

Autoimmune Hepatitis Triggered by Viral A Protracted Hepatitis

Heng R¹, Garioud A¹, Mokhtari C², Zougmore H¹, Medmoun M¹, Smail A³, Cazier A⁴, Paradis V⁵ and Cadranel JF^{1*}

¹Department of Liver and Digestive Diseases, GHPSO, Creil, Hauts-de-France, France

²Department of Virology and Immunology, GHPSO, Creil, France

³Department of Digestive Surgery, GHPSO, Creil, France

⁴Department of Pathology, GHPSO, Creil, France

⁵Department of Pathology, Beaujon Hospital, Clichy, France

Abstract

The Hepatitis A (HA) infection that occurs is usually resolved within a few weeks after the onset of the disease. Some rare cases of Autoimmune Hepatitis have been reported after acute viral infections including HA. The aim of this report is to describe a well-documented case of Autoimmune Hepatitis which was triggered by a protracted HA to report published cases and to discuss the mechanism of such a disease.

Keywords: Hepatitis A virus; Autoimmune hepatitis; Liver biopsy; Oral steroid; Acute hepatitis; Superimposed hepatitis; Auto antibodies

Abbreviations

HA: Hepatitis A; HAV: Hepatitis A Virus; BMI: Body Mass Index; ALT: Alanine Amino Transferase; AST: Aspartate Amino Transferase; GGT: Gamma Glutamyl Transferase; TB: Total serum Biliurubin; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis; UDCA: Ursodesoxycholic Acid

Introduction

A 57-year-old woman was referred for jaundice for Acute Hepatitis A. After a spontaneous improvement, she presented two months later with marked jaundice and high ALT activity. Antinuclear and the other specific autoantibodies were negative as well as other causes of acute hepatitis. A trans parietal liver needle biopsy made the diagnosis of Autoimmune Hepatitis (AIH) superimposed on prolonged acute HA. The liver biochemistry normalized after two months of oral steroid therapy. No further elevation of transaminases was observed with in ten months after the cessation of the treatment. Nine cases of AIH preceded by acute HA have been reported in the literature. Usually, the AIH occurred several months after an acute HA. Obviously, the HAV infection is a very rare trigger factor of the AIH. The patients suffering from HA need thus a careful follow-up after an acute hepatitis and to be investigated for an early diagnosis and management of AIH in case of a relapse.

Case Report

A 57-year-old woman was transferred from the heart diseases department where she had been admitted for a control coronarography on April 24th, 2018 to the Liver and Digestive Diseases Department for the exploration of acute hepatitis. Myocardial infarction, dyslipidemia, smoking habits and coronary heredity were the main components of this woman's past history. The treatments she received on admission were pantoprazole, ticagrelor, acetylsalicylic acid, bisoprolol, enoxaparin and atorvastatine. No hepatotoxic drug had been introduced within the past twelve months. On admission in the heart diseases department she presented symptoms of marked jaundice, right side upper abdominal pains, asthenia, vomiting and muscle pains. All drugs intake was stopped on her admission. The liver ultrasonography was normal and a marked increase in serum transaminases activities was noticeable (Figure 1). At the same day in the Liver and Digestive Diseases Department, the clinical examination showed jaundice. However, no ascites, hepatic encephalopathy signs or other abnormalities were identified. She had no past history of alcohol consumption, drug abuse nor hepatotoxic

medication. The patient was 167 cm tall and weighed 60 kg (BMI: 22 kg/m²).

