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CASE REPORT

False positive anti-hepatitis A virus immunoglobulin M in autoimmune hepatitis/primary biliary cholangitis overlap syndrome: A case report

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Abstract

BACKGROUND

Autoimmune hepatitis (AIH) is an immune-mediated liver disease affecting all age groups. Associations between hepatitis A virus (HAV) and AIH have been described for many years. Herein, we report a case of an AIH/primary biliary cholangitis (PBC) overlap syndrome with anti-HAV immunoglobulin M (IgM) false positivity.

CASE SUMMARY

A 55-year-old man was admitted with manifestations of anorexia and jaundice along with weakness. He had marked transaminitis and hyperbilirubinemia. Viral serology was positive for HAV IgM and negative for others. Autoantibody screening was positive for anti-mitochondria antibody but negative for others. Abdominal ultrasound imaging was normal. He was diagnosed with acute hepatitis A. After symptomatic treatment, liver function tests gradually recovered. Several months later, his anti-HAV IgM positivity persisted and transaminase and bilirubin levels were also more than 10 times above of the upper limit of normal. Liver histology was prominent, and HAV RNA was negative. Therefore, AIH/primary biliary cholangitis (PBC) overlap syndrome diagnosis was made based on the "Paris Criteria". The patient was successfully treated by immunosuppression.

CONCLUSION

This case highlights that autoimmune diseases or chronic or acute infections, may cause a false-positive anti-HAV IgM result because of cross-reacting antibodies. Therefore, the detection of IgM should not be the only method for the diagnosis of acute HAV infection. HAV nucleic acid amplification tests should be employed to confirm the diagnosis.

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Core Tip: Autoimmune hepatitis (AIH)/primary biliary cholangitis (PBC) overlap syndrome is the specific clinical manifestation of AIH, which is an immune-mediated liver disease. Environmental factors including viral infections have been documented to externally trigger AIH. The association between hepatitis A virus (HAV) and AIH has been described for many years. But relying solely on anti- HAV immunoglobulin M (IgM) to diagnose acute HAV infection is not adequate. This case highlights that false-positive anti-HAV IgM might be caused by the cross-reaction of antibodies in individuals with autoimmune diseases or chronic or acute infections. HAV nucleic acid amplification can be used more broadly during the diagnosis workup to confirm HAV infection, especially in patients testing positive for anti-HAV IgM with a low cutoff value.

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INTRODUCTION

The pathogenesis of autoimmune hepatitis (AIH) requires the interaction of epigenetic, environmental, and immunologic factors[1]. The shape of the immune repertoire plays an important role in the program of AIH. Environmental exposures, such as viral infections, are considered a potential trigger for AIH[2]. Some reported cases indicate that hepatitis A virus (HAV) infection is among the triggers of AIH[3-6]. However, if the diagnosis of acute HAV infection is solely based on Anti-HAV immunoglobulin (Ig)M, then it may be suspect. We describe herein a case of AIH/primary biliary cholangitis (PBC) overlap syndrome with anti-HAV IgM false positivity.

CASE PRESENTATION

Chief complaints

A 55-year-old man presented to the hepatology clinic of our hospital complaining of manifestations of anorexia and jaundice along with weakness.

History of present illness

The patient's symptoms started 10 d previously with manifestations of anorexia, jaundice, and weakness, and had worsened over the last 2 d.

History of past illness

The patient had no past medical history.

Personal and family history

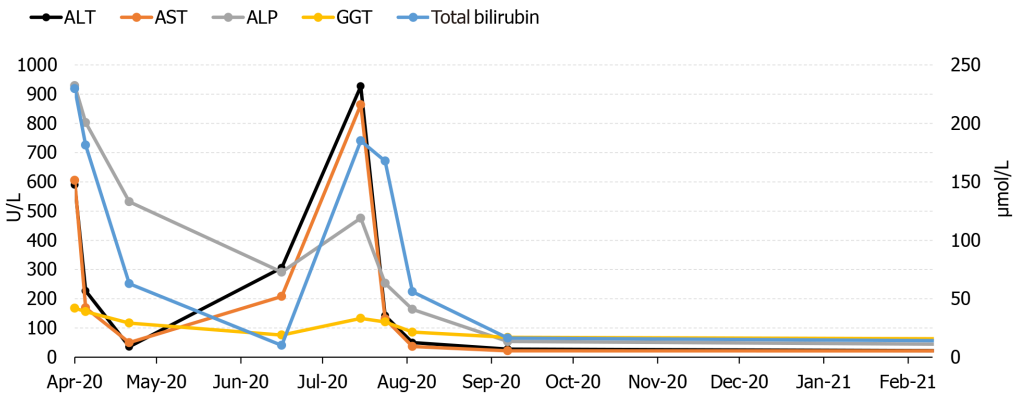
The patient did not abuse alcohol or substances. There was no family history of liver disease.

