagnostics, Raritan, New Jersey, USA), available since month 28, showed the presence of anti-HCV antibodies at the time of admission to our department, during treatment, and at follow up.

Discussion

This patient suffered from a severe chronic active hepatitis that presented serologically and histologically as one of autoimmune origin. The diagnosis severe autoimmune chronic active hepatitis, however, depends on non-specific criteria such as a 10-fold increase in serum transaminase activities, a twofold increase in the IgG concentration, the presence of auto-antibodies, and dense lymphoplasmic cellular infiltrate in the liver. Since the patient was a promiscuous homosexual male, he was considered more likely to have a viral disease than autoimmune type chronic active hepatitis. Chronic non-A, non-B hepatitis was the most likely diagnosis and probably explained the raised serum aminotransferase activities. The high IgG values may be related to the HIV infection.¹⁰ The response to two weeks of interferon treatment supported our suspicion of an HCV infection, which was subsequently virtually confirmed by the detection of anti-HCV

antibodies. The confirmatory value of the finding of persistent anti-HCV reactivity in this patient with a high serum IgG value could be questioned, however, in view of the recent finding of the non-specific reactivity of the anti-HCV test in patients with chronic active hepatitis and high serum IgG concentrations.¹¹

Prednisone treatment, probably life saving in the event of severe autoimmune chronic active hepatitis, was no longer considered once the beneficial effect of interferon treatment was observed. Interestingly, persistent clinical and biochemical remission of the severe chronic active hepatitis occurred in this anti-HIV positive patient after stopping interferon treatment. Such a result is remarkable, since persistent remission for six or more months after stopping interferon occurs in the minority of patients with chronic non-A, non-B hepatitis¹² and supposedly reflects adequate immune control.

This patient illustrates that a diagnosis of severe chronic active hepatitis of the autoimmune type requires the exclusion of HCV infection as well as HBV infection, toxic hepatitis, metabolic disorders, primary biliary cirrhosis, and primary sclerosing cholangitis. In addition, this case supports the observation that chronic HCV infection can progress rapidly where there is coinfection with HIV, as recently described by Martin *et al.*¹³ These patients, however, may be as responsive to interferon therapy as those with the usually milder form of HCV infection.

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