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Contents

Thrice Monthly Volume 9 Number 5 February 16, 2021

MINIREVIEWS

- 999 Remote nursing training model combined with proceduralization in the intensive care unit dealing with patients with COVID-19

Wang H, Kang K, Gao Y, Yang B, Li J, Wang L, Bi Y, Yu KJ, Dai QQ, Zhao MY

ORIGINAL ARTICLE

Case Control Study

- 1005 Metabolic syndrome, ApoE genotype, and cognitive dysfunction in an elderly population: A single-center, case-control study

Wang JY, Zhang L, Liu J, Yang W, Ma LN

- 1016 Serum neuron-specific enolase: A promising biomarker of silicosis

Huang HB, Huang JL, Xu XT, Huang KB, Lin YJ, Lin JB, Zhuang XB

Retrospective Study

- 1026 Biochemical recurrence of pathological T2+ localized prostate cancer after robotic-assisted radical prostatectomy: A 10-year surveillance

Yang CH, Lin YS, Ou YC, Weng WC, Huang LH, Lu CH, Hsu CY, Tung MC

Observational Study

- 1037 Clinical characteristics of perineal endometriosis: A case series

Liang Y, Zhang D, Jiang L, Liu Y, Zhang J

- 1048 Safety of gastrointestinal endoscopy in patients with acute coronary syndrome and concomitant gastrointestinal bleeding

Elkafrawy AA, Ahmed M, Alomari M, Elkaryoni A, Kennedy KF, Clarkston WK, Campbell DR

SYSTEMATIC REVIEWS

- 1058 Clinical features of SARS-CoV-2-associated encephalitis and meningitis amid COVID-19 pandemic

Huo L, Xu KL, Wang H

CASE REPORT

- 1079 Neuropathy and chloracne induced by 3,5,6-trichloropyridin-2-ol sodium: Report of three cases

Ma Y, Cao X, Zhang L, Zhang JY, Qiao ZS, Feng WL

- 1087 Effect of rifampicin on anticoagulation of warfarin: A case report

Hu YN, Zhou BT, Yang HR, Peng QL, Gu XR, Sun SS

- 1096 Severe lumbar spinal stenosis combined with Guillain-Barré syndrome: A case report

Xu DF, Wu B, Wang JX, Yu J, Xie JX

- 1103** Treatment of pediatric intracranial dissecting aneurysm with clipping and angioplasty, and next-generation sequencing analysis: A case report and literature review
Sun N, Yang XY, Zhao Y, Zhang QJ, Ma X, Wei ZN, Li MQ
- 1111** Imaging characteristics of a rare case of monostotic fibrous dysplasia of the sacrum: A case report
Liu XX, Xin X, Yan YH, Ma XW
- 1119** Primary aldosteronism due to bilateral micronodular hyperplasia and concomitant subclinical Cushing's syndrome: A case report
Teragawa H, Oshita C, Orita Y, Hashimoto K, Nakayama H, Yamazaki Y, Sasano H
- 1127** Management of corneal ulceration with a moisture chamber due to temporary lagophthalmos in a brain injury patient: A case report
Yu XY, Xue LY, Zhou Y, Shen J, Yin L
- 1132** Bronchoscopy for diagnosis of COVID-19 with respiratory failure: A case report
Chen QY, He YS, Liu K, Cao J, Chen YX
- 1139** Pembrolizumab as a novel therapeutic option for patients with refractory thymic epithelial tumor: A case report
Wong-Chong J, Bernadach M, Ginzac A, Veyssière H, Durando X
- 1148** Successful bailout stenting strategy against rare spontaneous retrograde dissection of partially absorbed magnesium-based resorbable scaffold: A case report
Liao ZY, Liou JY, Lin SC, Hung HF, Chang CM, Chen LC, Chua SK, Lo HM, Hung CF
- 1156** Chronic myelomonocytic leukemia-associated pulmonary alveolar proteinosis: A case report and review of literature
Chen C, Huang XL, Gao DQ, Li YW, Qian SX
- 1168** Obturator nerve impingement caused by an osteophyte in the sacroiliac joint: A case report
Cai MD, Zhang HF, Fan YG, Su XJ, Xia L
- 1175** Venetoclax in combination with chidamide and dexamethasone in relapsed/refractory primary plasma cell leukemia without t(11;14): A case report
Yang Y, Fu LJ, Chen CM, Hu MW
- 1184** Heterochronic triple primary malignancies with Epstein-Barr virus infection and tumor protein 53 gene mutation: A case report and review of literature
Peng WX, Liu X, Wang QF, Zhou XY, Luo ZG, Hu XC
- 1196** Negative conversion of autoantibody profile in chronic hepatitis B: A case report
Zhang X, Xie QX, Zhao DM
- 1204** Dumbbell-shaped solitary fibrous tumor in the parapharyngeal space: A case report
Li YN, Li CL, Liu ZH
- 1210** Spontaneous small bowel perforation secondary to *Vibrio parahaemolyticus* infection: A case report
Chien SC, Chang CC, Chien SC