The white blood cell count found 6,360 leukocytes/mm³ with 34% polymorphonuclear neutrophils and 51% lymphocytes. The hemoglobin value was 13.9 g/dl, and the platelet count was 273,000/mm³. The liver biochemistry was as follows: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (AP), Gamma-glutamyl Transferase (GGT) activities were 3795 IU/L (n<35), 3351 IU/L (n<35), 260 IU/L (n<105), and 102 IU/L (n<42) respectively. The Total serum Bilirubin (TB) concentration was 49 μmol/l (n<15) with 41.2 μmol/l of conjugated bilirubin (n<5) and the Prothrombin level was of 78%. The Immunoglobulin G (IgG) levels were 13.6 g/l (n<12.6) and the immunoglobulin M (IgM) was 5.16 g/l (n<1.7) whereas the Immunoglobulin A (IgA) was within normal range. The Hepatitis B Surface Antigen (HBsAg) was negative; the HCV antibodies were also negative, the IgM HEV antibodies, IgM CMV antibodies were negative, and the IgM EBV antibodies were negative as well. The serology for HAV was positive with a total Ig at 59.5 UI/ml and IgM anti HAV positive at 11.11 UI/ml establishing the diagnosis of Acute Hepatitis A. The RNA HAV viral load retrospectively measured was very high at 1,193,980 UI/ml (6.08 log).

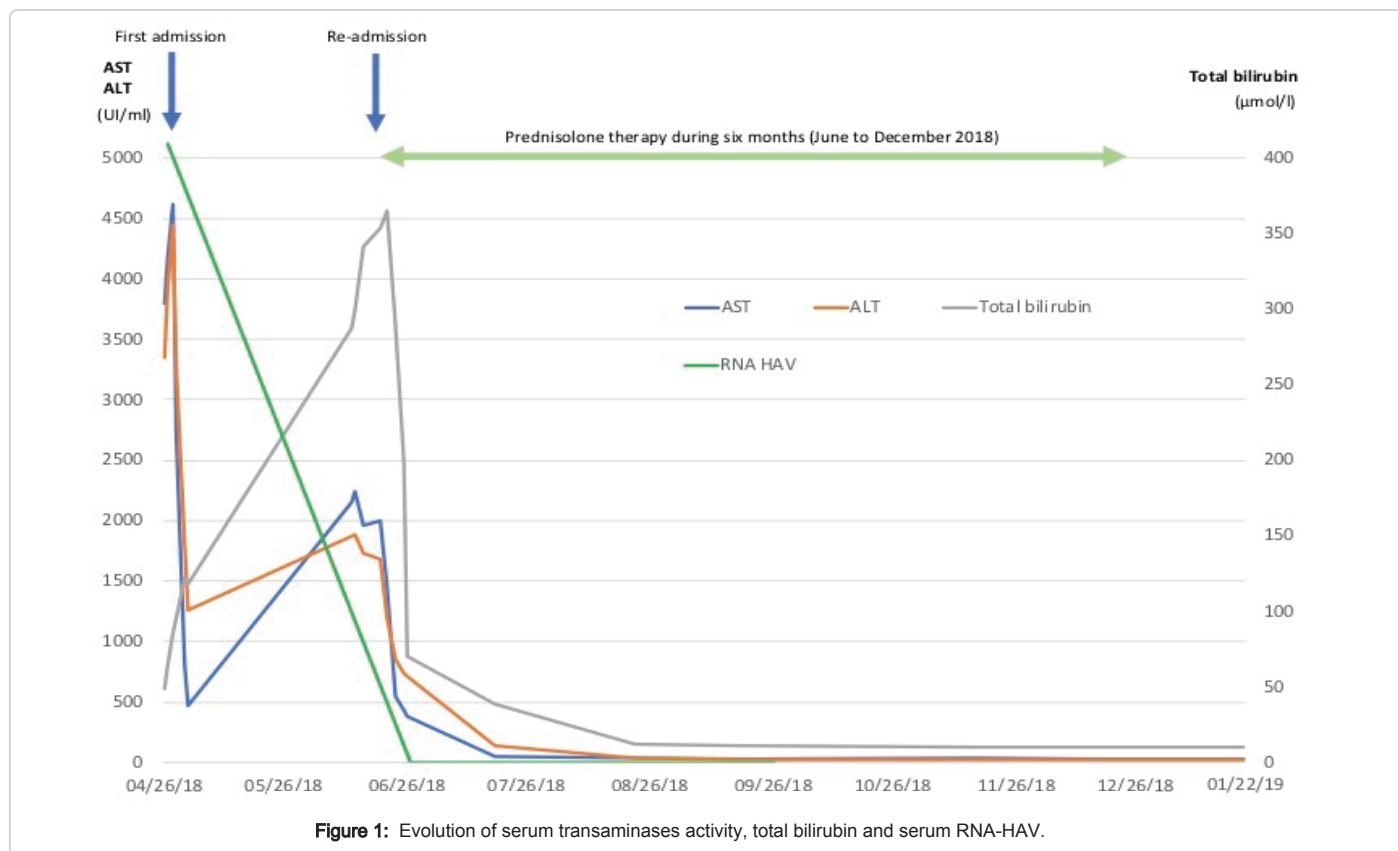
The serologic test for Human Immunodeficiency Virus (1 and 2) was negative. The antinuclear antibodies and auto antibodies to Smooth Muscle Antigen (SMA) were negative just as LKM1, LC1, SLA and M2/nPDC. During a 3 weeks period there was a gradual improvement of the symptoms with a spontaneous decrease of AST and ALT activities to 465 IU/L and 1262 IU/L respectively (Figure 1). On June 18th she presented symptoms of marked jaundice (Figure 1) two months after the onset hepatitis. The serum transaminases activities were very high. She was readmitted in our unit on June 19th, 2018. On re-admission she felt fatigue. Moreover, IgM HAV antibodies remained positive with a decreased titer at 1.8 UI/ml just as RNA

