



Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

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Received: 30 January 2023 / Accepted: 27 March 2023
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Abstract

Several vaccines have been developed for coronavirus disease 2019 (COVID-19) and are used worldwide. Here we report a case of severe acute hepatitis induced by COVID-19 vaccination. A 54-year-old woman received two doses of the Pfizer-BioNTech COVID-19 mRNA vaccine and an additional dose of the Moderna COVID-19 mRNA vaccine. Seven days after the third dose, she noticed fatigue, appetite loss and dark urine. Laboratory tests were consistent with severe liver injury and jaundice. Anti-smooth muscle antibody and HLA-DR4 were positive; thus, we suspected that she had autoimmune hepatitis (AIH). Intravenous methylprednisolone followed by oral prednisolone were administered. Because remission was not achieved, we performed percutaneous liver biopsy. Histologically, pan-lobular inflammation with moderate infiltration of lymphocytes and macrophages, interface hepatitis, and rosette formation were present. We regarded these findings as confirmation of the diagnosis of AIH. As she had not responded to corticosteroids, we added azathioprine. Liver biochemistry tests gradually improved, and prednisolone could be tapered without relapse of AIH. Dozens of cases of AIH after COVID-19 vaccination have been reported. Corticosteroids were effective in most cases, but some patients have died from liver failure after vaccination. This case illustrates the efficacy of azathioprine for steroid-refractory AIH induced by COVID-19 vaccination.

Keywords Autoimmune hepatitis · Azathioprine · SARS-Cov-2 · Vaccines · Adverse drug reactions

Introduction

The viral cause of coronavirus disease 2019 (COVID-19), i.e., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by rapid mutation and transmission and has caused a global pandemic of more than 660 million cases and millions of deaths [1, 2]. Several vaccines have been developed and introduced into national vaccination programs, among which mRNA vaccines are most

widely used [3–5]. The toxicity of these vaccines is generally acceptable; however, they can sometimes induce autoimmune disorders, including autoimmune hepatitis (AIH) [6]. Herein, we present a new case of AIH after COVID-19 vaccination. Unlike reported cases [7], remission was not achieved with corticosteroids alone, but addition of azathioprine was effective. This case report was prepared according to the CARE guidelines [8].

Case report

A 54-year-old woman presented to the emergency department with fatigue, appetite loss, and dark urine. She had no past medical history other than mild hypertension, and no laboratory abnormalities had been detected by annual check-ups. She was taking no drugs, herbs, or supplements, and she drank < 20 g alcohol /day. She received two doses of the Pfizer-BioNTech COVID-19 mRNA vaccine in June 2021 and a dose of Moderna COVID-19 mRNA vaccine in February 2022. Seven days after the third dose, she noticed

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fatigue, appetite loss, and dark urine. She was afebrile, and physical examination revealed apparent jaundice. Laboratory tests were consistent with severe liver injury: bilirubin 11.1 mg/dL [normal range, 0.4–1.5], aspartate aminotransferase 2001 U/L [13–30], alanine aminotransferase (ALT) 2472 U/L [7–23], alkaline phosphatase 352 U/L [38–113], gamma-glutamyl transferase 416 U/L [9–32], albumin 4.0 g/dL [4.1–5.1], and prothrombin time-international normalized ratio 1.03 [0.9–1.1]. Serology was negative for hepatitis A, B, C and E, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. The polymerase chain reaction test for COVID-19 was also negative. Anti-smooth muscle antibody (1:40) and HLA-DR4 were positive. Anti-nuclear, anti-liver-kidney microsomal, anti-mitochondrial, and anti-neutrophil cytoplasmic antibodies were negative. The serum ceruloplasmin and immunoglobulins (Ig) levels were normal: IgG 1358 mg/dL [861–1747], IgA 216 mg/dL [93–393], and IgM 162 mg/dL [50–269]. Ultrasonography and contrast-enhanced computed tomography revealed no apparent abnormalities in the liver and biliary tracts (Fig. 1). Based on these findings, AIH was suspected.

She was admitted, and we started intravenous administration of methylprednisolone (500 mg/day, 3 days). Liver enzymes decreased initially but worsened after oral prednisolone (40 mg/day) replaced the intravenous methylprednisolone (Fig. 2). We then resumed intravenous methylprednisolone (250 mg/day, 3 days) followed by higher dose of oral prednisolone (60 mg/day). Even on these therapies, serum ALT levels exceeded 2000 U/L, so we performed percutaneous liver biopsy. Histologically, pan-lobular inflammation with moderate infiltration of lymphocytes and macrophages, interface hepatitis, and rosette formation were present (Fig. 3), whereas no fibrosis was seen. Thus, we assumed the patient had an acute onset of liver injury. These findings were consistent with previous reports of AIH induced by COVID-19 vaccines [9]. According to the revised International Autoimmune Hepatitis Group criteria [10], the patient's pre-treatment score was 16 (definite diagnosis of AIH), on the basis that there was no history of using hepatotoxic drugs. Since there had been several reports of AIH induced by COVID-19 vaccination, we suspected a causal



