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What Kind of Hepatitis?

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Finding one major hepatotropic virus may not be enough to identify the aetiology of liver disease when risk factors are present, particularly in patients with past or present infection with other viral agents, or chronic liver disease. The pathogenic process in these cases is often complex. In the five cases we report, acute hepatitis (initiated by halothane, cytomegalovirus or Epstein-Barr virus) preceded the reactivation of hepatitis B infection, and these events occurred in patients with chronic hepatitis C infection. Each case demonstrates how several viruses can be implicated in the development of hepatitis, either as single agents or via cross-activation of T cells. The nosography of hepatitis, therefore, and the optimum therapeutic choices, can puzzle the clinical team.

KEY WORDS: Hepatitis B infection; Hepatitis C infection; Halothane; Cytomegalovirus; Epstein-Barr virus; Antibodies

Introduction

The laboratory investigations requested for a patient with raised serum transaminases usually include markers for the major hepatotropic viruses;[1–3] consequently, following the detection of hepatitis C virus (HCV) antibodies, HCV would often be pinpointed as the cause of a patient's liver disease.[3] When an assumption like this is made, however, the occurrence of events initiated by (or related to) other viruses may be overlooked, yet once a history of multiple, previous, or current viral infection has been ascertained, the sequence leading to development of liver disease becomes unclear. We report five cases where finding HCV antibodies (Ab) or Hepatitis B surface (HBs) antigen (Ag) was insufficient to describe either the sequence of events in disease pathogenesis, or to diagnose the aetiology of relapsing, acute hepatitis.

Case reports

CASE 1

A 27-year-old female operating theatre nurse was referred to our unit in February 1997 following detection of HCV antibodies. Haematological analyses undertaken in this patient a month later revealed a normal alanine transaminase (ALT) value, presence of HCV-RNA as revealed by reverse transcriptase-polymerase chain reaction (PCR), and positive HBsAb, anti-core antibodies (HBcAb) and anti-e antigen (HBeAb). Liver biopsy identified a mild lobular hepatitis. Three months later the patient underwent further haematological testing after the operating theatre in which she worked was contaminated by halothane. Her ALT value was approximately three times the upper normal range, rising 2 weeks later to 43 times the normal range, and a decrease in

natural-killer lymphocytes was oberved (from 95 to 37/mm^3). Immunoglobulin (Ig) M anti-cytomegalovirus (CMV) was also detected and the patient's IgG level was 597 mg/dl. One week later she tested positive for anti-HBc IgM for the first time and, subsequently, HBV-DNA was detected using dot-blot.

The clinical course then followed that of an acute hepatitis infection, with rapid disappearance of IgM anti-CMV, and progressive reduction and eventual disappearance of anti-HBc IgM, 6 weeks later.

CASE 2

For 3 consecutive years a 52-year-old male with compensated liver cirrhosis and moderate inflammatory activity had experienced a peak rise in ALT values. His background ALT value was 1.5 – 2.2-fold the upper normal range, reaching a level of 8.5-fold. The patient had HCV antibodies and tested positive for HCV-RNA; further studies showed HBV seroconversion and IgG anti-CMV, anti-Epstein-Barr virus (EBV) and anti-Parvovirus B-19 (PVB19). We found IgM anti-EBV and IgG increased to 642 mg/dl in this patient in December 1998; a month later his IgG EBV level was unchanged, IgM HBc and HBV-DNA were detected, and serum ALT values reached 9.7-fold the upper normal range. The clinical course of hepatitis in this patient was that of a mild acute infection with progressive disappearance of IgM EBV and HBV-DNA approximately 4 months later.

CASE 3

A 45-year-old female was referred in March 1998 after testing positive for HBsAg and HBV-DNA. Periodical recurrence of ALT activity up to nine times the normal range had been identified between January and February, and again between June and July, in the previous 2 years.

When we observed the patient in June 1998, her IgM anti-CMV value was 50 mg/dl and IgG was 845 mg/dl. Approximately 2 weeks later, ALT increased to 12.4-fold the normal range, remaining elevated for 6 weeks and returning rapidly to normal by September. A month later IgM-HBc and IgM-CMV disappeared and a liver biopsy indicated severe hepatitis (portal, interfacial and lobular) with fibrosis. In December 1998, IgM for EBV virocapsid were detected at 120 mg/dl. Weekly check-ups thereafter revealed IgG 420 mg/dl, and 28 days later presence of IgM-HBc, followed by a peak increase in ALT to 7.5-fold the normal value in March. All parameters returned to normal eventually, but in June 1999 ALT increased to 9.7-fold the normal range and the patient's serological profile was similar to that observed during her previous episode of hepatitis.

