HEPATOLOGY FORUM
doi: 10.14744/hf.2022.2022.0019

Acute liver injury and IgG4-related autoimmune pancreatitis following mRNA-based COVID-19 vaccination

Ankoor H. Patel[2], Rajan Amin[2], Alexander T. Lalos[2]

[1]*Internal Medicine, Robert Wood Johnson Medical School, Rutgers Biomedical and Health Sciences (RBHS), Rutgers University, New Brunswick, NJ, USA;*
[2]*Division of Gastroenterology and Hepatology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA*

Abstract

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disease that can affect multiple organs. Autoimmune pancreatitis type 1 is a manifestation of IgG4-RD and can often mimic tumor-like masses. Autoimmune phenomena following COVID-19 mRNA vaccination are being increasingly reported. Currently, there are no cases in which IgG4-RD involving the hepatobiliary system has been reported following the COVID-19 vaccination. We present the first case of IgG4-RD and AIP type 1 to be associated with the mRNA-based COVID-19 vaccination.

Keywords: Autoimmune pancreatitis; COVID-19; mRNA vaccine; IgG4.

Introduction

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder with multiorgan involvement that is associated with tissue infiltration of IgG4-positive plasma cells. The pathophysiology of IgG4-RD is not fully understood, but a mechanism of autoimmunity is strongly supported. Pancreatitis related to IgG4 disease is called autoimmune pancreatitis (AIP) type 1 or lymphoplasmacytic sclerosing pancreatitis. The biliary tree can also be affected by IgG4-RD with cholangiographic presentations sometimes similar to primary sclerosing cholangitis.

Autoimmune manifestations following COVID-19 vaccination are being increasingly reported. However, the question of a direct relationship between the vaccine and autoimmunity remains unclear. Masset et al. describe a patient who was diagnosed with IgG4-related nephritis following the mRNA COVID-19 vaccination.[1] However, there are no cases in which IgG4-RD involving the hepatobiliary system or AIP have been reported following COVID-19 vaccination. We report a case of a 63-year-old male who we believe developed the first case of IgG4-RD involving the pancreas (AIP type 1) shortly after receiving the mRNA-based COVID-19 vaccine.

How to cite this article: Patel AH, Amin R, Lalos AT. Acute liver injury and IgG4-related autoimmune pancreatitis following mRNA-based COVID-19 vaccination. Hepatology Forum 2022; 3(3):97–99.

Received: July 19, 2022; **Accepted:** July 26, 2022; **Available online:** September 23, 2022

Corresponding author: Ankoor H. Patel; Internal Medicine, Robert Wood Johnson Medical School, Rutgers Biomedical and Health Sciences (RBHS), Rutgers University, New Brunswick, NJ, USA
Phone: +1 908 463 8890; **e-mail:** ahp60@rwjms.rutgers.edu

Hepatology Forum - Available online at www.hepatologyforum.org

Case Report

A 63-year-old African American male was in his normal state without any significant medical issues until 2021. He had received two doses of the mRNA-based COVID-19 vaccine in March/April 2021. In June 2021, he presented with complaints of fatigue and a rapid 20 lb weight loss. At that time, he was found to be severely hyperglycemic, diagnosed with diabetes mellitus, and started on metformin. Liver enzymes were normal at that time. He denied a history of alcohol intake, illicit drug use or hepatotoxic medications, preexisting liver disease, or prior diagnosis of COVID-19. Bloodwork from 2020 showed a normal fasting blood sugar. The physical examination was unremarkable.

He was started on metformin and repaglinide, but his blood sugar remained uncontrolled. In September 2021, he was found to have liver enzyme abnormalities, and therefore repaglinide was stopped. However, he developed worsening jaundice and pruritus and was then referred to gastroenterology.

Routine blood examination revealed mild anemia, elevated transaminases (ALT 154 units/L >AST 86 units/L), and elevated alkaline phosphatase (169 units/L). Total bilirubin was 4.9 mg/dL with a direct bilirubin of 3.5 mg/dL (Table 1). Thyroid studies were normal. He was negative for hepatitis B and C. Chromogranin A, Ca 19-9, and CEA were normal. Immunoglobulin G (IgG) and IgG4 levels were elevated to 1703 mg/dL (ref. range: 600-1540 mg/dL) and 679.9 mg/dL (ref range: 4-86 mg/dL), respectively.