- 1215** Management protocol for Fournier's gangrene in sanitary regime caused by SARS-CoV-2 pandemic: A case report
Grabińska A, Michalczyk Ł, Banaczyk B, Syryło T, Ząbkowski T
- 1221** Infective bicuspid aortic valve endocarditis causing acute severe regurgitation and heart failure: A case report
Hou C, Wang WC, Chen H, Zhang YY, Wang WM
- 1228** Endoscopic repair of delayed stomach perforation caused by penetrating trauma: A case report
Yoon JH, Jun CH, Han JP, Yeom JW, Kang SK, Kook HY, Choi SK
- 1237** Bilateral musculocutaneous neuropathy: A case report
Jung JW, Park YC, Lee JY, Park JH, Jang SH

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Negative conversion of autoantibody profile in chronic hepatitis B: A case report

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Abstract

BACKGROUND

Autoimmune antibodies are detected in many diseases. Viral infections are accompanied by several immunopathological manifestations. Some autoimmune antibodies have been associated with the immune response induced by virus or drugs. Thus, a comprehensive diagnosis of chronic hepatitis B combined with autoimmune hepatitis is required, and immunosuppressant or antiviral therapy should be carefully considered.

CASE SUMMARY

We present a case of a patient who had negative transformation of autoimmune antibodies during chronic active hepatitis B. A 50-year-old female who had a history of asymptomatic hepatitis B virus carriers for more than 10 years presented to the hospital with the complaint of weakness for 1 wk. Blood tests revealed elevated liver enzymes; the detection of autoantibodies was positive. Hepatitis B viral load was 72100000 IU/mL. The patient started tenofovir alafenamide fumarate 25 mg daily. Liver biopsy was performed, which was consistent with chronic active hepatitis B. The final diagnosis of the case was chronic active hepatitis B. The autoimmune antibodies turned negative after 4 wk of antiviral therapy. The patient recovered and was discharged with normal liver function. There was no appearance of autoantibodies, and liver function was normal at regular follow-ups.

CONCLUSION

Autoimmune antibodies may appear in patients with chronic active hepatitis. It is necessary to differentiate the diagnosis with autoimmune hepatitis.

Key Words: Autoantibodies; Autoimmune hepatitis; Chronic hepatitis B; Immune

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Core Tip: This case involved dynamic changes in autoantibodies in the pathogenesis of hepatitis B. The patient showed positive hepatitis B surface antigen, which can cause an autoimmune phenomenon during the clearance of hepatitis B virus (HBV). Liver pathology was performed to differentiate from autoimmune hepatitis. It is possible that the virus has a role in inducing immune responses in HBV infection. This is closely related to hepatocyte injury caused by HBV infection, which is mainly mediated by immunity. Autoantibodies can appear during viral hepatitis, and the combination of liver pathology and dynamic monitoring is required.

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INTRODUCTION

Host immune responses induced by hepatitis B virus (HBV) infection substantially drive disease progression and significantly influence the efficacy of antiviral treatments in HBV-infected individuals. Some studies have shown that non-virus-specific inflammatory cells within the liver may also actively participate in HBV-associated liver pathogenesis.

We report a case of autoimmune antibody transformation from positive to negative during the course of HBV and refer to the relevant literature to explain the related reasons for the dynamic changes in these autoantibodies. Liver pathology can help diagnosis and differentiate between viral hepatitis and autoimmune hepatitis (AIH), which plays an important role in the treatment strategy.