***Corresponding author:** Cadranel JF, Department of Liver and Digestive Diseases, GHPSO, Creil, Hauts-de-France, France, +33344616000; E-mail: jfrancois.cadranel@ch-creil.fr

Received January 10, 2020; **Accepted** January 27, 2020; **Published** February 03, 2020

Citation: Heng R, Garioud A, Mokhtari C, Zougmore H, Medmoun M, et al. (2020) Autoimmune Hepatitis Triggered by Viral A Protracted Hepatitis. J Clin Case Rep 10: 1316

Copyright: © 2020 Heng R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



HAV viral load at 840 UI/ml (2.92 log). Despite the negativity of the autoimmunity tests, the diagnosis of triggered autoimmune hepatitis was evoked by hypergammaglobulinemia was at 26.85 g/l ($8 < n < 12$) with a high level of IgG at 20.7 g/l (< 12.6). The abdominal ultrasonography was normal. A transparietal liver needle biopsy under ultrasonography guidance was performed in 22nd June 2018. The Histological examination of more than 20 portal tracts showed normal parenchyma's architecture. An inflammatory infiltrate with lymphocytes, numerous plasma cells and eosinophil polynuclear cells were observed. An extended parenchymal necrosis often located in the centrilobular area and intraparenchymal lymphocytes and histiocytes were also observed. These findings confirmed that the autoimmune hepatitis probably superimposed on a prolonged acute hepatitis A (Figure 2).

Firstly, 60 mg/d (1mg/kg/d) of oral steroid (prednisolone) was administered with a dose reduction by 5 mg/d every week during the first 3 weeks then every two weeks up to 5mg/d in early November. The reduction of the dose was then continued mg per mg before being stopped on December 12th. A fast improvement of the liver biochemistry was perceived. Four weeks after the patient was re-admitted and the starting of prednisolone treatment, the serum levels of transaminases activities were close to the limit of the upper normal range with AST 50 UI/ml, ALT 131 UI/ml, GGT 121 UI/ml, normal ALP and RNA-HAV detectable but under 10 UI/ml. Four weeks later, the transaminases activities were normal; GGT 60 UI/ml and RNA-HAV were undetectable (Figure 2). Atorvastatine and other drugs were reintroduced without any modification of the liver tests. Twelve weeks after starting the treatment, the liver panel was normal with an IgG decreased at 12.8 g/l and a normalisation of the IgM level.

Currently, until mid-March 2019, the patient has received no treatment for Hepatitis and no further elevation of AST or ALT levels has been observed till October 31st, 2019.

