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Primary biliary cholangitis development after hepatitis C virus eradication with direct acting antivirals: a case report and review of the literature

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Abstract. – We report the case of an 84-year-old man with asymptomatic chronic hepatitis C virus (HCV) infection treated with direct antiviral agents. At the end of the antiviral therapy laboratory tests showed an abrupt increase in cholestasis parameters and aminotransferases, associated with anti-mitochondria antibodies positivity. Therefore, primary biliary cholangitis (PBC) was diagnosed. The patient was treated with ursodeoxycholic acid achieving a good biochemical response.

This is the second case described in literature of PBC onset after HCV eradication with an interferon-free antiviral regimen. In both cases an autoimmune damage of cholangiocytes secondary to the immunological derangement caused by virus clearance may be hypothesized. Indeed, according to the hygiene hypothesis, when two different triggers act simultaneously on the immune system they tend to be mutually inhibitory, and an immune tolerance develops; when one of these triggers disappears (as HCV in this case), the immune system may mount a response against self-antigens, causing autoimmune disorders such as PBC.

Key Words:
HCV, Direct-acting antiviral drugs, Primary biliary cholangitis, Hygiene hypothesis, Anti-mitochondria antibody.

Case Report

An 84-year-old man with chronic hepatitis C virus (HCV) infection (genotype 1b, diagnosed in 2005, naive to antiviral therapy) was treated in our outpatient clinic with a 12-week course of Elbasvir/Grazoprevir 50/100 mg orally once a day, a combination of direct-acting antiviral agents (DAAs) highly effective in the treatment of genotypes 1 and 4 HCV infection[1].

He was also affected by hypertension, hypothyroidism, monoclonal gammopathy, ureteral lithiasis and had a previous history of prostate adenocarcinoma successfully treated with radiation therapy. The patient was on treatment with levothyroxine, ramipril, nitrosorbide, low-dose aspirin, tamsulosin and propafenone.

Blood tests performed before starting antiviral therapy showed high serum HCV viral load (HCV-RNA 17,000,000 IU/ml) but without any elevation in aspartate (AST) and alanine aminotransferases (ALT) or gamma-glutamyl transpeptidase (GGT) or alkaline phosphatase (ALP).

After checking for the absence of drug interactions, the patient started and completed the course of DAAs therapy, without reporting any adverse event. At the 4th week of treatment course HCV-RNA was undetectable, whereas serum levels of GGT, AST and ALT were normal; at the 8th week of treatment only a slight increase of GGT was detectable (126 IU/L), and aminotransferases were within the normal range.

However, at the end of the antiviral therapy laboratory tests showed a significant increase in cholestasis (GGT 313 IU/L, ALP 252 IU/L) and cytonecrosis indices [AST and ALT × 1.5 and × 2 upper limit of normal (ULN), respectively]; total bilirubin was normal (0.55 mg/dl) as long as hepatic synthesis indices (albumin 4.1 g/dl, INR 1.01): nevertheless, serum HCV-RNA was undetectable, and serology for major and minor hepatotropic viruses such as hepatitis B, A, and E viruses, cytomegalovirus, Epstein Barr and Herpes simplex 1 excluded a recent infection and/or re-activation; the use of drugs potentially causing liver injury was also ruled out. An abdominal ultrasound did not show any biliary tract obstruction or bile duct dilation.

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Therefore, antibodies indicative of autoimmune liver disease were tested. Serum levels of anti-nuclear, anti-smooth muscle and anti-liver kidney microsomes-1 antibodies were undetectable, whereas anti-mitochondria antibodies (AMA) were positive with a titer of 1:40.

A close monitoring of blood tests showed a slight reduction in transaminase levels, but a progressive increase in cholestasis indices, with GGT and ALP reaching a peak of 14-fold the ULN (860 g/dl) and 4.2-fold the ULN (543 g/dl) respectively at 6 weeks from the end of therapy. A diagnosis of primary biliary cholangitis (PBC) was made according to the present guidelines for the diagnosis and management of this disease[2] and it was decided to avoid liver biopsy and start treatment with ursodeoxycholic acid at the dosage of 900 mg/day (13.5 mg/kg/weight), resulting in a rapid normalization of the aminotransferases and a progressive decrease in GGT and ALP levels.