Fig. 1 Radiological findings. No abnormalities are present in the contrast-enhanced CT (portal phase)

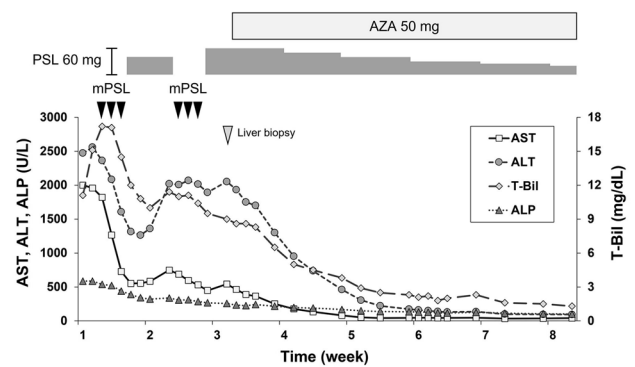


Fig. 2 Clinical course. *mPSL* methylprednisolone; *PSL* prednisolone; *AZA* azathioprine

relationship between COVID-19 vaccination and AIH. According to the DDW-Japan 2004 workshop scoring for drug-induced liver injury (DILI) [11], the score was 3 (possible diagnosis of DILI).

Because the patient had not responded to corticosteroids, we added azathioprine (50 mg/day) after verifying that she carried no risk allele in nudix hydrolase 15 gene (*NUDT15*). Liver biochemistry test then gradually improved (Fig. 2). We tapered the prednisolone dose while continuing azathioprine according to a standard treatment for AIH [12]. Liver enzymes normalized in May 2022, and prednisolone and azathioprine were discontinued in July 2022 and September

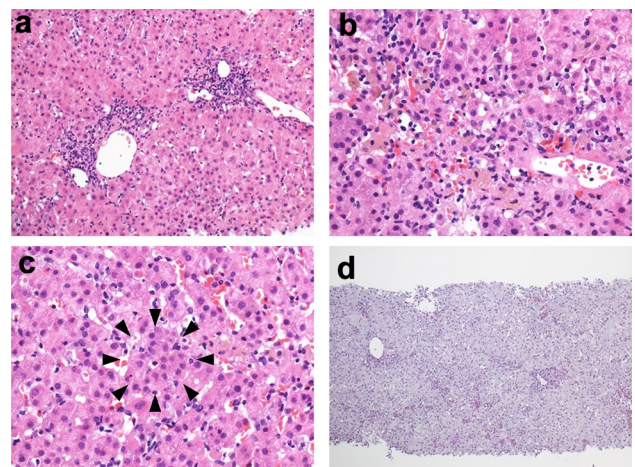


Fig. 3 Histological findings. **a** Mild infiltration of inflammatory cells with interface hepatitis are present in the periportal area. Infiltrating cells are mainly lymphocytes and macrophages. No apparent fibrosis is present (hematoxylin and eosin staining, $\times 20$). **b** Moderate inflammation is present around the central vein (hematoxylin and eosin staining, $\times 40$). **c** Rosette formation of hepatocytes is present (arrowheads) (hematoxylin and eosin staining, $\times 40$). **d** Pan-lobular infiltration of macrophages containing diastase-resistant particles are present (periodic acid-Schiff-diastase staining, $\times 10$)

2022, respectively. At the time of this writing (January 2023), no relapse of liver injury has been observed.

Discussion

Here we reported a case of severe acute hepatitis after COVID-19 vaccination. This report also first described the efficacy of azathioprine in the treatment of vaccine-induced hepatitis refractory to corticosteroid therapy. The patient's clinicopathological findings were typical for AIH, and definitive diagnosis of AIH was made according to the revised International Autoimmune Hepatitis Group criteria [10]. Her symptoms started immediately after the vaccination, and liver fibrosis was nearly absent in the liver biopsy. Thus, acute liver injury caused by COVID-19 vaccination was suspected.

Azathioprine is commonly used for treating AIH, often in combination with corticosteroids, which has been superior to either alone [13]. The American and the European guidelines recommend combination of these drugs as first-line treatment of AIH [14, 15]. In mild cases, azathioprine is often added two weeks after the initiation of corticosteroids to assess the response to steroid therapy alone and to learn the results of *NUDT15* analysis [15]. In severe cases, withholding azathioprine until cholestasis is resolved is recommended [14, 15]. On the other hand, the Japanese guidelines recommend azathioprine for cases with incomplete response, treatment intolerance, or relapse with steroid treatment [16], and its efficacy has been reported in such cases [17]. Other immunosuppressive agents, such as mycophenolate mofetil and tacrolimus, are also mentioned in the American and the European guidelines, but their use is not approved in Japan by national health insurance. Based on this background, we initially treated the patient with corticosteroids alone and added azathioprine after a poor response to steroids was established.