Discussion

The initial diagnosis of acute HA relies here on compatible clinical symptoms in association with high titers of IgM-HAV antibodies. However, this patient presented a prolonged course of acute Hepatitis. A. Schiff ER. described that a biphasic or relapsing form of viral hepatitis A occurred in 6% to 10% of cases and IgM anti-HAV and HAV RNA were persistent throughout the entire course [1]. The diagnosis of secondary AIH triggered by HAV hepatitis relies here on compatible clinical symptoms, and the exclusion of other causes of acute cytolysis (see supra). We excluded the possibility of an infection by other hepatitis viruses (HBV, HCV, HEV) or hepatotropic viruses (EBV, CMV or other herpes group viruses) and performed a liver biopsy. The results of liver biopsy specimen examination showed interface hepatitis, periportal inflammation with lymphoplasmocytes and piece meal necrosis of parenchyma which strongly argued in favour of an autoimmune Hepatitis. The quick decrease of jaundice and liver panel after the initiation of oral steroid treatment without the re-ascension of RNA HAV were also in favour of the diagnosis of an AIH. In the nine rare cases describing an AIH triggered by an acute HA, a steroid therapy was initiated which fastly resulted into a decline of the serum transaminases levels (Table 2) [2-12]. In one case, some UDCA was introduced but six months after. The serum transaminase and IgG were within normal limits and the treatment was discontinued without relapse six months later [13]. In our case, we have planned to maintain the treatment for a total period of six months until December 2018. The complete normality of the liver panel and total bilirubin

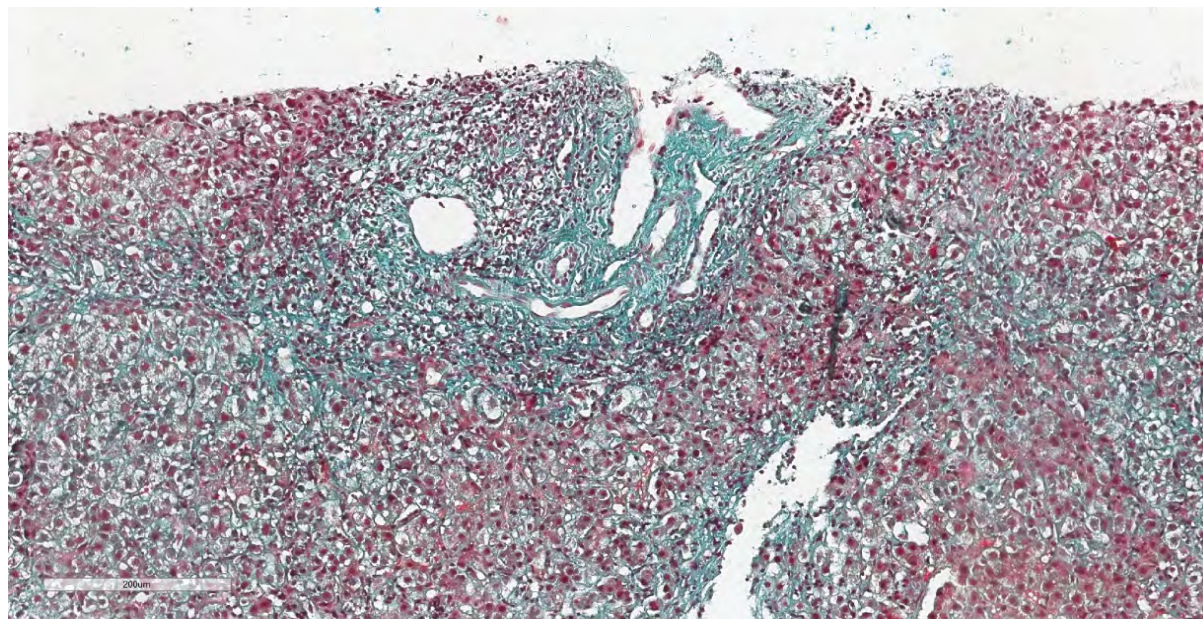


Figure 2: Liver biopsy specimen with courtesy of Pr V Paradis: Masson Trichroma, 20x. Dense inflammatory infiltrate made of lymphocytes, plasma cells and eosinophilic polynuclear cells within portal space and within parenchyma; extended necrosis.