AIH may have an association with some pathogens^[1]. Although a few investigations associated with autoantibody positivity in patients with chronic hepatitis C have been reported, autoantibody positivity in patients with chronic hepatitis B are rare in the literature^[2]. In this case, the antinuclear antibody (ANA) profile included anti-SSA antibody, anti-SSB antibody, anti-liver/kidney microsomal-1 antibody (LKM-1) and anti-soluble liver antigen/liver-pancreas antibodies in a patient with chronic hepatitis B became negative during the clearance of HBV.

CASE PRESENTATION

Chief complaints

A 50-year-old female who had a history of positive hepatitis B surface antigen for more than 10 years presented to The Infectious Department of our hospital complaining of aggravating anorexia and fatigue. During her presentation in The Infectious Department, she had nausea and vomit symptoms.

History of present illness

The patient's symptoms started a week ago with gradually increasing gastrointestinal symptoms including anorexia and nausea. Her liver function tests showed elevated transaminases.

History of past illness

She had a past medical history of being a carrier of HBV for more than 10 years without antiviral treatment. She had no cardiac function abnormalities, arterial hypertension or diabetes mellitus. She had no negative drug history, and no alcohol intake.

Personal and family history

The patient reported that her four siblings were infected with HBV, her mother died from hepatocellular carcinoma, and her father was in good physical condition.

Physical examination

After admission, the patient's temperature was 36.6 °C, heart rate was 91 bpm, respiratory rate was 20 breaths per minute, blood pressure was 145/104 mmHg and oxygen saturation in room air was 99%. The patient was 160 cm tall and weighed 53 kg. The clinical examination revealed light scleral icterus without any other pathological signs.

Laboratory examinations

Laboratory values on admission and during hospitalization are shown in [Table 1](#). A series of tests were performed after admission to The Infectious Disease Department. Blood analysis revealed the following: Alanine aminotransferase, 575 U/L; Aspartate aminotransferase, 593 U/L; Total bilirubin, 108.3 µmol/L; Alkaline phosphatase 116 IU/L; Positive hepatitis B surface antigen, anti-LKM-1 > 1:80; Positive anti-soluble liver antigen/liver-pancreas; Positive anti-mitochondrial antibody; and Positive anti-SSA antibody and anti-SSB antibody.

Imaging examinations

The hematoxylin and eosin staining of liver tissue: The structure of hepatic lobules is unclear. The hematoxylin and eosin staining showed varying degrees of hepatocyte edema with moderate to severe piecemeal necrosis and scattered eosinophilic bodies ([Figure 1A](#), arrows). Small bile duct in the portal area was accompanied by lymphocyte-predominant inflammation with a small amount of eosinophil infiltration ([Figure 1A](#), filled triangles).

Immunohistochemistry analysis of liver tissue: The proliferation of small bile ducts in the portal area were obvious ([Figure 1B](#), arrows), with more infiltration of lymphocytes and plasma cells and positive marker detection including hepatitis B surface antigen (+), HBcAg (+-), bile duct epithelium (CK19+), IgG (+), and IgG4 (-) combined hepatocellular and cholangiocarcinoma. Findings were consistent with mild chronic hepatitis compatible with HBV infection, without histological stigmata of autoimmunity ([Figure 1B](#)).

Mesh fiber staining of liver tissue: The reticular fiber staining showed that the hepatic lobular stent was significantly damaged ([Figure 1C](#), arrows). The characteristic floral ring structure of AIH was not seen ([Figure 1C](#)).

Masson staining of liver tissue: The portal area was enlarged with fibrosis, the formation of bridging fiber band was visible in the focal area, and collagen fiber proliferated in the portal area by Masson staining ([Figure 1D](#), arrows).

FINAL DIAGNOSIS

Chronic active hepatitis B (pathological grade and stage: G3S3).

TREATMENT

The patient, following her clinical manifestations and laboratory tests in our department, was started on tenofovir alafenamide fumarate 25 mg QD orally without corticosteroids. Other transfusion treatment including compound magnesium isoglycyrrhizinate and reduced glutathione was used for more than 20 d until nucleic acid testing was performed, and autoantibodies were found to be positive and liver biopsy was performed. According to the pathology of hepatic tissue, it did not meet the diagnostic criteria of AIH. Blood work showed completely normal liver enzymes and decreased HBV viral load.

