Cholestatic Jaundice Induced by Atorvastatin: A Possible Association with Antimitochondrial Antibodies

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Various adverse effects have been described following treatment with statins, including liver function abnormalities and induction of different autoantibodies such as myasthenia gravis and systemic lupus erythematosus-associated antibodies. The exact mechanisms underlying these adverse effects are unknown and both direct toxicity and immuno-allergic mechanisms have been proposed [1].

Antimitochondrial antibody is a specific autoantibody found in 85%–90% of patients with primary biliary cirrhosis – a chronic liver disease that may progress to liver cirrhosis. M2 is one of the subtypes of antimitochondrial antibodies, directed against a family of mitochondrial antigens, pyruvate-dehydrogenase complex, 2-oxoglutarate and branched chain 2-oxo acid dehydrogenase complexes. Anti-PDC M2 autoantibody is detected by immunoblotting or enzyme-linked immunosorbent assay in 95% of PBC patients with active disease [2], but it can also be detected in asymptomatic patients and in other diseases such as chronic bacterial infections, active tuberculosis, and following exposure to drugs such as halotane [3]. The presence of antimitochondrial and M2 antibodies in patients with statin-mediated liver injury has not been reported.

PATIENT DESCRIPTION

A 68 year old man was admitted to our internal medicine ward complaining of fever, dark urine and an urticarial rash. His medical history was significant for prostate and colon cancer in remission, hyperlipidemia, hyperuricemia, fatty liver and chronic urticaria. His regular medications included atorvastatin 20 mg/day, doxazosin 2 mg/day, aspirin 100 mg/day, allopurinol 100 mg/day and dutasteride 0.5 mg/day.

Physical examination was notable for diffuse urticaria and icterus. Abnormal laboratory results included elevated liver function tests with a cholestatic pattern: total bilirubin 7.4 mg/dl (normal 0.2–1.0 mg/dl), conjugated bilirubin 4.5 mg/dl, alkaline phosphatase 555 U/L (normal 39–117 U/L), alanine aminotransferase 250 U/L (normal 4–41 U/L), aspartate aminotransferase 50 U/L (normal 5–38 U/L), and lactate dehydrogenase 540 U/L (normal 240–480 U/L). Extra- and intrahepatic biliary obstruction was ruled out by ultrasonographic examination. Abdominal computed tomography and magnetic resonance imaging were normal. Anti-Epstein-Barr virus antibodies (immunoglobulin G) were detected, but tests for hepatitis B virus, cytomegalovirus (IgM) and polymerase chain reaction for hepatitis C virus were negative. Immunoglobulin electrophoresis did not demonstrate a monoclonal spike. A working diagnosis of drug-induced hepatotoxicity was made and atorvastatin and allopurinaol were withheld. This was followed by a rapid biochemical and clinical improvement.

During the following 4 weeks the patient was discharged and readmitted twice with a similar clinical and laboratory presentation. Liver biopsy performed on his fourth admission demonstrated severe inflammatory infiltrate with lymphocytes in some of the portal spaces, bile duct proliferation, a few granulomas and fibrotic septa in some of the portal spaces. These findings were interpreted as compatible with granulomatous hepatitis, toxic hepatitis or primary biliary cirrhosis. Additional serological tests demonstrated elevated levels of AMA, antinuclear antibody and anti-PDC (M2) antibodies. Further investigation revealed that between admissions and prior to each recurrent bout of cholestatic hepatitis the patient had renewed his treatment with atorvastatin. Complete cessation of atorvastatin was followed by a return to normal values of liver function tests and a complete clinical recovery. Levels of AMA, ANA and M2 antibodies remained elevated.

COMMENT

Our patient presented with repeated cholestatic liver damage without evidence of bile obstruction but with

PDC = pyruvate-dehydrogenase complex
PBC = primary biliary cirrhosis

IgM = immunoglobulin M

AMA = antimitochondrial antibody
ANA = antinuclear antibody

positive serology for ANA, AMA and M2 autoantibodies. Liver biopsy had demonstrated non-specific liver damage compatible with both toxic hepatitis and primary biliary cirrhosis. These clinical and biochemical findings raised two major possible diagnoses: drug-mediated toxic hepatitis and PBC.

Several clinical features and laboratory findings strongly suggest that this patient did not suffer from active symptomatic PBC. These include the patient's male gender, the absence of pruritus, and the fluctuating bilirubiln and liver enzymes that normalized after interruption of the culprit drug rather than progressing over time. Furthermore, the absence of PBC-associated typical high titers of IgM and of other features of autoimmunity does not support the diagnosis of symptomatic PBC.

The detection in our patient of AMA and M2 antibodies, which are 98% specific for PBC [4], requires an explanation. A positive serology for AMA may precede the clinical onset of the PBC and may suggest that this patient has a latent asymptomatic disease that was detected accidentally. However, the prevalence of an incidental finding of AMA in the general population has been reported to be 0.07%–9.9% and it is controversial whether every person who is positive for AMA has PBC or will eventually develop PBC [4]. None of the patients in one large cohort [4] developed PBC during a mean follow-up of 3.5 years. Thus, the presence of these autoantibodies in our patient may be an incidental finding and does necessarily indicate the presence of latent PBC or predict its future development.

Several drugs have been reported to induce AMA. These include chlorpomazine and halothane, which was most recently linked to the appearance of M2 antibodies by means of a molecular mimicry mechanism. Fluctuating titers of drug-induced AMA over long periods was also reported.

Statins were not reported thus far to induce AMA and/or M2 antibodies. Nevertheless, these drugs were associated with a variety of autoimmune features including vasculitis, polymyalgia rheumatica, myasthenia gravis and dermatomyositis, and induction of different autoantibodies such as anti-acetylcholine receptor and antinuclear antibodies [5]. It is conceivable, therefore, that exposure to a statin may have also induced AMA and M2 autoantibodies in this patient.

In conclusion, the temporal correlation between the clinical bouts of cholestatic damage and remission upon drug cessation strongly suggests atorvastatin as the most plausible explanation for this patient's clinical and laboratory presentation. Taken together with the well-established ability of statins to induce autoimmune phenomena, it is strongly suggested that the presence of AMA and M2 autoantibodies was also due to atorvastatin rather than being an incidental serological finding in this patient. Further follow-up is needed to investigate whether this patient will eventually develop active PBC.

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