Case report

Acute delta hepatitis without circulating HBsAg

K M DE COCK, SUGANTHA GOVINDARAJAN, AND A G REDEKER

From the University of Southern California, Liver Unit, Rancho Los Amigos Hospital, Downey, California, USA

SUMMARY Infection with the delta agent can only occur in the context of coexistent hepatitis B virus infection. We describe a patient in whom the clinical features of acute delta hepatitis developed when seroconversion from hepatitis B surface antigen to antibody had already occurred and diagnosis of recent acute hepatitis B was based on high titre IgM antibody to hepatitis B core antigen. We discuss the significance of such a serological profile, not previously described.

Rizzetto and colleagues¹ first recognised the existence of the delta agent in 1977 while staining liver tissue by immunofluorescence for hepatitis B core antigen (HBcAg). An early observation was that delta antigen was only present in the livers of hepatitis B surface antigen (HBsAg) carriers. Infectivity studies in chimpanzees showed that delta infection could occur with both acute and chronic hepatitis B (HBV) virus infection.² In contrast, delta hepatitis could not be induced in HBsAg negative animals with circulating antibody to HBsAg (anti-HBs). Seroepidemiological investigations confirmed that the delta antigen-antibody system was only detectable in HBsAg carriers, except in rare individuals recently recovered from acute HBV and delta infection.³

We describe a patient with acute delta hepatitis who at presentation had serological evidence of recent HBV infection but was HBsAg negative. The implications of such a serological profile, not previously described, are discussed.

Methods

HBsAg, hepatitis Be antigen (HBeAg), anti-HBs and antibody to HBeAg (anti-HBe) were tested for using commercially available radioimmunoassay kits (Ausria II, Abbott-HBe, Ausab, Abbott Labora-

tories, North Chicago, Illinois). Hepatitis A virus IgM antibody (anti-HAV IgM) was assayed by radioimmunoassay from the same source (HAVAB-M). The presence of IgM antibody to HBcAg (anti-HBc IgM) was detected by separation of serum IgM using a QAE sephadex A50 column followed by radioimmunoassay of the IgM fraction using a kit (CORAB, Abbott Laboratories). 1/50, 1/100, 1/250, and 1/1000 serum dilutions were tested to determine the titre of anti-HBc IgM. An immunoglobulin capture solid phase radioimmunoassay was used for detection of anti-delta IgG and IgM antibody, as previously described.^{4,5} The results of this assay are expressed as the ratio of counts per minute (cpm) of test sera to cpm of a negative control serum (S/N ratio).

Case report

A 22 year old Hispanic intravenous drug user was admitted to hospital with increasing jaundice. He began to complain of excessive tiredness three weeks previously, noted dark urine two weeks before admission, and suffered malaise, nausea, and vomiting for one week before presentation.

On examination he appeared lethargic and was deeply icteric. He was well oriented, lacked asterixis and showed no stigmata of chronic liver disease. The liver was palpable four finger breadths below the right costal margin. Examination was otherwise unremarkable.

Sequential biochemical and serological data are shown in the Table. HBsAg was negative on

Address for correspondence: Dr Kevin M De Cock, USC Liver Unit, Rancho Los Amigos Hospital, 7601 E Imperial Highway, Downey, California, 90242, USA.

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Table Laboratory findings

Day	Bilirubin ($\mu\text{mol/l}$)	AST (IU/l)	ALT (IU/l)	Prothrombin activity (%)	HBsAg	Anti-HBs (S/N)	HBeAg	Anti-delta IgM (S/N)	Anti-delta IgG (S/N)
1*	465.5	2980	2860	48	Neg	11.3	Pos	4.8	3.5
3	403.4	3360	3230	36					
4				24					
6	443.1	2385	1120	27					
7	463.8	1958	1133	28	Neg		Pos	4.8	3.5
8	427.6	1220	723	30	Neg	92.1		4.8	4.6
10	494.8	740	590	38	Neg			4.9	3.1
16	422.4	730	497	117	Neg	55.2	Neg	6.0	4.6
30	91.4	217	77		Neg	21.5	Neg	Neg	Neg

* day 1 = day of admission.

admission and remained so throughout the clinical course. Anti-HBc IgM was positive at a titre greater than 1:1000. Anti-HBs was weakly positive initially, but increased significantly over subsequent days. HBeAg, anti-delta IgM, and anti-delta IgG were positive. Anti-HAV IgM was negative.

His condition deteriorated over the next three days and he complained of increased nausea, vomiting, and fatigue. Aminotransferase levels increased, prothrombin activity fell, and there was concern that he was developing fulminant hepatitis. The S/N ratios for anti-delta IgM and IgG, with the IgM fraction predominating, are consistent with acute delta hepatitis.

He began to improve on the fifth hospital day and was discharged nine days after admission. He continued to recuperate and HBeAg and anti-delta antibodies disappeared from the serum. He was well on the 30th day of illness, at which time he was only mildly jaundiced. He has been lost to follow up since then.

Discussion

This HBsAg negative patient already had a low titre of circulating anti-HBs at presentation, before the height of clinical hepatitis. Evidence for recent acute HBV infection was the high titre of anti-HBc IgM⁶ combined with the observed loss of circulating HBeAg and acquisition of high titre anti-HBs. The changes in levels of IgM and IgG antibody to delta agent are typical of acute delta hepatitis. This serological profile with absence of detectable HBsAg has not been previously documented.

Delta infection was initially thought unlikely in view of the negative HBsAg status, but was subsequently considered because of the length and severity of illness. This patient illustrates that clinical delta hepatitis is possible even when the only evidence of HBV infection is circulating anti-HBc

IgM in high titre. This might be especially important in patients diagnosed to have fulminant hepatitis B, who sometimes rapidly clear HBsAg and have their diagnosis based on high titres of anti-HBc IgM alone.⁷ Some such patients may represent unrecognised cases of delta infection, which is known to predispose to fulminant hepatitis.⁸

Observations in humans^{9,10} and in experimentally infected chimpanzees² have shown that acute delta infection in chronic hepatitis B suppresses the synthesis of HBV products. While such suppression is usually transient, we have seen three chronic HBsAg carriers in whom it resulted in permanent clearance of HBsAg with seroconversion to anti-HBs. (In preparation).

The effect of simultaneous delta infection on the level and persistence of markers of acute HBV infection has not been studied. The circulating delta agent is coated with HBsAg¹¹ which has to be available for delta infection to be established. Presumably in the patient described here infection with delta occurred along with acute HBV infection, but subsequently the delta agent suppressed HBV replication. There must have been circulating HBsAg for delta infection to establish itself, but the delta agent probably then caused rapid clearance of HBV with early development of high titre anti-HBs. The clinical manifestations of delta hepatitis followed these serological events. In this situation clearance of the delta infection is then guaranteed, as shown by the loss of both delta antibodies (Table), because the essential helper function of HBV is no longer available.

The suppression of HBV replication in chronic HBsAg carriers by superinfection with delta is most often transient, and chronic delta infection usually results.¹² Combined acute infections rarely lead to the carrier state.¹² It is possible that the suppressive effect of delta in combined acute infections virtually ensures clearance of HBsAg.

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