At present, 6 months after the beginning of ursodeoxycholic acid, the serum levels of ALP and GGT have normalized (131 IU/L and 64 IU/L respectively), as long as aminotransferases (ALT 9 IU/L, AST 19 IU/L) (Figure 1).

A sustained viral response (SVR) was achieved and maintained 12 and 24 weeks after the end of DAAs treatment.

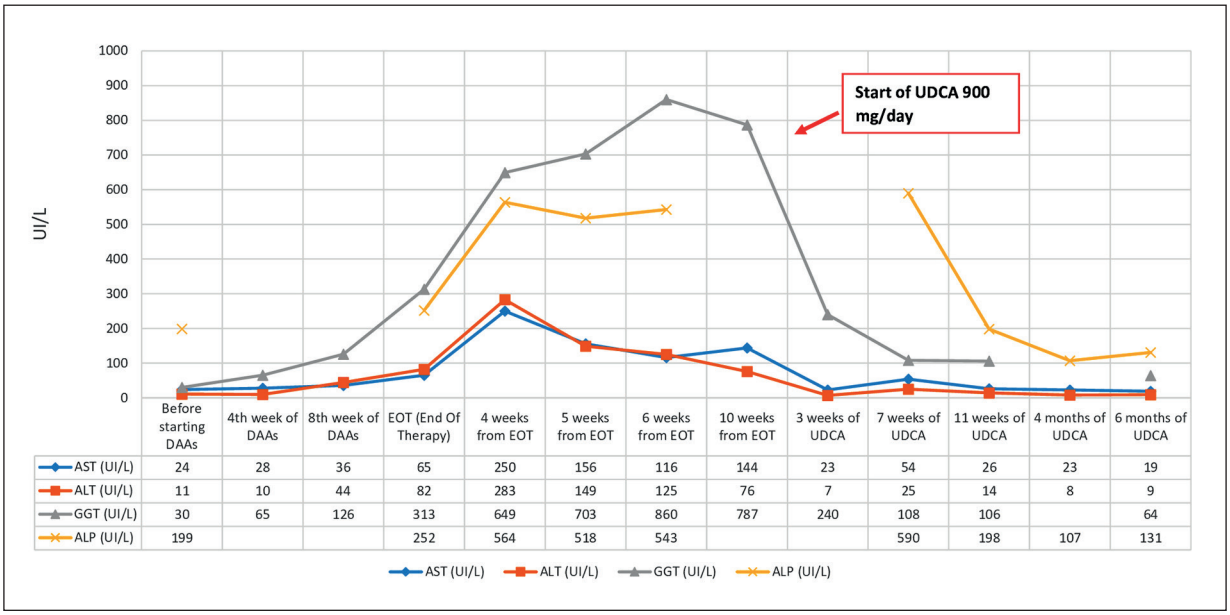
Discussion

HCV clearance in patients with chronic infection is associated with a reduction in HCV-related complications, liver disease severity and mortality.

In the past, the standard of care for HCV infection treatment was pegylated interferon alpha (PEG-IFNα) and ribavirin[3]. Several reports[4,5] in the literature have described the onset of PBC and other autoimmune diseases during IFN-based regimens. Indeed, IFN has well-known immunostimulating properties and is able to induce a great imbalance in the immune system, interfering with T helper 1 (Th1) and T helper 2 (Th2) lymphocytes activity[6].

On the contrary, the occurrence of autoimmune diseases after DAAs, which are now the gold standard for the treatment of HCV chronic infection, is uncommon. To our knowledge, this is the second case described in literature of PBC onset after HCV eradication with an IFN-free antiviral regimen.

