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CASE REPORT

# Overlap syndrome of autoimmune hepatitis and primary biliary cirrhosis triggered by fluvastatin

**Satoshi Nakayama · Naoya Murashima**

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**Abstract** Although statins are generally well-tolerated drugs, recent cases of autoimmune hepatitis (AIH) associated with their use have been reported. A 59-year-old Japanese man reported with liver damage, which appeared one month after beginning treatment with fluvastatin and continued after discontinuation of the drug. Although drug-induced liver injury was possible, positive autoantibody tests (antinuclear antibodies >1/1280, anti-mitochondrial M2 antibodies 21 index value) also suggested autoimmune liver disease. Liver biopsy findings were consistent with an overlap of autoimmune hepatitis and primary biliary cirrhosis. Treatment with prednisone and ursodeoxycholic acid led to a good response. In this patient, manifestation of AIH and primary biliary cirrhosis overlap syndrome was possibly triggered by statin use. Autoimmune liver disease should be considered as a possible diagnosis in patients with evidence of prolonged liver damage after discontinuation of statins.

**Keywords** Hydroxy-3-methylglutaryl coenzyme A reductase · Lymphocyte stimulation tests · Statins

## Introduction

Statins, a group of drugs that inhibit hydroxy-3-methylglutaryl coenzyme A reductase are used widely in the treatment of cardiovascular disease and are generally well-tolerated. In a previous clinical trial, between 0.1% to 2.7% of patients receiving statins showed elevations in serum aminotransferase levels exceeding three times the upper limit of normal [1]. Another report that reviewed 40 cases of statin hepatotoxity from 26 publications between 1990 and 2008 identified six cases in whom statin use appeared to trigger autoimmune hepatitis (AIH) [2]. A recent report suggested that drug-induced AIH accounts for approximately 9% of cases with AIH [3]. Whereas several other drugs (nitroprocainamide, minocycline, etc.) are known to trigger AIH [3], the role of statin as a precipitant is less well known.

## Case report

A 59-year-old Japanese man with coronary arteriosclerotic disease was prescribed fluvastatin sodium 20 mg/day, aspirin 10 mg/day and lansoprazole 15 mg/day. The patient had never demonstrated any abnormalities in annual blood tests (including liver function), and his hepatobiliary enzyme levels prior to therapy were within normal limits: serum asparate aminotransferase (AST) 23 U/L (normal value 8–38); alanine aminotransferase (ALT) 35 U/L (normal 4–44) and γ-gultamyl transferase (GGT) 31 U/L (normal 16–70). Although he reported consuming alcohol twice a week, his average intake was less than 20 g ethanol equivalent per day. One month after beginning medications, the blood tests showed elevated serum aminotransferase levels that continued to rise one month after discontinuation of all drugs. The patient was admitted to our hospital and his liver biochemical tests showed: serum AST 448 U/L; ALT 1010 U/L; GGT 172 U/L; alkaline phosphatase (ALP) 303 U/L (normal 104–338); total bilirubin 1.1 mg/dL (normal 0.2-1.0); albumin 4.0 g/dL (normal 4–5); prothrombin activity 96% (normal ≥70).

S. Nakayama (✉) · N. Murashima
Department of Gastroenterology, Mishuku Hospital,
5-33-12, Kamimeguro, Meguro-ku,
Tokyo, 153–0051, Japan
e-mail: s-nakayama@mishuku.gr.jp

Of the three drugs prescribed, only fluvastatin sodium elicited a positive reaction in lymphocyte stimulation tests ([3H] thymidine incorporation assay; SRL, Inc, Tokyo). Viral serological tests for hepatitis A, hepatitis B, hepatitis C, cytomegalovirus and Epstein-Barr virus were all negative. These results suggested fluvastatin-induced liver injury. In addition, immunoserological tests showed evidence of autoimmune liver disease. Homogeneous and speckled-type antinuclear antibodies (ANAs) were both present at titers exceeding 1:1280, anti-mitochondrial M2 antibodies (AMAs-M2) were detected (21 ELISA index value; positive >7), and serum immunoglobulin G levels (IgG) were high (2031 mg/dL; normal 870–1700). An abdominal ultrasonogram showed no abnormalities except for a slightly dull-edged liver. Percutaneous liver biopsy on the eighth day of hospitalization showed varying degrees of portal area expansion with heavy lymphocyte, plasma cell and eosinophil infiltration, periductal infiltration by lymphocytes, and some vanishing bile ducts (Fig. 1). All lobular areas showed spotty necrosis and marked mixed cellular infiltration. These findings were consistent with a syndrome of overlapping AIH and primary biliary cirrhosis (PBC).

Although the patient's human leukocyte antigen (HLA) profile (types DR1 and DR15) was not typical for AIH, this diagnosis was confirmed using simplified diagnostic criteria for AIH (score 7 points; cut-off 7) [4].