Physical examination

The clinical examination revealed that the skin and sclera were jaundiced.

Laboratory examinations

Blood samples revealed (Figure 1) alanine aminotransferase (ALT) 893 U/L, serum



HAV-IgM	+	+
ANA	1:100	1:100
AMA	+	+
ASMA	-	-
LKM1	-	-
IgG	16.3 g/L	14.9 g/L
IgM	1.38 g/L	1.09 g/L

Figure 1 Time course of liver function tests and anti-hepatitis A virus immunoglobulin M, autoantibodies, immunoglobulin levels. Total bilirubin: Upper limit of normal (ULN) < 28 μmol/L, aspartate aminotransferase ULN < 40 IU/L, alanine aminotransferase ULN < 45 IU/L, γ-glutamyl transferase ULN < 50 IU/L, alkaline phosphatase ULN < 105 IU/L. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; ASMA: Anti-smooth muscle antibodies; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; HAV: Hepatitis A virus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LKM 1: Anti-liver kidney microsome type 1.

aspartate aminotransferase (AST) 831 U/L, γ-glutamyl-transpeptidase (γ-GGT) 423 U/L, alkaline phosphatase (ALP) 150 U/L, and total bilirubin 342 μmol/L. Thyroid-stimulating hormone, blood count, triiodothyronine, prothrombin time, and thyroxine were all normal. Serum anti-HAV IgM (1.93) was positive. Other viral serology viral tests were negative. Antibody screening found positive anti-mitochondria antibody (AMA) but negative anti-smooth muscle antibody (ASMA) and anti-liver kidney microsome type 1 (LKM 1). IgA, IgM and IgG levels were normal.

Imaging examinations

Abdominal ultrasound imaging was normal.

Diagnosis procedure

Based on the patient's medical history and evaluation, he was diagnosed with acute hepatitis A (Hep A); PBC could not be excluded. After symptomatic treatment, we discharged the patient on the 20th day of hospitalization with AST 36 U/L, γ-GGT 323 U/L, total bilirubin 62 μmol/L, ALT 50 U/L, and normal ALP and prothrombin time. The patient continued to take ursodeoxycholic acid after discharge.

Two months after discharge, his aminotransferase levels began to increase. In the subsequent months, repeated blood examinations revealed ALT 927 U/L, AST 864 U/L, γ-GGT 476 U/L, ALP 133 U/L, and total bilirubin 185 μmol/L. The patient's serum anti-HAV IgM (3.09) remained positive. Antinuclear antibody (1:100) and AMA were positive while ASMA and anti-LKM were negative. Liver histology showed interface hepatitis accompanied by plasma cell infiltration. Moreover, we observed florid bile duct damage with lymphocytic cholecystitis as shown in Figure 2. Histologic lesions were graded G4S2-3 as per the modified Scheuer score. We also assayed HAV RNA, which was negative.

FINAL DIAGNOSIS

On the basis of the "Paris Criteria", AIH/PBC overlap syndrome diagnosis was made, but not acute Hep A.