CT abdomen/pelvis revealed a hypervascular arterial enhancing pancreatic head mass measuring up to 5.5 cm with moderate intrahepatic biliary dilatation and mild common bile duct dilatation to the pancreatic head (Fig. 1a). Triple phase liver protocol showing a hypervascular arterial enhancing mass at the pancreatic head measuring up to 3.6 × 2.6 × 5.5 cm in the largest dimension (Fig. 1b, c). CT chest and neck did not demonstrate mass or adenopathy.

He underwent an ERCP with biliary stent placement and endoscopic ultrasound-guided pancreas biopsy. The biopsy specimen was diffusely positive for IgG4 but was “overstained” and nondiagnostic. A liver biopsy was not obtained.

AIP was suspected given the absence of malignancy on biopsy, normal Ca 19-9 and CEA levels, and the very elevated IgG4 level. He was started on prednisone 40 mg daily with a tapering schedule. Within 4 weeks, liver enzymes became normal (Table 1). At 6 weeks, his prednisone was reduced to 15 mg daily, and imaging obtained at that time showed resolution of the pancreatic mass with continued normal liver transaminases (Fig. 1d). The patient felt well and had gained 10 lb. Biliary stent removal was planned.

Table 1. Liver function panel pre- and posttreatment with steroid therapy

	Pretreatment	Posttreatment*	Reference range
AST	86	16	0–40 IU/mL
ALT	154	28	0–44 IU/mL
Alkaline phosphatase	169	100	44–121 IU/mL
Total bilirubin	4.9	0.4	0.0–1.2 mg/dL
Direct bilirubin	3.5	NA	0.0–0.4 mg/dL

*: Posttreatment: Labs drawn following 4 weeks of steroid therapy (prednisone 40 mg daily); AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

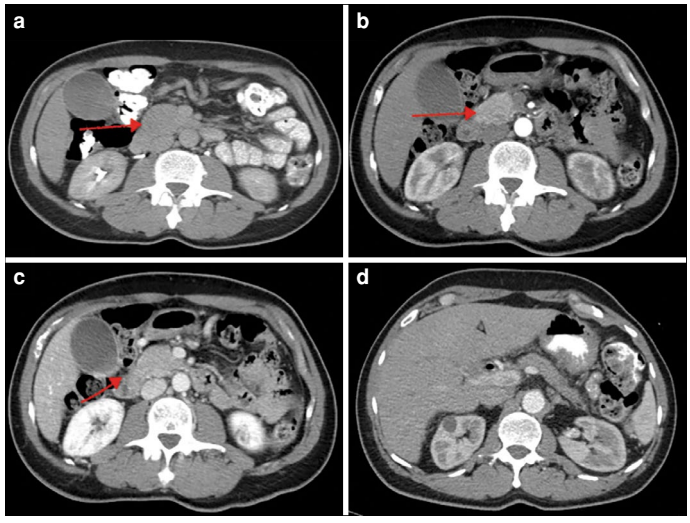

Figure 1. (a) CT abdomen/pelvis with IV/PO contrast showing increased fullness to the pancreatic head with a hypo-enhancing mass-like lesion measuring up to 3 cm. **(b, c)** CT triple phase liver showing hypervascular arterial enhancing pancreatic head mass measuring up to 3.6 X 2.6 X 5.5 cm in the largest dimensions. **(d)** Compared with prior studies (previous images), the pancreas is no longer swollen and edematous, but appears somewhat atrophic. No definite enhancing masses are seen in the head of the pancreas.

Discussion

IgG4-RD is an uncommon, systemic autoimmune disease characterized by infiltration of IgG4-expressing plasma cells into involved organs resulting in chronic inflammation and fibrosis.[2] AIP is the most common of its organ-specific manifestations. Pancreatic disease is seen in 60% of patients with IgG4-RD.[3] Patients with AIP type 1 are typically in their sixth or seventh decade and are predominantly males. The most common presentation is painless obstructive jaundice, which has been reported in up to 70% of patients with AIP.[4]

Among patients with AIP type 1, 70%-80% have elevated transaminases in a cholestatic pattern.[5] Patients will typically have significantly elevated titers of IgG (>1800 mg/dL) and its subset IgG4 (>140 mg/dL).[6] IgG4 levels greater than 140 mg/dL were 86% sensitive and 90%-96% specific for the diagnosis of AIP.[7,8] Another study showed levels greater than twofold of normal (>280 mg/dL) were only found in 1% of patients with pancreatic cancer and 53% in AIP.[9]

