**CASE REPORT**

**Development of Autoimmune Hepatitis during Direct-acting Antiviral Therapy for Chronic Hepatitis C Virus Infection**

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**Abstract:**
An 81-year-old woman developed liver dysfunction after two months’ treatment with direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection. She was positive for serum anti-nuclear antibody, with an elevated immunoglobulin G level. A liver biopsy revealed high-grade interface hepatitis and infiltrate of lymphocytes and plasma cells. DAA-associated drug-induced autoimmune hepatitis (DI-AIH) was considered. Her liver dysfunction improved after discontinuing DAA therapy and starting prednisolone treatment.

**Key words:** autoimmune hepatitis, direct-acting antivirals, chronic hepatitis C virus infection, prednisolone

**Introduction**
Although previous reports of autoimmune hepatitis (AIH) have suggested the involvement of drugs in disease development (1), no cases of AIH that developed during direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection have been reported. HCV may induce an autoimmune phenomenon that is sometimes accompanied by AIH (2); however, we encountered a case in which the onset of AIH occurred after the serum HCV-RNA findings became negative, suggesting that the immunological trigger was not the immune response against HCV.

We herein report this interesting case and include considerations from the literature.

**Case Report**
An 81-year-old woman with serogroup 1 chronic HCV infection visited our internal medicine outpatient facility. She was started on treatment with DAAs (Elbasvir 50 mg daily and Grazoprevir 100 mg daily). Two months later, she visited the regular outpatient facility and complained of general malaise and appetite loss lasting a few days. She developed liver injury, and her serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated on blood chemistry. She had a history of blood transfusions when she was 36 years old, no remarkable family history, and no history of autoimmune disease or significant alcohol consumption. She was taking no oral medications other than the DAAs until the liver injury developed.

Upon admission, a physical examination showed palpebral conjunctiva anemia but no obvious icterus. Her consciousness was clear. The results of her laboratory tests are shown in the Table. The total white blood cell count was within the normal limits, without eosinophilia. The platelet count was 10.7×10⁴/μL; this value was already low before starting DAA therapy. The serum AST level was elevated to 1,413 U/L, and the ALT level was 739 U/L. The total bilirubin level was not elevated. The prothrombin time (PT) was prolonged to 49.1%. Tests for IgM-type antibodies against hepatitis A virus (anti-HA-IgM) and the hepatitis B virus core antibody (anti-HBc-IgM) were negative. Serum HCV-RNA was undetectable by polymerase chain reaction. Serology for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) was also negative. The anti-nuclear antibody (ANA)
The onset of AIH is assumed to involve an autoimmune mechanism, and environmental factors, such as drug use or viral infection, can act as triggers in patients with certain genetic backgrounds, such as HLA-DR4 (4). HCV infection is sometimes accompanied by autoantibody positivity with a high immunoglobulin level and complications of autoimmune disease of the extrahepatic organs (2); therefore, in some cases, it is difficult to distinguish HCV-associated autoimmune phenomena from AIH. The present patient had chronic HCV infection with bridging fibrosis. The serum HCV-RNA was continuously undetectable; the patient achieved a sustained viral response (SVR12).

**Discussion**

The present patient had chronic HCV infection with bridging fibrosis. The serum HCV-RNA was continuously undetectable; the patient achieved a sustained viral response (SVR12).
aminotransferases appeared. The clinical findings revealed our patient to be positive for ANA with a high serum IgG level, and high-grade interface hepatitis with inflammatory cell infiltrate mainly composed of lymphocytes and plasma cells was observed on a histological examination. At this point, the patient was confirmed to have AIH based on both diagnostic criteria, with a score of 8 points (≥7 points indicates AIH, definite) with the simplified criteria and 15 points (10-15 points indicates AIH, probable) with the international diagnostic criteria. The disease severity was “severe” according to the diagnostic criteria of the practice guideline for the treatment of AIH in Japan, 2013. Furthermore, the liver disorder worsened after the discontinuation of DAA therapy. We therefore diagnosed the patient with AIH induced by DAAs.

However, the Digestive Disease Week Japan (DDW-J) 2004 score for the diagnosis of drug-induced liver injury (DILI) (5) was 4 points (3 or 4 points indicates possible DILI). We decided to start steroid therapy as immunosuppressive therapy, but given the risk of osteoporosis, the long-term administration of steroids is unadvised in older women. In the future, we must carefully consider the discontinuation of steroid therapy.

