Prolonged and biphasic acute hepatitis A in hepatitis B virus carrier

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ABSTRACT

Acute hepatitis A is generally a self-limited disease in healthy subjects within few weeks, but an uncommon type of prolonged and biphasic acute course of hepatitis A infection has been also described. This type of presentation is observed in about 6-10% of patients, but a small number of reports, concerning this topic, are available in literature. In addition, hepatitis A virus (HAV) infection in hepatitis B virus (HBV) carriers has rarely been discussed. A 41-year-old Italian man, already known to our Department for HBV infection as an inactive carrier HBsAg(+)ve, experienced a prolonged and biphasic course of acute hepatitis A, lasting about 7 months. In this patient possible factors, causing the second flare of transaminases, were excluded (in particular autoimmunity). Liver biopsy as well HAV RNA search in blood/stools were not performed. In conclusion, the hepatologist should take into account this type of atypical course in patients with HAV-related hepatitis and should promote HAV vaccination in subjects with HBV-chronic hepatitis, to prevent possible life-threatening acute exacerbation of hepatic damage, mainly in HBV-carriers with more severe forms of liver diseases.

Introduction

Acute hepatitis A may represent a possible pitfall for the hepatologist, because of its epidemiology and heterogeneous clinical presentation. Moreover, an increase in the prevalence of hepatitis A was recently reported with an ongoing outbreak in Italy.[1] Furthermore, hepatitis A infection, which is transmitted *via* an oral fecal route, can be asymptomatic, although some subjects can also present both jaundice and/or a fulminant course (0.5-1%). About 70% of the adult population generally shows a symptomatic illness with nausea, vomiting, abdominal pain, headache and fever but only 30% of these patients develop jaundice.[2] Extrahepatic manifestation of hepatitis A, such as cutaneous vasculitis and peripheral neuropathy, have been reported, although with a lower frequence.[3] Then, in some situations acute hepatitis A acts as a trigger for the development of autoimmune hepatitis.[4] On the basis of its clinical course, acute HAV infection is generally a self-limited disease, within few weeks (within 4-6 weeks), but in 6-10% of cases hepatitis A course can be prolonged (more than 4 months), even though it is not defined as chronic.[5-7] In the past, several case reports, concerning this atypical type of presentation, have been described. In particular, in 1992 Glikson *et al.*[8] reviewed their experience, concerning 14 cases of hepatitis A, showing a relapse, as well as 68 cases reported in the literature. They found that the relapse occurred at a rate, ranging between 3 and 20% of patients with acute hepatitis A, and it rarely showed a polyphasic course (multiple relapses). After a stage of typical hepatitis A, a remission phase developed, with the partial or complete resolution of clinical and biochemical manifestations. Relapse usually occurred after a short period (usually less than 3 weeks) with a usually lower clinical severity than one, observed in the first phase, with variable liver function abnormalities and a tendency toward a more marked cholestatic feature. They concluded that the clinical course in patients, undergoing a relapse of hepatitis A infection, was almost al-

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ways benign and uneventful recovery is the rule with few exceptions. Steroid treatment, first reported in the past, resulted in marked clinical improvement and it was suggested that relapsing hepatitis A was associated with a persistent viremia as well as the presence of virus in stools during the relapse phase. The pathogenesis of prolonged hepatitis A probably involves an interaction between persistent viral infection and immune mechanisms responding to the persistent antigenic stimulation. Furthermore, there are few studies, concerning the natural history of hepatitis A in subjects known as inactive HBsAg (+)ve carriers. Some of these Authors[9] reported an increased risk of hepatitis A virus (HAV) superinfection with possible development of liver failure, in patients with a chronic hepatic damage, such as cirrhosis (especially among the elderly individuals), while other Authors[10] observed that the decrease in hepatitis B virus (HBV) DNA, in patients with HAV/HBV co-infection were not associated with a different clinical course in comparison with individuals without HBV infection. However, HAV vaccination, introduced in 1996, represents the best strategy to control the incidence of HAV infection and of its possible clinical complications (such as liver failure or the amount of fibrosis). In our paper, we report the case of a patient with chronic HBV-infection, undergoing an episode of acute and prolonged HAV-related hepatic injury.