Variables		Points
Auto-antibodies	AAN ou AML ou LKM \geq 1/40	1
	AAN ou AML ou LKM \geq 1/80 SLA/LP positifs (>20 unités)	2
IgG (ou -globulins)	Upper normal limit	1
	>1.10 times normal limit	2
Liver histology	Compatible with AIH	1
	Typical for AIH	2
Absence of viral hepatitis	Yes	2
	No	0

\geq 6: Probable AIH
 \geq 7: Definite AIH
 *Addition of points achieved for all autoantibodies (Maximum, 2 points).

Table 1: Simplified diagnostic criteria for Autoimmune Hepatitis of International Autoimmune Hepatitis Group (IAIHG).

was obtained after two months of oral steroid treatment without any relapse observed until ten months after the treatment cessation.

In some cases, when the serum transaminase re-increased 8 weeks after the initial improvement, IgM anti-HAV and HAV RNA were positive but at very low titers. Therefore, it could be assumed that the relapse was not related to a persistent HAV infection. In fact, a protracted course of HAV hepatitis has been described, the low ARN title as well as the liver tests pattern at the time of the second hospitalization strongly argued against a HAV relapse. Moreover, since the pathophysiology of viral A hepatitis is linked to a direct pathogenic effect of the virus, we can then rule out a relationship between the low replication load and the secondary liver tests abnormalities. In addition, the genetic pattern observed in our case was similar to the one described in one of the 9 other cases published (Table 2). As the patient was a middle-aged woman, and the IgG level was more elevated than at initial admission, we could hypothesize that the patient developed a course similarly to autoimmune hepatitis triggered by HAV infection. Using the simplified diagnosis criteria of the International Autoimmune Hepatitis group scoring as 6 points, this patient fulfilled the criteria for a probable diagnosis of AIH despite the negativity of AAN or other specific autoantibodies for AIH (Table 1).

While a viral infection has been known to trigger AIH (HBV, CMV, EBV and so on), 9 cases of AIH and one case of overlap syndrome with AIH and Primary Biliary Cholangitis (PBC) preceded by acute HA have been described [4-14]. In most of those cases, the AIH did not occur at the same time as the acute hepatitis, but the AIH often appeared several months after the onset of an acute HA (Table 2). Our patient presented an acute HA with an initially normal course before a re-ascension of transaminases higher than 1500 IU/L with jaundice two months after the beginning of acute Hepatitis A. However some atypical manifestations of HAV such as hemolysis, acalculous cholecystitis, prolonged cholestasis and acute renal failure have been reported in HAV(1) that were not observed in our case report.

RNA-HAV and IgM-HAV were very low at the time of the AIH and the serum IgG gammaglobulin was at a higher level than at the onset of the Hepatitis, arguing excessive immune reactions rather than a relapse of the HA. We stated the hypothesis that this excessive immune reaction may lead to the onset of the AIH. No studies were conducted about the AIH during the early stages of the acute hepatitis. Besides, excessive immune reactions during the acute HA were not documented. The HLA group I assessment conducted after the re-admission revealed: A*02/*32; B*40/*50; DRB1*03/*13, DQB1*02/*06.

Names	Age	Sex	Interval (Week)	Therapy	HLA
Vento S, et al. [4]	13	F	17	Steroid	A1, A19, B8, B44, DR7, DR3
Vento S, et al. [4]	18	M	19	Steroid	A2, B15, B40, DR7, DR4
Rahaman SM, et al. [6]	55	F	10	Steroid	ND
Huppertz HI, et al. [5]	7	M	10	Steroid	A1, A2, Bw52, Bw62, Cw3, Cw6, DR7, DRw8, DQw2
Oshikata S, et al. [9]	70	M	28	Steroid	ND
Hilzenrat N, et al. [7]	55	F	ND	Steroid	A26, B38, DRB1*0401, DRB44*01, DQB1*02
Tamura T, et al. [10]	39	F	8	Steroid	ND
Rintaro M, et al.	48	F	16	UDCA	ND
Tanaka H, et al. [11]	57	F	-	Steroid	A24, B52, B61, DR15, DR9
Present case	57	F	8	Steroid	A02, A32, B40, B50; DRB1*03/*13, DQB1*02/*06

ND: Not Described.