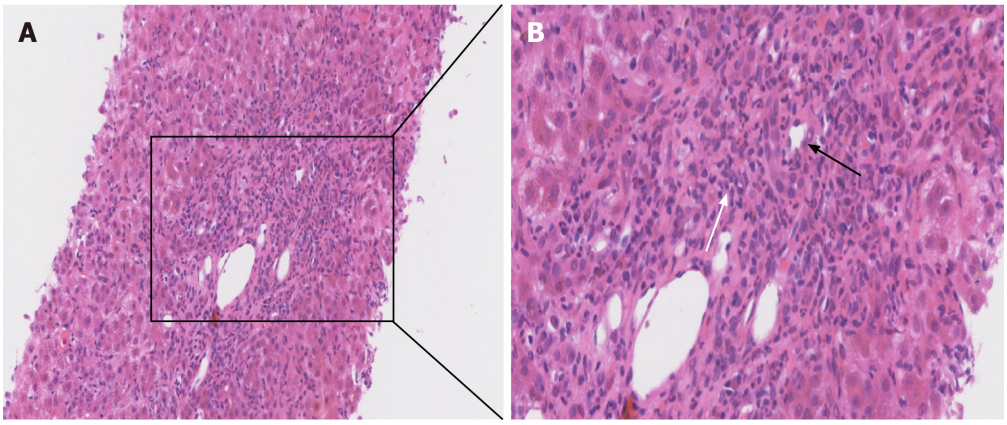


Figure 2 Hematoxylin-eosin staining. A: Liver biopsy tissue shows chronic hepatitis with moderate interface hepatitis accompanied by plasma cell infiltration (hematoxylin-eosin staining; magnification: × 200); B: Image of the box shown in A at 2 × magnification. Showing plasma cell infiltration (white arrow) and bile duct lesions (black arrow).

TREATMENT

Treatment with prednisone (30 mg/d) along with ursodeoxycholic acid (15 mg/kg/d), in combination with azathioprine (50 mg/d) after 2 wk was prescribed.

OUTCOME AND FOLLOW-UP

Liver function tests normalized within 50 d. On the 6th month of follow-up, anti-HAV IgM became negative.

DISCUSSION

HAV infection is commonly self-limiting, with patients completely recovering after about 3 mo. The diagnosis of acute hepatitis A primarily involves serological testing of anti-HAV IgM, which is highly specific and sensitive without testing for the pathogen itself. However, other factors can result in anti-HAV IgM seropositivity in the clinical evaluation[7], potentially leading to an incorrect diagnosis of acute hepatitis A. A Hep A false-positive result might also be caused by the cross-reaction of antibodies in individuals with autoimmune diseases or chronic or acute infections. Polyclonal activation of B lymphocytes can trigger the generation of anti-HAV IgM seropositivity [8]. Therefore, in our case, AIH/PBC overlap syndrome was an immune-triggered inflammatory liver disease that may have caused a false-positive anti-HAV IgM result because of cross-reacting antibodies. There is a report of a false positive hepatitis A serology result in a patient with an acute Epstein-Barr virus infection[9].

In our patient, the anti-HAV IgM result is closely related to the duration from the peak-ALT value to the day of testing[10]. Besides, true positive anti-HAV IgM tests have values that are often 9 to 10 times above the acute HAV cutoff, yet less than four times the cutoff is considered as a false positive result[11]. Our patient had persistent anti-HAV IgM positivity that had a low index of two or three times the cutoff when the ALT values peaked. Therefore, we had to consider that it was a false positive.

An HAV nucleic acid amplification test (NAAT) would be an ideal method to confirm positive results when a low anti-HAV IgM level is obtained. Although the time since the manifestation of clinical symptoms can affect the HAV assay result, previous NAAT experience documents that the viremic phase duration is frequently prolonged by more than 2 mo after the initial symptoms of infection[12], and that there is a positive association between HAV RNA and ALT[13]. Unfortunately, there was also no HAV RNA assay to confirm HAV infection in our patient even though ALT had been elevated to 20 times the upper limit of normal. A Hep A diagnosis can be ruled out in the absence of detectable HAV RNA in the serum[14].

Although viral infections can serve as environmental triggers resulting in the loss of self-tolerance to autoantigens in individuals genetically predisposed to AIH[2], and numerous case reports have documented a strong relationship of HAV with the onset

of AIH. Anti-HAV IgM testing has proven valuable in the diagnosis of acute HAV infection. However, anti-HAV IgM false positives can result in misdiagnosis and inappropriate treatment, therefore the detection of IgM should not be the only method for the diagnosis of acute HAV infection. Other methods, such as NAATs should be employed to confirm the diagnosis, particularly in patients who test positive for anti-HAV IgM with a low cutoff value.

CONCLUSION

False anti-HAV IgM serological results can lead to misdiagnosis or premature termination of diagnostic tests. Relying solely on anti-HAV IgM to diagnose acute HAV infection is not sufficient. HAV nucleic acid tests can be used more broadly, especially in patients who test positive for anti-HAV IgM with a low cutoff value.

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