OUTCOME AND FOLLOW-UP

The comprehensive medical treatment was successfully accomplished by improving liver function and antiviral therapy with tenofovir alafenamide fumarate tablets 25 mg

Table 1 Laboratory values on admission and during hospital course

Parameters	Day 1	Day 7	Day 15	Day 25	2 mo	Reference ranges
WBC ($\times 10^9/L$)	3.05	4.18	4.93	3.76	556	3.5-9.5
PLT ($\times 10^9/L$)	101	93	102	112	216	125-350
AST (U/L)	593	224	75	28	34	0-34
ALT (U/L)	575	266	89	26	28	0-49
ALP (U/L)	112	132	116	79	76	45-129
GGT (U/L)	58	134	113	55	36	0-38
LDH (U/L)	267	208	159	159	221	120-246
ALB (g/L)	34.8	34.3	28.9	33.7	27.8	35.0-53.0
TBIL ($\mu\text{mol/L}$)	38.30	45.90	108.30	51.45	11.30	5.00-21.00
DBIL ($\mu\text{mol/L}$)	22.50	33.20	84.92	37.37	8.09	0-6.80
HBV-DNA (copies/mL)	7.21×10^8			1.62×10^4	≤ 500	≤ 500
HBsAg (IU/mL)	> 52000			3373	135	< 0.05
ANA	$< 1:80$			$< 1:80$	$< 1:80$	Negative ($< 1:80$)
Anti-SM (RU/mL)	41.17			< 20	< 20	< 20
Anti-SS-A (RU/mL)	42.70			< 20	< 20	< 20
Anti-SS-B (RU/mL)	176.31			< 20	< 20	< 20
CENTRO (RU/mL)	39.59			< 20	< 20	< 20
AMA-M2 (RU/mL)	19.99	25.87		< 20	< 20	< 20
LKM-1 (RU/mL)	223.38	> 400		< 20	< 20	< 20
SLA/LP (RU/mL)	39.61	43.04		< 20	< 20	< 20
SP100 (RU/mL)	16.26	20.59		< 20	< 20	< 20
Anti-HCV	Negative			Negative	Negative	Negative
HAV-IgM	Negative			Negative	Negative	Negative
HEV-IgM	Negative			Negative	Negative	Negative
Anti-HIV	Negative			Negative	Negative	Negative

ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA-M2: Anti-mitochondrial antibody subtype II; AST: Aspartate transaminase; CENTRO: Anti-centromere B antibody; DBIL: Direct bilirubin; GGT: Glutamyltransferase; HAV: Hepatitis A virus; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; LDH: Lactate dehydrogenase; LKM-1: Anti-liver/kidney microsomal-1 antibody; SLA/LP: Anti-soluble liver antigen/liver-pancreas; SP100: Anti-SP100 antibody; TBIL: Total bilirubin; WBC: White blood cell.

QD orally during hospitalization and follow-up (at least 5 years). The process of liver puncture was accomplished smoothly. The antiviral effect was remarkable, and liver enzymes levels dropped significantly (Table 1). Some positive markers were retested, and the markers of AIH were negative (Table 1). The patient recovered well and was discharged from the hospital 25 d after the treatment. At a follow-up visit, 12 wk later (2 mo after hospital discharge), the patient was asymptomatic, there was no appearance of autoantibodies, and liver function was normal (Table 1). The patient continued to take the antiviral drug and maintained regular follow ups every 6 mo for 5 years.

DISCUSSION

Autoantibodies can be detected in patients with chronic hepatitis B or hepatitis C infection. Acay *et al*^[3] reported that 67 patients with chronic hepatitis B who had a positive ANA rate was 12%. Many cases reports have shown that autoimmune markers can be detected in patients with hepatitis C^[4]. Other hepatitis viruses like