Bril F, et al. firstly reported a case of AIH after COVID-19 vaccine, in April 2021 [18]. Since then, dozens of similar cases have been reported worldwide. We have summarized the treatment in 39 cases of new-onset or exacerbation of liver injury after COVID-19 vaccination (Table 1); details of each case are presented in Table S1 [6, 18–55]. As first-line treatment, corticosteroids were used in 34 patients (75.6%), and they were effective in 31 patients (91.2%). In the three patients who did not improve with corticosteroid treatment, one patient recovered with N-acetylcysteine, but two died from liver failure. Azathioprine was used in ten patients as initial or maintenance therapy. In a most recent case series of 87 cases, which was not included in the table, one patient who did not respond to corticosteroids required liver transplantation [7]. Thus, we should appreciate that COVID-19 vaccine-induced hepatitis can be fatal and learn

Table 1 Summary of treatment in previous case reports ($N=45$)

Parameters	Values
Number of vaccine doses before liver injury	
One	28 (62.2%)
Two	15 (33.3%)
Three	2 (4.4%)
Type of vaccine	
Pfizer-BioNTech BNT162b2	24 (53.3%)
Moderna mRNA-1273 vaccine	12 (26.7%)
ChAdOx1 nCoV-19 vaccine	6 (13.3%)
Sinovac CoronaVac (inactivated vaccine)	2 (4.4%)
Sinopharm COVID-19 vaccine (inactivated vaccine)	1 (2.2%)
Initial therapy	
Prednisolone	22 (48.9%)
Methylprednisolone	3 (6.7%)
Budesonide	2 (4.4%)
Steroids (details not available)	2 (4.4%)
Steroids and azathioprine	2 (4.4%)
Steroids and IVIg	2 (4.4%)
Other treatment	6 (13.3%)
No treatment	5 (11.1%)
NA	1 (2.2%)
Response to initial therapy	
Present	34 (75.6%)
Absent	4 (8.9%)
NA	7 (15.6%)
Additional therapy in refractory cases	
Methylprednisolone	1 (2.2%)
N-acetylcysteine	1 (2.2%)
Plasma exchange	1 (2.2%)
None	1 (2.2%)
Additional therapy for maintenance	
Azathioprine	8 (17.8%)
Steroids (e.g., prednisolone after methylprednisolone)	5 (11.1%)
None	34 (75.6%)
NA	1 (2.2%)
Outcome	
Improved	41 (91.1%)
Death from liver failure	3 (6.7%)
NA	1 (2.2%)

IVIg intravenous immunoglobulin; NA not available

how to manage this adverse event when it is refractory to corticosteroids. Among the reports mentioned above, there was no report of the efficacy of azathioprine for corticosteroid-refractory liver injury. Our experience suggests that addition of azathioprine is a promising treatment option in cases refractory to steroid therapy. Although continuation of immunosuppressive treatment after achieving remission is recommended in the Japanese AIH guidelines [16], we finally discontinued both prednisolone and azathioprine. In

case of COVID-19 vaccine-induced hepatitis, immunosuppressive therapy can be safely discontinued in some patients, while relapse after discontinuation has been also reported [56]. Therefore, we should carefully determine whether to and when to discontinue these therapies. mRNA vaccines strongly stimulate innate immune cells and lead to production of type I interferon and other proinflammatory cytokines [57]. In addition, Boettler T, et al. showed that activation of acquired immunity could also contribute to acute hepatitis after COVID-19 vaccination [48]. Whereas molecular mimicry is most likely responsible for the activation of acquired immunity, epitope spreading or bystander activation may also be involved [6]. Heterogeneity in the degree and pathway of immune-system activation may be the reason that corticosteroids are not always effective for treatment of vaccine-induced hepatitis. It will need further discussion for the appropriate term for this phenomenon, AIH, DILI, or other terms, while it has been often dealt as AIH in past reports. Chow KW, et al. used the term “AIH-like syndrome following COVID-19 vaccination” in their systematic review, in which fulfilling the AIH criteria was not required [9].

We emphasize that our aim of this case report is not to discourage clinicians from promoting COVID-19 vaccination. According to a recent large-scale study, the risk of liver injury after COVID-19 vaccines is extremely low [58]. Therefore, we believe that the benefits of vaccination outweigh the risks of adverse effects, and vaccination to prevent spreading of COVID-19 should be promoted.

In conclusion, clinicians should be aware that COVID-19 vaccines can induce acute-onset liver injury. Azathioprine appears to be an effective treatment for steroid-refractory AIH after COVID-19 vaccination.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12328-023-01794-x>.

Acknowledgements The authors thank Dr. William R Brown, director of the International Medical Editing Service, LLC, USA, for the English language review. The authors also thank Dr. Ken Takahashi for kind advice on an earlier version of this paper.

Author contributions MU and HT contributed to the study conception and design. The patient was managed by MU, HT, RF, TK, and YM. Pathological evaluation was conducted by JI and KN. Data collection and analysis were performed by MU. The first draft of the manuscript was written by MU and HT, with advice from MM. All authors read and approved the final manuscript.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethics statement This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments. According to the protocol of the Medical Ethics Committee of Kurashiki Central Hospital, ethics review was not required.

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