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CASE REPORT | LIVER

It Can't Be a Coincidence: A Comparison of Cases of Autoimmune Hepatitis After Vaccination Against COVID-19

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ABSTRACT

While rare, there is now a documented cohort of patients presenting with autoimmune hepatitis secondary to vaccination against COVID-19. With this case report, we aim to compare the published cases in order to discern any unifying characteristics among those affected, and share the story of a seventy-two-year old patient presenting with autoimmune hepatitis less than two weeks after receiving his first dose of the Pfizer COVID-19 vaccine.

KEYWORDS: autoimmune hepatitis; COVID-19 vaccination; Adverse Response to vaccination

The novel coronavirus disease 2019 (COVID-19) has had a devastating impact on the world, leading to the rapid development of vaccinations to prevent serious disease. Since the wide distribution of these vaccinations, there have been multiple case studies associating the COVID-19 vaccine with autoimmune hepatitis (AIH) (Table 1).

The pathogenesis of AIH is believed to be an environmental trigger leading to T-cell-mediated destruction of hepatocytes, chronic inflammation, and fibrosis of the liver.[1] Diagnosis of AIH requires elevated aspartate aminotransferase (AST), alanine transaminase (ALT), and immunoglobulin G (IgG); the presence of associated antibodies (type 1 AIH: anti-nuclear antibody [ANA] and anti-smooth muscle antibody [ASMA] vs type 2 AIH: anti-liver kidney microsome type 1), and pathology demonstrating lymphoplasmacytic interface hepatitis.[2] While AIH does have known markers of disease, it remains a diagnosis of exclusion.

The mechanism behind COVID-19 vaccination-induced autoimmune disease is believed to be related to molecular mimicry. Studies have shown that there is significant peptide sharing between an antigen of COVID-19, severe acute respiratory syndrome coronavirus 2 spike glycoprotein, and mammalian proteins, which may lead to T-cell cross-reactivity.[3] Other hypotheses suggest that the vaccine's activation of the interferon pathway may lead to autoimmune conditions.[4] Furthermore, the COVID-19 virus itself also has an affinity for the liver as both hepatic and bile duct cells express angiotensin-converting enzyme 2, an enzyme which allows the virus to invade cells.[5,6]

Although rare, there have been case reports describing AIH after COVID-19 vaccination, which we compared in Table 1. Multiple vaccine formulations have led to AIH cases, including Pfizer, Moderna, AstraZeneca, and Covishield, to name a few. Among the patients described in the literature, 64% were women; 62% were older than 50 years; and all had biopsy-proven AIH with histology showing interface lymphoplasmacytic hepatitis. Two patients had preexisting autoimmune disease, both involving the thyroid, and 2 patients were postpartum at the time of diagnosis. All patients had elevated AST and ALT (with both values $>$500 in 93% of cases) and elevated total bilirubin. 75% had elevated IgG levels, and 86% were positive for ANA, ASMA, or both. One patient in the cohort was unable to recover liver function, but all others responded well to steroid treatment and were able to taper their immunosuppression completely over the subsequent months or to the minimum dose required to prevent reactivation of disease.

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Table 1. Comparison of case reports

Case report	Patient history, laboratory values on presentation, and course								
Authors	Sex, age	Autoimmune disease history	Vaccine received	AST (U/L)	ALT (U/L)	Auto-antibody positive?	IgG level (mg/dL)	Histology	Outcomes
Vuille-Lesard et al[7]	F, 76	Hashimoto	Moderna	811	579	ANA 1:1,280, ASMA 1:1,280, anti-actin 84U, ANCA >1:1,280	3,940	Active hepatitis with interface hepatitis, plasma cells, feathery degeneration and pseudorosettes	Successfully treated with 40 mg prednisolone
Ghielmetti et al[4]	M, 63	None	Moderna	1,127	1,038	ANA 1:640, anti-gastric parietal cells antibody 1:320	1,996	Interface hepatitis, lobular and centrilobular inflammation with centrilobular necrosis without fibrosis or steatosis	Successfully treated with 40 mg prednisone
Avci and Abasiyanik[8]	F, 61	Hashimoto	Pfizer	913	455	ANA 1/100 (<1/100 negative), ASMA 1/100 (<1/100 negative)	4,260	Lymphocyte infiltration, severe portal and periportal inflammation, interface hepatitis, and mild fibrosis	Successfully treated with 20 mg prednisone
Bril et al[9]	F, 35	None, patient postpartum	Pfizer	754	2,001	ANA 1:1,280, dsDNA 1:80	1,081	Panlobular hepatitis and lymphoplasmacytic infiltrate with rosette formation and scattered hepatocyte necrosis	Successfully treated with 20 mg prednisone
Lodato et al[10]	F, 43	None	Pfizer	51	52	Negative	WNL	Portal inflammatory infiltrate and interface hepatitis with biliary injury and mild ductular proliferation	Successfully treated with 1 mg/kg/d methylprednisolone
McShane et al[11]	F, 71	None	Moderna	1,469	1,067	ASMA 1:2,560	2,177	Inflammatory cell infiltrate including eosinophils, interface hepatitis, and periportal/portal central bridging necrosis	Successfully treated with prednisolone
Rocco et al[12]	F, 80	Hashimoto	Pfizer	1,401	1,186	ANA 1:160	3,500	Interface hepatitis with a moderate degree of lymphoplasmacytic infiltrate and confluent foci of lobular necrosis	Successfully treated with 1 mg/kg/d prednisone
Londono et al[13]	F, 41	None	Moderna	993	1,312	ANA 1:80, ASMA 1:40, and anti-SLA-positive	2,080	lymphoplasmacytic infiltration, severe interface hepatitis and lobular inflammation with necroinflammatory foci, apoptotic bodies, and hepatocyte ballooning.	Successfully treated with 1 mg/kg/d prednisone
Clayton-Chubb et al[14]	M, 36	None	Oxford-AstraZeneca	633	1,744	ANA 1:160	1,280	Interface hepatitis with a lymphocytic inflammatory infiltrate without fibrosis	Successfully treated with prednisolone 60 mg
Rela, M. et al[15]	F, 38	Hypothyroid (not specified if Hashimoto)	Covishield	1,101	1,025	ANA 1:80	1,650	Multiacinar hepatic necrosis and diffuse portal and periportal neocholangiolar proliferation	Successfully treated with 30 mg prednisolone
	M, 62	None	Covishield	1,361	1,094	Negative	—	Portal central bridging necrosis and lymphoplasmacytic inflammation with mild portal fibrosis	Treatment attempted with 30 mg prednisolone and plasma exchange; however, his liver function did not recover, and he died 3 weeks into admission
Tan et al[16]	F, 56	None, patient postpartum	Moderna	1,124	1,701	ANA and ASMA-positive	3,260	Portal inflammation with interface hepatitis, lobular inflammation with plasma cell aggregates, rosette formation, and apoptotic hepatocytes	Successfully treated with budesonide
Tun et al[17]	M, 47	None	Moderna	—	1,048	ANA-positive	2,510	Widespread bridging necrosis, marked interface hepatitis, lymphoplasmacytic infiltration including eosinophils, ballooned hepatocytes, multinucleated giant cells, and emperipolesis	Successfully treated with prednisolone 40 mg
Camacho-Dominguez et al[18]	M, 79	None	AZD1222	2,003	1,994	ANA 1:80, ASMA 70 U	2,058	Focal cholestasis and lobulation of the parenchyma, marked ductular proliferation, lymphocytic infiltrate in the portal spaces with the presence of eosinophils	Successfully treated with hydrocortisone and prednisone