In patients with a history of medication before the appearance of liver disorder, such as in the present case, it is difficult to accurately identify the type of liver disorder. Three clinical scenarios have been proposed that refer to drug-induced autoimmune liver disease (DIALD): AIH with

Figure 1. The histological findings in the liver. a: Parenchymal collapse was observed in the periportal to mid-zonal area, and interface and panlobular hepatitis with lymphoplasmacytic inflammation and bridging necrosis in the portal area were observed. (Hematoxylin and Eosin (H&E) staining, magnification: ×100). b: Plasma cell infiltration (arrows). (H&E staining, magnification: ×400). c: Emperipolesis (invasion of lymphocytes into hepatocytes) can be seen (arrows). (H&E staining, magnification: ×400). d: Rosette formation (arrows). (PAS with Diastase stain, magnification: ×400). PAS: periodic acid-Schiff.
DILI, drug-induced AIH (DI-AIH), and immune-mediated DILI (IM-DILI) (6). The first report of DI-AIH by Reynolds et al. (7) in 1971 was of lupoid hepatitis induced by oxyphenisatin, which is frequently used as a laxative. Since then, AIH due to various drugs (8-20), including nitrofurantoin (21) and clometacin (22), has been reported. The results of the current study suggest that DI-AIH cases make up approximately 9-15% of AIH cases (7, 23).

Sometimes DILI has clinical features similar to AIH, such as autoantibodies and hypergammaglobulinemia (24, 25). Distinguishing DILI from AIH is often difficult and can be challenging. Suzuki et al. (26) performed a standardized histologic evaluation to explore potential hallmarks to differentiate DILI and AIH. Interface hepatitis, focal necrosis, and portal inflammation were more severe in AIH than in DILI. Portal and intra-acinar plasma cells, rosette formation, and emperipolesis were features that favored AIH, while intra-acinar lymphocytes and canalicular cholestasis favored hepatocellular DILI. Tsutsui et al. (27) showed that the DDW-J scale was useful for differentiating AIH from DILI in cases with a DDW-J scale score of ≥5, and the scores for pathological findings, such as cobblestone hepatocellular change, interface hepatitis, and prominent plasma cells in portal areas, were higher in the AIH group than in the DILI group. Given the above, the combination of distinct histological findings, such as hepatocellular change, the types of inflammatory cells in different areas, the severity of injury/inflammation, and the presence of cholestasis, are helpful for differentiating DILI and AIH.

Antiviral treatments used for chronic HCV infection often use interferon (IFN) and ribavirin (RBV), but there have been many reports of AIH being caused by such treatment (28-30). To our knowledge, this is the first reported case of DAA-related DI-AIH.

The autoimmune mechanism underlying hepatocellular injury in DI-AIH is still unknown. Miyakawa et al. (31) examined the association of autoantibodies with drug-metabolizing enzymes and suggested that specific autoantibodies produced for cytochrome P-450 and expressed on hepatocyte membranes may induce hepatocellular injury. In the present case, both Elbasvir and Grazoprevir were metabolized by CYP3A4, but unfortunately, we were unable to measure the autoantibodies against cytochrome P-450. Robin et al. (32) considered that a drug metabolite could become a hapten, which can combine strongly with a cell component and acquire antigenicity; a cell-mediated immunity mechanism could then cause hepatocellular injury for this hapten carrier. Similarly, it was suggested that free radical metabolites and reactive oxygen are combined with microsomal proteins during the first phase of drug metabolism; the consequently modified protein can then induce an autoimmune reaction (33, 34).

In patients with HCV infection, the infection itself may be involved in the onset of AIH with an autoimmune phenomenon (2). In the present case, an immunological mechanism different from that inducing HCV infection likely caused drug intervention to trigger the onset of AIH, based on the fact that while the blood test for HCV-RNA was negative at four and eight weeks after DAA treatment initiation, liver disorder was not recognized until eight weeks after treatment initiation. Regarding the onset of AIH, it was suggested that decreased numbers and proliferation capacity

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Figure 2. The clinical course of the patient.
of regulatory T cells (Treg) impaired the immunological tolerance. In contrast, it was reported that increased numbers of Treg inhibited the antiviral CD8-positive T cell responses in sustained HCV infection (35). In the present case, decreased numbers of Treg and a increased production of specific autoantibody against CYP might have caused hepatocyte disorder, as HCV had been under control by DAA therapy.

The authors state that they have no Conflict of Interest (COI).

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