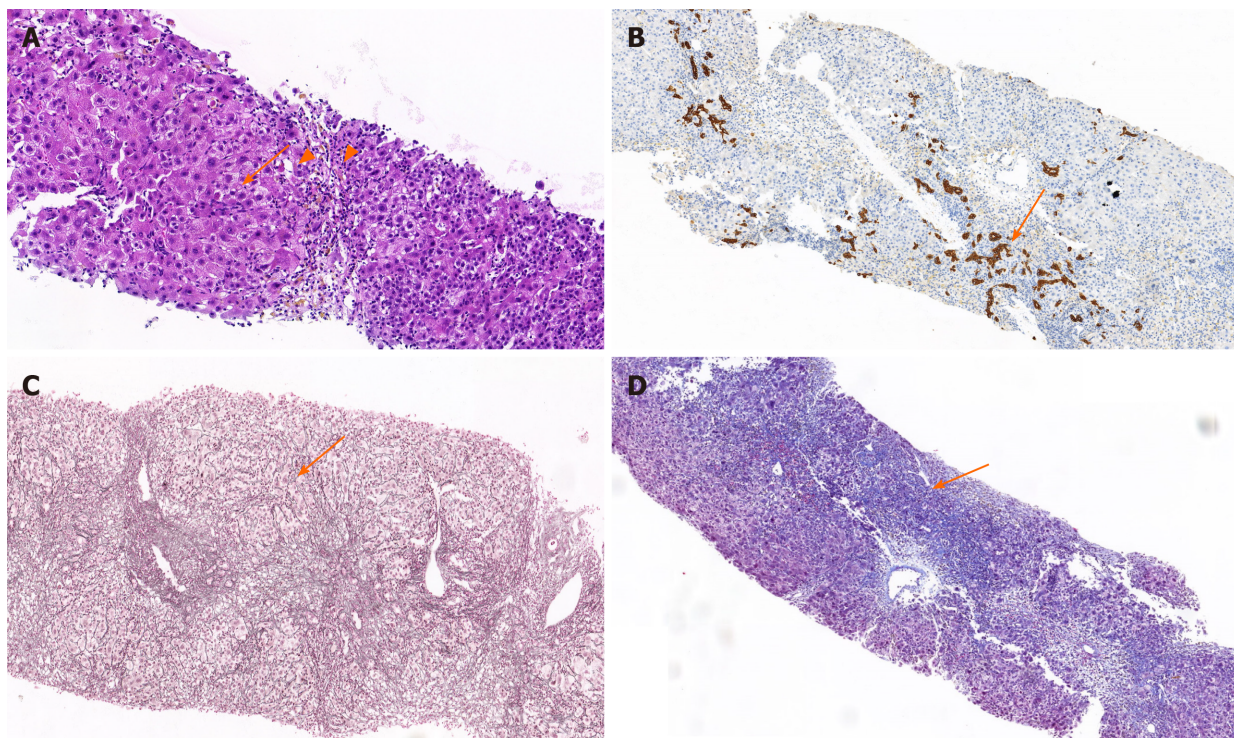


Figure 1 Imaging examinations results. A: In the hematoxylin and eosin staining of liver tissue, the structure of hepatic lobules was unclear. The hematoxylin and eosin staining showed varying degrees of hepatocyte edema with moderate to severe piecemeal necrosis and scattered eosinophilic bodies (arrows). Small bile ducts in the portal area were accompanied by lymphocyte-predominant inflammation and a small amount of eosinophil infiltration (filled triangles); B: The proliferation of small bile ducts in the portal area were obvious (arrows) with more infiltration of lymphocytes and plasma cells and positive marker detection including hepatitis B surface antigen (+), HBcAg (+/-), bile duct epithelium (CK19+), IgG (+), and IgG4 (-) combined hepatocellular and cholangiocarcinoma. Findings were consistent with mild chronic hepatitis compatible with hepatitis B virus infection, without histological stigmata of autoimmunity; C: Mesh fiber staining of liver tissue showed that the hepatic lobular stent was significantly damaged (arrows). The characteristic floral ring structure of autoimmune hepatitis was not seen; D: Masson staining of liver tissue showed the portal area was enlarged with fibrosis, the formation of the bridging fiber band was visible in the focal area, and collagen fiber was proliferating the portal area (arrows).

hepatitis A or hepatitis E can also act as triggers of autoimmune phenomena or diseases^[5]. Some studies have shown that autoimmune markers were identified in adult patients^[6]. HBV infection has been presented with circulating non-organ-specific autoantibodies associated to a variety of immunopathological manifestations^[7]. This included smooth muscle antibody, ANA and anti-LKM1^[8]. The serologic autoimmune phenomenon was also reported in patients who had received treatment with interferon^[9]. At present, the role of immune factors in the pathogenesis of chronic hepatitis B has been widely recognized^[10]. A cohort study was conducted to study the detection of autoantibodies in patients diagnosed with chronic hepatitis B. The result showed that low level titers of antibodies were detected in 8 of 47 patients (17%) with treatment-naïve, histologically proven chronic hepatitis B^[11]. Another study showed a similar positive rate in chronic hepatitis B or C^[3]. This may indicate some interaction mechanisms occur during the period of immunity elimination. Some researchers have indicated that there is more than a single mechanism responsible for viral autoimmunity^[12]. It was shown that viral hepatitis such as hepatitis A virus, hepatitis C virus or hepatitis E virus may have triggered an autoimmune response in many cases^[13].