We believe that this case of AIP type 1 is likely a consequence of autoimmunity related to the COVID-19 vaccine. The temporal association with the vaccine could be coincidental, but the patient had completely normal blood sugar and liver tests 1 year earlier. The significantly elevated IgG4 level supports the diagnosis. The stain on the biopsy was compromised by "overstain" but was not negative. The patient developed insulin-dependent diabetes shortly after the COVID-19 vaccination. Abnormalities in endocrine function of the pancreas and diabetes mellitus are seen up to 78% in patients with AIP.[10] Finally, a complete response following initiation of prednisone therapy further supports a diagnosis of IgG4 RD. Although evidence of a therapeutic response on imaging is typically seen as early as 2 weeks, imaging after 6 weeks of therapy showed complete regression of the pancreatic mass in our patient. Response to steroid treatment in patients with a high suspicion for AIP is considered HISORt (histology, images, serology, other organs involved, response to treatment) diagnostic criteria.[11]

Several reports have highlighted an increased risk of immune diseases following mRNA-based COVID-19 vaccination.[12] Other vaccines, such as human papillomavirus, influenza, and hepatitis B, have been suspected of triggering autoimmunity through molecular mimicry.[13] In regards to hepatobiliary disease, several cases of autoimmune hepatitis were reported in association with the COVID-19 vaccine, with one case ending in fulminant liver failure requiring liver transplantation.[14,15] Interestingly, pancreatitis is a complication of COVID-19 as pancreatic cells express ACE-2 receptors, a target of the COVID-19 virus.[16] Other studies have suggested that COVID-19 infection itself could trigger autoimmunity, but this patient did not have the infection at any point, to our knowledge.

In summary, we suggest that patients who present with new-onset diabetes mellitus or cholestasis with or without signs of obstructive jaundice in the era of widespread COVID-19 vaccination should be screened for IgG4-RD.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AHP, RA, ATL; Design – AHP, RA, ATL; Supervision – AHP, RA, ATL; Fundings – AHP, RA, ATL; Materials – AHP, RA, ATL; Data Collection and/or Processing – AHP, RA, ATL; Analysis and/or Interpretation – AHP, RA, ATL; Literature Search – AHP, RA, ATL; Writing – AHP, RA, ATL; Critical Reviews – AHP, RA, ATL.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Masset C, Kervella D, Kandel-Aznar C, Fantou A, Blancho G, Hamidou M. Relapse of IgG4-related nephritis following mRNA COVID-19 vaccine. Kidney Int 2021;100(2):465-466. [CrossRef]
2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366(6):539-551. [CrossRef]
3. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, et al. IgG4-related disease: dataset of 235 consecutive patients. Medicine (Baltimore) 2015;94(15):e680. [CrossRef]
4. Lopes Vendrami C, Shin JS, Hammond NA, Kothari K, Mittal PK, Miller FH. Differentiation of focal autoimmune pancreatitis from pancreatic ductal adenocarcinoma. Abdom Radiol (NY) 2020;45(5):1371-1386. [CrossRef]

5. Brito-Zerón P, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. Autoimmun Rev 2014;13(12):1203-1210. [CrossRef]
6. Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol 2006;41(7):626-631. [CrossRef]
7. Choi EK, Kim MH, Lee TY, Kwon S, Oh HC, Hwang CY, et al. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. Pancreas 2007;35(2):156-161. [CrossRef]
8. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol 2007;102(8):1646-1653. [CrossRef]
9. Kiyama K, Yoshifuji H, Kandou T, Hosono Y, Kitagori K, Nakashima R, et al. Screening for IgG4-type anti-nuclear antibodies in IgG4-related disease. BMC Musculoskelet Disord 2015;16:129. [CrossRef]
10. Ito T, Nakamura T, Fujimori N, Niina Y, Igarashi H, Oono T, et al. Characteristics of pancreatic diabetes in patients with autoimmune pancreatitis. J Dig Dis 2011;12(3):210-216.
11. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol 2007;42(Suppl 18):39-41. [CrossRef]
12. Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology 2022;165(4):386-401. [CrossRef]
13. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol 2018;15(6):586-594. [CrossRef]
14. Efe C, Harputluoğlu M, Soylu NK, Yilmaz S. Letter to the editor: Liver transplantation following severe acute respiratory syndrome-coronavirus-2 vaccination-induced liver failure. Hepatology 2022;75(6):1669-1671. [CrossRef]
15. Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, Magro B, Friedrich Stättermayer A, Cengiz M, et al. Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. Hepatology. 2022 May 14. doi: 10.1002/hep.32572. Epub ahead of print. [CrossRef]
16. Correia de Sá T, Soares C, Rocha M. Acute pancreatitis and COVID-19: A literature review. World J Gastrointest Surg 2021;13(6):574-584. [CrossRef]