CASE 4

A 56-year-old female with past history of tuberculosis was referred to our unit in January 1997 because her liver was enlarged and firm, having a bright pattern on ultrasound. The patient's ALT and HCVAb values were normal, although further tests revealed HCV-RNA, HBV seroconversion (HBsAb, HBcAb, HBeAb), CMV IgG 98 mg/dl, normal lymphocyte sub-populations and no autoantibodies. Liver biopsy revealed a moderate portal fibrosis, chronic lobular hepatitis and diffuse, mild steatosis. The patient's condition remained stable for 6 months, then in June 1997 her ALT value reached seven times the upper normal range and, after 4 weeks, blood tests revealed anti-CMV IgM 140 mg/dl and IgG 380 mg/dl. The patient felt well and was concerned that any treatment would reactivate the tubercular infection. After 3 months IgM anti-CMV disappeared, her IgG CMV level was

285 mg/dl and ALT value was 5-fold the upper normal range. No further changes were observed until November 1998, when her ALT was 1.2 times the upper normal range and IgG anti-CMV was 137 mg/dl: these levels decreased slowly and returned to normal after approximately 6 months.

CASE 5

A 47-year-old male with chronic HCV-related hepatitis was referred to our unit when a sharp increase in ALT values occurred at the end of a 6-month course of therapy with 3 MIU recombinant α-interferon-2a. Before interferon treatment his clinical records showed presence of HCV-RNA, HBV seroconversion and ALT levels fluctuating between 2.5 and 5.4-fold the normal range. At the end of the 6-month course of interferon therapy, HCV-RNA became seronegative. Liver biopsy performed at this time revealed a chronic lobular hepatitis and mild lobular fibrosis. We observed recurrence of HCV-RNA and ALT (the latter reaching 25 times the upper normal range); further studies detected HBV-DNA in serum although HBc-IgM remained negative; his IgM anti-ABV level was 170 mg/dl and his IgG level was 389 mg/dl. Five months later, the patient's ALT level returned to normal, with the disappearance (in sequence) of: IgM HBc, EBV and HCV-RNA. The patient's serum transaminase level remains normal but HCV-RNA has been positive three times over alternate months following PCR analysis.

Discussion

These five cases were selected from a series of 152 patients with chronic liver disease, all of whom had evidence of past or present infection caused by different viruses, with no history of drug or alcohol abuse and no clinical or serological evidence of HIV infection. Finding HBsAg or HCVAb in each case was insufficient to describe the aetiology and complete the diagnostic picture for each individual. If we imagine taking cross-sections at certain points in the clinical courses of each case, one or multiple potential aetiological factors may emerge.

These five cases cannot be described merely as HBV or HCV infections. In the presence of HCV and/or HBV antigens an intermediate, toxic (i.e. halothane) and/or viral factor (i.e. CMV or EBV), either circulating or integrated in the genome of host hepatocytes, co-operated with the major hepatotropic viruses, thus causing hepatitis.

We do not know the mechanism(s) underlying the hepatitis infections observed in these patients, but the report of a proliferative response of CD8 lymphocytes many years after exposure to HBV, and in absence of circulating HBV-DNA, is provocative.[4] This finding indicates that HBV seroconversion warrants consideration as a serious risk factor for hepatitis infection: one that may easily be neglected in epidemiological studies evaluating the potential hazard of HCV infection.[5,6] A cross-reactivation of CD8 and CD4 lymphocytes by short peptides from different sources that bear some homologies, accommodated on the cleft of human leukocyte antigen-II, may now be speculated: recent reports have discussed the role of activated/effector cells resident in the liver.[7,8]

If the viral co-operation observed in the five cases we describe represents a more general phenomenon, it could explain the diverse pattern of HCV-related liver disease that we see, ranging from normal or mild, lobular hepatitis to severe active cirrhosis or hepatocellular carcinoma. It is possible that different manifestations of this liver disease are related to other risk factors associated with HCV. Different aetiological factors may be present concurrently in cases of hepatitis

with complex pathogenesis, in the absence of autoantibodies or hazardous xenobiotics, but how we describe and treat these cases is subject to question.

When a case of chronic hepatitis fails to respond to therapy, it is also possible that a misleading interpretation of the aetiology may have occurred. A major hepatotropic virus might be present, but the cause of hepatitis could be another viral agent. We wish to emphasize that the pathogenic process can be more complex than it appears at the first approach, and should be identified accurately in patients with chronic liver disease, so that the optimum therapeutic options can be selected.

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