Interval: from Hepatitis A infection to onset of AIH (Week)

Table 2: Reports of AIH cases triggered by HAV infection with HLA assessment.

Therefore, cross immune reactions to viral proteins may also cause the damage in liver tissue at the same time [16-19] (Table 2).

Conclusion

We haven't highlighted a possible correlation with other series since the cases under study were not widely described. However, one female patient with the same age presented the same HLA DQB1*02 as our patient's case. We thus presented the new case of a patient with an AIH which had been triggered by an acute HA. This situation occurred in the months following an acute HA that related to a relapse of an acute Hepatitis. Even if this presentation is rare, patients suffering from an acute HA need a careful follow-up after an acute Hepatitis. Indeed, an early diagnosis must be analysed and the AIH managed in case of a relapse of the acute Hepatitis.

References

- Schiff ER (1992) A typical clinical manifestations of hepatitis A. *Vaccine* 10: 18-20.
- Lohse AW, Mieli-Vergani G (2011) Autoimmune hepatitis. *J Hepatol* 55: 171-182.
- Garioud A, Cadranet JF (2015) Autoimmune hepatitis. *Rev Prat* 65: 163-169.
- Vento S, Garofano T, Di Perri G (1991) Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type I in susceptible individuals. *Lancet* 337: 1183-1187.
- Huppertz HI, Treichel U, Gassel AM (1995) Autoimmune hepatitis following hepatitis A virus infection. *J Hepatol* 23: 240-248.
- Rahaman SM, Chira P, Koff RS (1994) Idiopathic autoimmune chronic hepatitis triggered by hepatitis A. *Am J Gastroenterol* 89: 106-108.
- Hilzenrat N, Zilberman D, Klein T (1999) Autoimmune hepatitis in a genetically susceptible patient. is it triggered by acute viral hepatitis A. *Dig Dis Sci* 44: 1950-1952.
- Munoz Bertran E, Rosa Salazar V, Hostalet Robles F (2002) Autoimmune hepatitis caused by acute hepatitis due to hepatitis A virus. *Gastroenterol Hepatol* 25: 501-504.
- Oshikata S, Miyanaga O, Kikuchi I (1996) A case of autoimmune hepatitis presumably induced by acute hepatitis type A. *Acta Hepatol Japonica* 37: 738-743.
- Tamura T, Suzuki S, Yamato A (2000) Autoimmune hepatitis diagnosed by the opportunity of hepatitis a virus infection. *Nihon Shokakibyo Gakkai Zasshi* 97: 1043-1047.
- Tanaka H, Tujioka H, Ueda H (2005) Autoimmune hepatitis triggered by acute hepatitis A. *World J Gastroenterol* 11: 6069-6071.
- Singh G, Palaniappan S, Rotimi O (2007) Autoimmune hepatitis triggered by hepatitis A. *Gut* 56: 304.
- Mikata R, Yokosuka O, Imazeki F (2005) Prolonged acute hepatitis A mimicking autoimmune hepatitis. *World J Gastroenterol* 11: 3791-3793.
- Heurgué A, Bernard-Chabert B, Picot R (2009) Overlap syndrome triggered by acute viral hepatitis A. *Eur J Gastroenterol Hepatol* 21: 708-709.
- Dusheiko GM (1994) Rolling review: The pathogenesis, diagnosis and management of viral hepatitis. *Alim Pharmacol Ther* 8: 229-253.
- Al-Hamoudi WK (2009) Severe autoimmune hepatitis triggered by varicella zoster infection. *World J Gastroenterol* 15: 1004-1006.
- Oldstone MB (1989) Virus-induced autoimmunity: Molecular mimicry as a route to autoimmune disease. *J Autoimmun* 2: 187-194.
- Treichel U, Poralla T, Hess G, Manns M, Buschenfelde KH (1990) Autoantibodies to human asialoglyco-protein receptor in autoimmune-type chronic hepatitis. *Hepatol* 11: 606-612.
- Vento S, O'Brien CJ, McFarlane IG, Williams R, Eddleston AL (1987) T-cell inducers of suppressor lymphocytes control liver-directed autoreactivity. *Lancet* 1: 886-888.