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Autoimmune hepatitis and primary biliary cholangitis overlap syndrome after mRNA COVID-19 vaccination

Nadir Süleyman Çetinkaya[1], Mustafa Cengiz[2], Emine Gül Aydın[2]

[1]University of Health Sciences Türkiye, Gülhane Faculty of Medicine & Gülhane Training and Research Hospital, Ankara, Türkiye

[2]University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Department of Gastroenterology, Ankara, Türkiye

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Corresponding Author:
Nadir Süleyman Çetinkaya, M.D., University of Health Sciences Türkiye, Gülhane Faculty of Medicine & Gülhane Training and Research Hospital, Department of Internal Medicine, Ankara, Türkiye
+90 537 554 19 19
drnscetinkaya@gmail.com

ORCID:
orcid.org/0000-0002-8579-9944

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ABSTRACT

The overlap syndrome indicates an association between autoimmune hepatitis (AIH) and sclerosis cholangitis or primary biliary cholangitis (PBC). We report a case of a 32-year-old patient who experienced overlap syndrome ten days after receiving the first dose of the mRNA Coronavirus disease-2019 (COVID-19) vaccine. Liver biopsy showed primarily AIH and "overlap syndrome" for PBC. Serum IgG was elevated, and ANA (1/100) and anti-mitochondrial antibody was positive. The patient's treatment plan included prednisolone, ursodeoxycholic acid and azathioprine. Overlap syndrome related to the mRNA COVID-19 vaccines is a very rare entity. After the histopathological diagnosis of the patient, remission was achieved following treatment.

Introduction

The first case of Coronavirus disease-2019 (COVID-19) was reported in December 2019 in China. The World Health Organization declared it a pandemic on March 11, 2020 (1). Although various treatment modalities have emerged, no effective treatment has yet been found. Inactivated mRNA COVID-19 vaccines are still used as the most effective choice for protection. However, as with all other vaccines, it may have various adverse effects.

The overlap syndrome indicates an association between autoimmune hepatitis (AIH) and sclerosis cholangitis or primary biliary cholangitis (PBC) (2). Considering its immunological and clinical features, 1 to 14 percent of patients with PBC have a variant form of AIH (3,4). Features of AIH may present at diagnosis or may develop during follow-up. Paris criteria for diagnosis of AIH and PBC (overlap syndrome) are used according to laboratory and biopsy results (5). Serum alanine aminotransferase (ALT) level 5 fold ULN, immunoglobulin G level 2 fold or the presence of smooth muscle antibodies, and interface hepatitis on histological examination are the three characteristics associated with AIH that are required by the Paris criteria for the AIP-PBC overlap syndrome. Additionally, two of the following PBC-related characteristics are required to make the diagnosis: florid duct lesions or destructive cholangitis on

histological examination and serum alkaline phosphatase level 2-fold ULN or gamma-glutamyl transferase (GGT) level 5-fold (6). Here we report a case of AIH and PBC (overlap syndrome) that developed after mRNA vaccination.

Case Presentation

A 32-year-old male patient without a remarkable medical history was admitted to our gastroenterology clinic with icterus, dark urine, weakness, nausea, and vomiting. There was no alcohol or drug abuse history. COVID-19 history was negative. He had received the first dose of the mRNA COVID-19 vaccine 10 days ago. His physical examination revealed icterus in the sclera and mucous membranes when he was hospitalized. The patient's laboratory results were as follows; aspartate transaminase 808 U/L (range 15-40 U/L), ALT 960 U/L (range 10-40 U/L), total bilirubin 15.4 mg/dL (range 0.3-1.2 mg/dL), direct bilirubin 8.1 mg/dL (range 0-0.2 mg/dL), alkaline phosphatase 211 U/L (range 35-120 U/L), GGT 128 U/L (range 0-55 U/L), amylase 93 U/L (range 28-100 U/L), lipase 87 U/L (range 10-67 U/L), international normalized ratio 1.17 (range 0.8-1.2), C-reactive protein 9.8 mg/L (range 0-5 mg/L), antinuclear antibodies (ANA) positive (1/100) and anti-mitochondrial antibody-M2 (AMA-M2) 45.5 U/mL (range positive >10 U/mL), immunoglobulin G level was 1787 mg/dL (range 700-1600 mg/dL). The hepatitis panel, viral serology, and other serological markers were negative. The laboratory results of patients are presented in Table 1. Abdominal ultrasonography revealed gallbladder sludge. Contrast-enhanced abdominal computed tomography showed no pathology except for edema in the periportal area and pericholecystic fluid collection. Abdominal magnetic resonance imaging/magnetic resonance cholangiopancreatography revealed periportal edema and a few minimally enlarged lymph nodes. The findings were reported to suggest inflammatory conditions of the biliary system.

A percutaneous liver biopsy was performed. The liver biopsy sample included more than 12 total portal tracts and was longer than 20 mm. Hematoxylin and eosin and Masson trichrome stains showed inflammation with moderate lymphoplasmacytic and eosinophilic leukocytes, marked cholestasis, and bile duct proliferation in the portal areas. In addition to moderate severe interface and parenchymal inflammation, local hepatocyte necrosis and degeneration were detected. Immunohistochemical studies showed disrupted reticulin framework, stage 3 fibrosis with Masson's trichrome (Figure 1B), and minimal iron deposition with iron staining. There were mixed inflammatory infiltrates including mononuclear cells, eosinophils, and scattered neutrophil infiltration in the bile ducts in the portal areas (Figure 1A). Immunohistochemical studies showed common CD38, CD138, and CD68 staining and plasma cells and histiocytes and duct proliferation with CK7 and CK19 staining. These findings suggested primarily an AIH diagnosis and fluoride duct lesion, but the presence of AMA autoantibodies and bile duct damage was suggestive of an "overlap syndrome" with PBC (7).