ALT, alanine transaminase; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; SLA, soluble liver antigen; WNL, within normal limits.

In this study, we present 1 such case of AIH after vaccination against COVID-19. A 72-year-old man with a history of well-controlled pulmonary sarcoidosis presented with scleral icterus 2 weeks after receiving his first dose of COVID-19 Pfizer vaccination. Blood work showed aminotransferase values in the 1000s. He had never been told before this that he had liver problems, which was confirmed with medical record review. He endorsed significant fatigue, stomach upset, nausea, constipation, and anorexia. He lost 11 pounds over a 2-month period.

His home medications included vitamins D3, B12, and Echinacea supplements. He was asked to stop all supplements when the jaundice began, with no improvement in transaminase values. Abdominal CT showed diminished attenuation of the liver suggesting steatosis. He was referred to our tertiary care hepatology clinic.

On physical examination, he appeared fatigued with icteric sclera. Abdominal examination was grossly unremarkable. Laboratory data on initial presentation showed white blood cell count (WBC) 6.9 K/cu mm; hemoglobin 13.8 g/dL; mean corpuscular volume 96 fL; platelets 267 K/cu mm; creatinine 1.4 mg/dL; total bilirubin 7.2 mg/dL; alkaline phosphatase 215 U/L; AST 1,177 U/L; and ALT 1,221 U/L. Follow-up laboratory test results were notable for peak values as follows: WBC 22.4 K/cu mm; AST 1,234 U/L; ALT 1,221 U/L; total bilirubin 18.6 mg/dL (direct 14.8); iron 256 ug/dL; ferritin 3,066 ng/mL; and international normalized ratio (INR) 1.1. Viral hepatitis panel showed negative hepatitis A IgM, negative hepatitis B surface antigen, negative hepatitis B core IgM, and negative hepatitis C antibody. ASMA was weakly positive (1:22), and ANA direct was positive. Antimitochondrial antibody and anti-liver kidney microsome type 1 antibody were negative; alpha-1 antitrypsin was mildly elevated at 208 mg/dL; ceruloplasmin was within normal range; and hemochromatosis gene testing was negative. Serum IgG was elevated at 3,480 mg/dL. Liver biopsy showed fulminant hepatitis with severe panlobular plasma cell-rich inflammation, extensive hepatocellular swelling, and frequent acidophil bodies. Reticulin stain showed evidence of chronic injury and fibrosis, but it was not clear whether this was true fibrosis or a result of his acute presentation. Ki-67 stain was consistent with regenerative response.

The patient was initiated on prednisone 60 mg daily. Laboratory test results after treatment initiation showed significant decrease in liver enzymes. The prednisone dose was tapered by 10 mg weekly until he reached a dose of 30 mg. His liver enzymes did not fully normalize and plateaued with an ALT of 118 IU/L and AST of 56 IU/mL. He was thus started on mycophenolate mofetil 1 g BID with complete normalization of liver enzymes over the subsequent month. He was then weaned to 500 mg BID of mycophenolate for 30 days before stopping his immunosuppressive regimen completely. He was advised to avoid further vaccination against COVID-19.

In this report, we presented the case of a 72-year-old man with onset of severe, biopsy-proven AIH just 13 days after receiving his first dose of the Pfizer COVID-19 vaccine. There is now a well-documented cohort of patients presenting with autoimmune response to the COVID-19 vaccine. What we can conclude from the literature thus far is that this response is more common in women older than 50 years without preexisting autoimmune disease, presents as type 1 AIH, and responds well to steroid treatment. At this point, AIH has been observed with most vaccination formulations. Of course, this should not deter anyone from receiving the vaccine against COVID-19, but instead give providers something to add to the differential when a patient presents with a new, unexplained hepatitis.

DISCLOSURES

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