The first case was reported by Rendina et al[7], in which the authors postulated that PBC may have been triggered by HCV clearance with a mechanism related to the 'hygiene hypothesis': in summary, when two different antigens act simultaneously on the immune system they



	Before starting DAAs	4th week of DAAs	8th week of DAAs	EOT (End Of Therapy)	4 weeks from EOT	5 weeks from EOT	6 weeks from EOT	10 weeks from EOT	3 weeks of UDCA	7 weeks of UDCA	11 weeks of UDCA	4 months of UDCA	6 months of UDCA
AST (UI/L)	24	28	36	65	250	156	116	144	23	54	26	23	19
ALT (UI/L)	11	10	44	82	283	149	125	76	7	25	14	8	9
GGT (UI/L)	30	65	126	313	649	703	860	787	240	108	106		64
ALP (UI/L)	199			252	564	518	543			590	198	107	131

Figure 1. Kinetics of liver enzymes in the patient during and after HCV treatment. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyltranspeptidase; HCV, hepatitis C virus; ULN, upper limit of normal.

tend to be mutually inhibitory, but when one of these stimuli disappears, the immune system may mount a response against self-antigens, causing autoimmune disorders[8]. This explanation may also be applied to our patient, who abruptly developed alteration of cholestasis and cytonecrosis parameters soon after HCV-RNA eradication.

Another interesting case was described in 2018 by Matsumoto et al[9], reporting the onset of autoimmune hepatitis during DAA treatment for HCV infection. HCV affects the human immune system via several mechanisms in order to escape surveillance and hinder the elimination by the host. Specific changes in the innate and adaptive immune responses that promote the persistence of the infection are described[10,11]. One of these mechanisms is the ability to reduce the activity of cells responsible for the elimination of virus-infected cells, in particular the exhaustion of cytotoxic T lymphocytes (CTLs) [the so-called "exhausted phenotype"][12,13]. Furthermore, during chronic HCV infection, natural killer (NK) cells become activated but their typical responses are disordered, preventing the elimination of the virus and leading to chronic hepatitis[14]. Prezzi et al[15] have also suggested that an imbalance between the Th1 and Th2 responses may be involved in the development of chronic hepatitis C, with a depressed Th1 and overactive Th2 response.

Conversely, dynamic changes in the innate immune response during DAA therapy for HCV infection have been described[16-19]. In particular, immunological analyses have revealed the reversal in the exhaustion of CTLs with a restoration of HCV-specific CD8+ T cell function in patients treated with DAAs[16,17]. The viral load decline during treatment reduces serum levels of NK cell-stimulating cytokines and causes correction of the altered NK cell phenotype observed in chronic HCV patients[20]. Moreover, HCV treatment has demonstrated to induce lymphocytes polarization towards Th1 over Th2 phenotype, a mechanism implicated in the pathogenesis of PBC[21]. A biological proof of concept of these important immunomodulatory effects of HCV treatment with DAA is the so-called "end of treatment (EOT)+/SVR": a fraction of chronic HCV patients treated with DAAs achieve SVR despite having detectable viremia at the EOT. This observation has been related to reversal of CTLs exhaustion induced by DAAs, which is able to clear the infection after the end of treatment[22]. Indeed, DAAs have dramatically changed the treatment of HCV not only for their high antiviral efficacy, but also for their ability to awake the immune system by releasing it from the burden of chronic antigen load. These effects of DAA agents may be relevant not only in determining the response to therapy, but also in the modulation of the immune response.

Other effects of the immune modulation occurring during DAA treatment for HCV infection have already been described, including hepatitis B virus (HBV) reactivation and recurrence of HCC[10]. In fact, it has been postulated that abrupt changes in the immune surveillance can be responsible in some cases for HBV reactivation in patients with inactive or resolved HBV infection[23,24] and for the recurrence of hepatocellular carcinoma (HCC) in patients with previous successfully treated cancer[25,26]. Also in these cases, the modification of the immunological milieu and the different behavior of the immune cells after the HCV eradication with DAAs are the mechanisms most probably involved[27].

Conclusions

In summary, when an abrupt increase in cholestasis indices and/or aminotransferases occurs during or immediately after the end of treatment with DAAs, it is important to look for the onset of an autoimmune disorder that may have remained silent until HCV eradication.

Indeed, the profound immunological changes occurring during treatment with DAAs can potentially be responsible for the unmasking of a silent autoimmune disease, that becomes clinically relevant as a consequence of the immune system reconstruction. We did not test our patient for AMA before starting anti-HCV therapy, but it is well known that liver autoantibodies in asymptomatic patients may precede the subsequent development of overt autoimmune disease by many years. For further investigation, it will be useful to establish if the development of an autoimmune disease after HCV eradication with DAAs can be predicted by the presence of autoantibodies prior to the start of therapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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