Case Report

In the 2003, a 31-year-old Italian man was examined at our Department because of the first detection of HBsAg positivity. His past medical history was characterized by the following points: in 1982, when he was 10 years old, he experienced concussion and thoracic trauma after an accidental fall. He received a blood transfusion, during treatment because of multiple trauma, then when he was 18 years old he had viral meningitis with a self-limited course and no clinical consequences. Apart from the transfusion, his personal history was negative for risk factors for HBV infection and also for alcohol, smoke, drug intake and familiarity for chronic liver disease. He worked in a commercial firm and he was married with two sons in good health. Results of his blood test were the following: HBsAg(+)ve, HBeAb(+)ve, HBeAg(-)ve, HBcAb (+)ve, HBcAb immunoglobulin M (IgM) (-)ve, HBsAb (-)ve, HBV DNA 500 U/mL, aspartate aminotransferase (AST) 23 U/L, alanine aminotransferase (ALT) 33 U/L, alkaline phosphatase (ALP) 71 U/L, gamma-glutamyl transferase (GGT) 22 U/L, total bilirubin 0.6 mg/dL, normal platelets count, antibody profiles for hepatitis C and D virus and HIV were negative. On physical examination, neither hepatomegaly/splenomegaly nor chronic liver signs were detectable. An abdomen ultrasound (US) scan, excluded signs of chronic liver disease and/or portal hypertension while liver stiffness measurement (LSM) (with FibroScan) was equal to 3.8 kPa [interquartile range (IQR) 0.8]. Later, the patient was followed in our Department. We concluded that the patient suffered from chronic HBV infection in the phase of inactive carrier HBsAg (+)ve. In August 2013, he was admitted to our medical Department because he experienced a symptomatic clinical course characterized by fever, malaise with headache, dyspepsia, vague abdominal pain and jaundice. He denied alcohol use or herbal medicine intake. He reported that one-week, before he had eaten uncooked fish. We planned a biochemical investigation, that showed: ALT 4300 U/L, AST 2533 U/L, GGT 213 U/L, ALP 100 U/L, creatinin 0.75 mg/dL, total bilirubin 7.0 mg/dL, direct 5.2 mg/dL, albumin 2.9 g/dL, international normalized ratio 1.4 ammonium, 81 mcmol/L, white blood cells count 5680/mmc, hemoglobin 14.9 g/dL, mean corpuscular volume 90 fL, platelets 231,000/mmc, HAV IgM (+)ve, HBV DNA 684 U/mL, ferritin 8051 ng/mL. In addition, blood markers of autoimmunity (mitochondrial antibody, smooth muscle antibody, antinuclear antibody, extractable nuclear antigen antibodies, anticytoplasmic autoantibodies, native DNA, liver kidney microsomal antibodies) as well as antigen and/or antibody profiles of the most important hepatotropic viruses (cytomegalovirus, Epstein-Barr virus, *Herpes simplex* virus -1 and -2) were negative. Major genetic mutations for hemochromatosis [*C282Y* and *H63D*] were excluded. Abdomen US scan showed signs of chronic hepatic disease with slight steatosis and associated fibrosis, gallbladder polypus (4 mm), reactive hilar node, splenomegaly (longitudinal diameter 12.5 cm), normal caliber of portal vein. A case of acute hepatitis A in HBV chronic infection, was diagnosed and medical therapy with parenteral hydration was started, with an initial reduction in the hypertransaminasemia (Table 1) and a subsequent subjective improvement. So we discharged the patient from our hospital, but after one week he experienced a second peak of increased transaminases (Table 1) with asthenia and occasional headache. We repeated specific laboratory tests with the aim to exclude main causes of ALT flare, that were again negative with persistent IgM HAV Ab positive. Our patient was monitored with a bi-weekly biochemical profile (Table 1 and Figure 1). During the follow-up, the normalization of transaminases, negative IgM HAV antibodies and HBV DNA drop (<20 UI/mL on March 2014) were observed. We performed a second FibroScan that showed LSM values equal to 7.3 kPa (IQR 1). Now the patient is well and continues with periodic clinical, laboratory and imaging follow-ups at the Hepatology Department of our Institution.

Table 1. Biochemical profile of the patient.