Subsequently, the patient developed jaundice (total bilirubin 3.1 mg/dL), and was treated with prednisone (starting with 20 mg/day) and ursodeoxycholic acid (900 mg/day). Four months later, his hepatobiliary enzyme levels had returned to normal, but ANAs and AMAs-M2 remained high (exceeding 1:1280 and 10 index value, respectively).

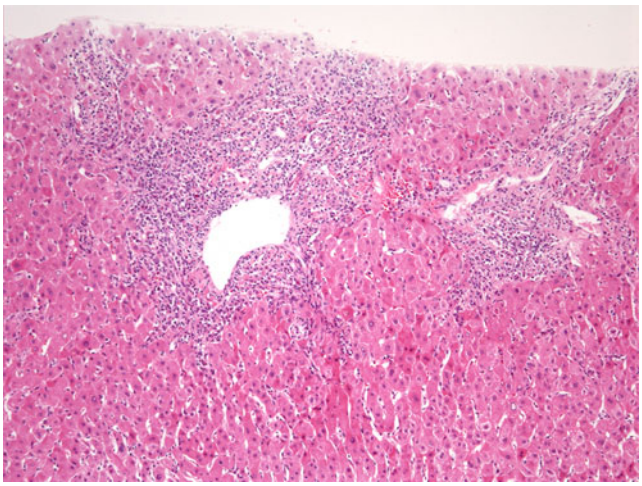

**Fig. 1** Portal areas are expanded and heavily infiltrated with lymphocytes, plasma cells and eosinophils. Periductal infiltration of lymphocytes and partially vanishing bile ducts are also shown (hematoxylin and eosin; ×100)

Fluvastatin is the only statin metabolized by cytochrome P450 (CYP) 2C9, and polymorphisms in CYP2C9 have been shown to influence its pharmacokinetics [5]. Our patient was found to be homozygous for the wild-type CYP2C9 allele. His HLA-DR typing revealed presence of DR1 and DR15.

## Discussion

We presume that our patient had a syndrome of overlapping AIH and PBC triggered by fluvastatin sodium, since he lacked viral serological markers and only this drug showed positive results in the lymphocyte stimulation test, which is the most conclusive test for drug-induced immunoallergic reaction. Whereas some previous reports have demonstrated association between statin use (atrovastatin, rosuvastatin, simvastatin and fluvastatin) and AIH [2, 6–9], this is the first reported case of an overlapping syndrome of AIH and PBC triggered by a statin.

Pathogenesis of statin-induced AIH remains undefined [2]. One report proposes that statins might serve as haptens for cellular targets in genetically predisposed hosts with specific HLA haplotypes (DR3, 4 or 7) that are known to be associated with an increased risk of AIH [5]; our patient did not have these typical HLA haplotypes. Another report proposes that cases with statin-induced AIH could represent sporadic AIH presenting in someone who happened to receive statins [2]. Similar to our case, many other reported cases of liver injury following statins did not have resolution of liver injury on discontinuation of statins. In these cases, AIH was diagnosed subsequently by the presence of autoantibodies, a compatible liver biopsy, and response to immunosuppressive therapy [2]. A causal relationship between statin intake and AIH may be difficult to establish, since autoantibodies are often not tested before statin administration, and may also positive for several months after stopping these drugs [2].

Association between statin use and the occurrence of other autoimmune diseases, including systemic lupus erythematosus (SLE) with simultaneous AIH, dermatomyositis, and pemphigoides have been reported [10]. In patients with statin associated SLE, both cellular apoptosis following release of nuclear antigens into the circulation, as well as direct immunomodulatory effects on T cells have been proposed as the mechanisms underlying immune manifestations [10].

Although statins are generally well-tolerated, they can occasionally cause serious liver autoimmune disease. In cases of liver damage continuing after stopping statin administration, we recommend consideration of autoim-

mune disease as a differential diagnosis. Future data will be required to resolve the pathogenic mechanisms linking statin intake to liver autoimmunity.

## References


1. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology. 2005;41:690–5.
2. Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. Semin Liver Dis. 2009;29:412–22.
3. Björnsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology. 2010;51:2040–8.
4. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48:169–76.
5. Conforti A, Magro L, Moretti U, et al. Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. Drug Saf. 2006;29:1163–72.
6. Alla V, Abraham J, Siddiqui J, et al. Autoimmune hepatitis triggered by statins. J Clin Gastroenterol. 2006;40:757–61.
7. Castiella A, Fernandez J, Zapata E. Autoimmune hepatitis after treatment with fluvastatin. Liver Int. 2007;27:592.
8. Pelli N, Setti M, Ceppa P, et al. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol. 2003;15:921–4.
9. Wolters LM, Van Buuren HR. Rosuvastatin-associated hepatitis with autoimmune features. Eur J Gastroenterol Hepatol. 2005;17:589–90.
10. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. J Eur Acad Dermatol Venereol. 2007;21:17–24.