Table 1. Laboratory test results

Test	At diagnosis	After treatment	Reference range
Aspartate transaminase	808 U/L	13 U/L	15-40 U/L
Alanine aminotransferase	960 U/L	20 U/L	10-40 U/L
Total bilirubin	15.4 mg/dL	0.8 mg/dL	0.3-1.2 mg/dL
Direct bilirubin	8.1 mg/dL	0.24 mg/dL	0-0.2 mg/dL
Alkaline phosphatase	211 U/L	94 U/L	35-120 U/L
Gamma-glutamyl transferase	128 U/L	36 U/L	0-55 U/L
Amylase	93 U/L	88 U/L	28-100 U/L
Lipase	87 U/L	48 U/L	10-67 U/L
Prothrombin time	13.5 seconds	10.6	9.7-14.3 seconds
International normalized ratio	1.17	0.88	0.8-1.2
Partial thromboplastin time	38.7 seconds	22.4 seconds	22-38 seconds
C-reactive protein	9.8 mg/L	1.7 mg/L	0-5 mg/L
Erythrocyte sedimentation rate	77 mm/h	27 mm/h	0-20 mm/h
Antinuclear antibodies	Positive 1/100		
Anti-mitochondrial antibody-M2	45.5 U/mL positive		Positive >10 U/mL
Immunoglobulin G	1787 mg/dL		700-1600 mg/dL
Immunoglobulin M	178 mg/dL		40-230 mg/dL
Immunoglobulin A	407 mg/dL		70-400 mg/dL
Seruloplasmin	0.4 g/L		0.2-0.6 g/L

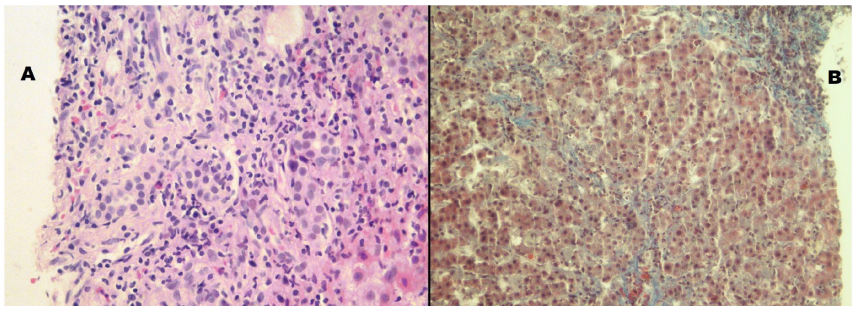

Figure 1. Liver biopsy result was compatible with an overlap syndrome. A) Mixed inflammatory infiltrate including mononuclear cells, eosinophils and scattered neutrophils in bile ducts in the portal areas (hematoxylin-eosin stain). B) Fibrotic band formation in liver parenchyma (Masson's trichrome stain)

Discussion

mRNA COVID-19 vaccination can stimulate innate immunity (8). AIH cases have been reported after Severe acute respiratory syndrome-Coronavirus-2 vaccination in the literature (8-14). The first case of AIH after the mRNA COVID-19 vaccine was reported by Bril et al. (9). However, to the best of our knowledge, an overlap syndrome related to the mRNA COVID-19 vaccines has not been reported before. Our patient's biopsy findings were similar to those described by Bril et al. (9). We used the Paris criteria for AIH and PBC (overlap syndrome) diagnosis (5) and our patient had histological features of AIH and PBC.

The patient was seropositive for ANA and AMA, and AMA, ANA, and IgG levels were consistent with the literature (8-11,14). Biopsy findings were also consistent with overlap syndrome. Most patients reported previously were female, while our patient was male (8-13). Clayton-Chubb et al. (14) reported a similar case, a 36-year-old man who developed AIH after the mRNA COVID-19 vaccine. Another case (15) similar to the current report showed symptoms and laboratory results in a 57-year-old man who developed AIH-PBC overlap syndrome after COVID-19. Nevertheless, no liver biopsy was performed for that patient. Our patient's histopathological findings were compatible with AIH-PBC overlap syndrome.

Treatment included prednisolone 40 mg/day, ursodeoxycholic acid 15 mg/kg, and azathioprine 50 mg/day. The patient's symptoms regressed after one month of treatment, and the laboratory results were in the normal range (Table 1). Similar responses were reported in other AIH cases (8-14).

AIH has been linked to various drugs (minocycline, alpha methyldopa, nitrofurantoin, infliximab, and statins). On the other hand, AIH/PBC coexistence is difficult to distinguish histopathologically, and making a clear differentiation between PBC and PBC-AIH overlap syndrome is important before selecting treatment options (16).

Conclusion

We present here that the mRNA COVID-19 vaccine may be associated with a diagnosis of overlap syndrome of AIH and PBC. Hence, clinicians should pay attention to this uncommon adverse effect of the mRNA COVID-19 vaccine and care should be taken especially in patients who develop hepatic dysfunction after vaccination.

Ethics

Informed Consent: The patient consented to the publication of this report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practice - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: N.S.Ç., M.C., E.G.A.

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