	13/08/2013	27/08/2013	05/09/2013	24/09/2013	01/10/2013	14/10/2013	29/10/2013	12/11/2013	21/11/2013	29/11/2013	19/12/2013	14/01/2014	13/02/2014	29/03/2014	22/04/2014
WBC (10^3/mcL)	5680	-	-	7050	-	7580	5850	7010	6940	-	7200	7650	-	-	-
Hb (g/dL)	14.9	-	-	14.0	-	13.7	13.4	14.9	15.0	-	15.5	15.2	-	-	-
MCV (fL)	88	-	-	91	-	94	91	90	89	-	87	85	-	-	-
PLT (10^3/mcL)	231	-	-	195	-	225	252	272	256	-	267	232	-	-	-
AST (U/L)	2533	141	294	688	604	787	476	303	248	194	121	57	40	29	29
ALT (U/L)	4300	343	734	1863	1739	2091	1304	938	732	576	351	144	82	50	30
BT (mg/dL)	7.0	3.0	1.8	1.6	1.2	1.4	0.8	0.7	0.5	0.4	0.4	0.6	0.5	-	-
BD (mg/dL)	5.2	1.2	1.1	0.7	0.6	0.8	0.4	0.3	0.2	0.2	0.2	0.2	-	-	-
GGT (U/L)	213	76	76	242	252	331	254	196	168	140	101	65	39	-	-
ALP (U/L)	100	73	73	89	98	104	96	80	82	89	81	68	71	-	-
HBV DNA (U/mL)	684	-	35	55	-	-	<20	-	-	-	-	-	-	<20	<20
AFP (ng/mL)	2.8	-	-	7.1	-	-	-	-	-	-	-	-	-	-	-
INR	1.40	0.95	0.98	1.05	1.09	1.01	1.02	1.0	0.97	0.94	-	0.97	-	-	-
ALB (g/dL)	2.9	-	-	3.5	3.2	-	-	3.2	-	3.6	-	-	-	-	-
Ab HAV IgM	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative

WBC, white blood cells count; Hb, hemoglobin; MCV, mean corpuscular volume; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BT, total bilirubin; BD, direct bilirubin; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; HBV, hepatitis B virus; AFP, α-fetoprotein; INR, international normalized ratio; ALB, albumin; Ab HAV IgM, immunoglobulin M antibody to hepatitis A virus.

Discussion and Conclusions

We reported an uncommon type of HAV infection, characterized by a prolonged increase, lasting about 7 months, related to HAV infection with bimodal course, although it never reached the range of normality. Moreover, antibody profiles IgM HAV usually persist positive for about 13 weeks from the beginning of the infection, but the peak of transaminases often reaches a plateau after 4 weeks and decreases later and normalizes within 8 weeks.[11] In prolonged HAV-infection, persistence of IgM anti-HAV antibodies (more than 13 weeks) is proportional to the persistence of circulating immune complexes and this is much more frequent in males.[12] Although it was not possible to search HAV RNA in our hospital, we concluded that the second flare was attributable to persistent hepatitis A infection, after excluding the main causes of hypertransaminasemia (in particular autoimmunity and HBV flare). Moreover, it is interesting to note that IgM HAV absence was associated with transaminases reduction. On the basis of the presumed long-lasting HAV infection, a liver biopsy, which is an invasive examination, was not considered. Studies have shown that the excretion of Ag-HAV in stools approximately is associated with the persistence of ALT flares and this element is very important in considering the infectiousness of these subjects.[13] We did not know why in some of these patients an infection with a prolonged course develops, but the immune response probably plays a major role, as suggested by the decrease in HBV DNA. In short, the suppression of hepatitis B virus replication is mediated by hepatitis A-induced cytokine production. In fact, the sharp rise in gamma-interferon production may be pivotal in the suppression of HBV replication in chronic HBV infection.[14] The reasons for the different courses of hepatitis A infection in different patients remain unclear. We concluded, in accordance with different Authors,[8] that the follow-up of these patients might be a sufficient tool, because the prognosis of HAV infection is usually benign, even if it relapses,

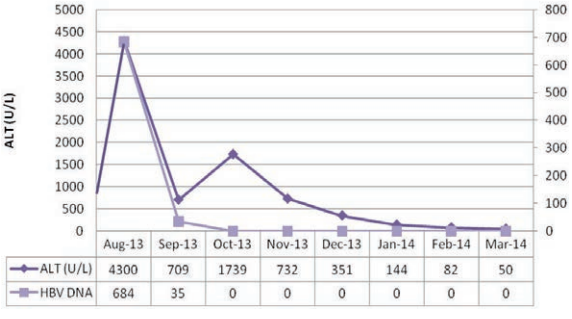

Figure 1. Biochemical profile of the patient. ALT, alanine aminotransferase; HBV, hepatitis B virus.

mainly in young patients with milder forms of liver injury, such as chronic hepatitis, whereas, elderly subjects with more serious forms of hepatic damage, such as cirrhosis, may be at higher risk of fulminant hepatitis and death. In conclusion, the hepatologist should take into account this type of atypical course in patients with HAV-related hepatitis and should promote HAV vaccination in subjects with HBV-chronic hepatitis, to prevent possible life-threatening acute exacerbation of hepatic damage, mainly in HBV-carriers with more severe forms of liver diseases.

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