However, detection of autoantibodies in chronic liver disease does not necessarily indicate a diagnosis of AIH. The presence of a homogenous pattern of antibodies may be more relevant. It is believed that there are many kinds of specific autoantibodies in patients with AIH^[14,15]. The characteristic of AIH is the presence of interface hepatitis, which shows inflammation of hepatocytes at the junction of the portal tract and hepatic parenchyma. According to the simplified criteria for AIH diagnosis, hepatocellular rosette formation is a typical histological feature of AIH^[16]. Although the precise mechanisms of AIH are unknown, environmental factors may trigger disease onset in genetically predisposed individuals.

Several observations in many cases suggest that an extractable nuclear antigen antibody profile was prevalent in patients with chronic hepatitis B, and it was strongly correlated with both compensated and decompensated cirrhosis^[17]. Liver biopsy was

carried out showing signs of severe fragmented necrosis and fibrogenesis, and lymphocyte and plasmocyte infiltrations were observed. Based on a simplified diagnostic scoring system for AIH^[18], AIH is generally divided into type 1 (AIH-1) and type 2 (AIH-2). The autoantibodies related to AIH-1 mainly include ANA, anti-smooth muscle antibody, anti-soluble liver antigen/liver-pancreas and anti-neutrophil antibody; the autoantibodies related to AIH-2 mainly include anti-LKM antibody and anti-liver cytosol type 1^[19]. The appearance of autoantibodies in the pathogenesis of chronic HBV infection is also one of the manifestations of autoimmune disorders^[20]. In general, the human immune system starts to recognize antigens and gradually produces increasing affinity of the relevant antibody after antigen exposure^[21]. T follicular helper cells can be over the augmented capacity to help B cells for antibody secretion, which can induce liver inflammation and the production of antibodies in extrahepatic manifestations^[22].

In the 1980s, some studies showed that glucocorticosteroid pretreatment therapy can clear the makers of viral replication in patients with chronic HBV infection^[23], but in a large trial, the glucocorticosteroid did not indicate any beneficial effect of prednisone pretreatment^[24]. It is recommended that antiviral drugs are the major therapy for chronic active hepatitis B based on the current guidelines^[25]. Our case showed that the antibody titers vary from gradually decreased to disappeared along with treatment (Table 1). This also reminded us that an autoantibody is not a specific marker for the diagnosis during autoimmune liver diseases. Some specific antibodies can also be found in patients with viral hepatitis, drug-related hepatitis and alcoholic and nonalcoholic fatty liver disease. The effect of steroids is unclear in such cases; thus, treatment with steroids should be delayed until HBV is appropriately suppressed.

There is likely a role for induced immune responses with chronic HBV and hepatitis C virus infection. One generally accepted hypothesis is that the molecular stimulation between exogenous antigens and autoantigens leads to the destruction of immune tolerance. The most reported association between hepatitis and AIH is documented for chronic hepatitis C virus^[26]. Gregorio *et al*^[27] observed that the majority of patients infected with hepatitis C virus generated smooth muscle antibody or ANA, which reacted to mimicking molecular mimicry of amino acid sequences between regions of the hepatitis C virus polyprotein and regions of some smooth muscle proteins. We think that the dynamic change of autoantibodies indicates that an immune reaction occurs in the process of spontaneous clearance of HBV^[28].

CONCLUSION

Some autoimmune pathological processes are accompanied by liver inflammation. Although autoantibodies were initially positive in our patient, detection of autoantibodies in chronic liver disease did not necessarily indicate a diagnosis of AIH, likely because of an autoimmune interaction and the production of a variety of heterophile antibodies during the course of the immune response. There are theories suggesting that some interaction mechanisms and immune responses occur during the period of chronic active HBV infection.

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