Autoimmune hepatitis following influenza virus vaccination
Two case reports

Tokio Sasaki, MDa, Yuji Suzuki, MD, PhDa,*, Kazuyuki Ishida, MD, PhDb, Keisuke Kakisaka, MD, PhDc, Hiroaki Abe, MDb, Tamotsu Sugai, MD, PhDb, Yasuhiro Takikawa, MD, PhDa

Abstract

Rationale: Although immunization could possibly cause autoimmune hepatitis (AIH), to date, no cases of AIH have been reported secondarily to influenza virus vaccination. This paper describes 2 women who developed AIH after receiving influenza virus vaccination.

Patient concerns and diagnoses: Two women presented with elevation of liver enzymes after receiving influenza virus vaccination. Both patients were diagnosed with AIH using the International Autoimmune Hepatitis Group criteria.

Intervention and outcomes: Both patients were treated with prednisolone. After the initiation of prednisolone, serum aminotransferase levels were observed to return to the reference range in both patients.

Lessons: Influenza virus vaccination could trigger the development of AIH. Clinicians should be mindful of the fact that AIH can occur after influenza virus vaccination.

Abbreviations: AIH = autoimmune hepatitis, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANA = antinuclear antibody, AST = aspartate aminotransferase, GGT = gamma-glutamyl transpeptidase, IAIHG = International Autoimmune Hepatitis Group, IgG = immunoglobulin G.

Keywords: autoimmune hepatitis, influenza virus vaccine

1. Introduction

Autoimmune hepatitis (AIH) is an immune-mediated liver disorder that primarily affects women and is characterized by elevated serum transaminase levels, hyperglobulinemia, and the presence of circulating autoantibodies.[1,2] The pathogenesis of AIH is attributable to the action of an environmental agent that triggers immune-mediated reactions against hepatocytes in a genetically predisposed individual.[3] A few viruses including Epstein–Barr, varicella zoster, and hepatitis A viruses could serve as potential triggers for the development of AIH.[4–7] Additionally, a few reports have described the development of AIH associated with vaccination against the hepatitis A virus.[8–12] suggesting that immunization might possibly precipitate AIH. However, no cases of AIH have been reported following influenza virus vaccination. We report 2 cases of women in whom the influenza virus vaccine served as a trigger for the development of AIH.

2. Case report 1

A 49-year-old woman presented to her primary care physician with complaints of fever, general malaise, muscle pain in her bilateral upper arms, and arthralgia of her fingers. She had received the influenza virus vaccine for the first time in 30 years, a week prior to presentation. The vaccine included the A/New Caledonia/20/99 (H1N1), A/Wyoming/3/2003 (H3N2), and B/Shanghai/361/2002 viral strains. The patient was assessed for liver injury and referred to our hospital for further evaluation. She did not use any medication and did not report a history of alcohol abuse or of any illness including autoimmune disorders or allergies. Her physical examination was unremarkable. Initial laboratory tests revealed mildly elevated liver enzymes: aspartate aminotransferase (AST) 115 U/L (reference range 13–42 U/L), alanine aminotransferase (ALT) 61 U/L (reference range 10–64 U/L), and alkaline phosphatase (ALP) 399 U/L (reference range 106–322 U/L). Other laboratory tests including a complete blood count and serum biochemistry were unremarkable. Viral serologies for hepatitis A, B, C, and E were negative. Antinuclear antibody (ANA) was positive at a titer of 1:320, and antimitochondrial antibodies were negative. Serum immunoglobulin G (IgG) was 3453 mg/dL (reference range 861–1747 mg/dL). Considering AIH was a possible cause, a liver biopsy was
performed, and the histopathological findings showed non-specific chronic inflammation: Portal hepatitis with lymphoid follicles and mild lobular necroinflammatory activity including acidophilic bodies (Fig. 1). Based on the International Autoimmune Hepatitis Group (IAIHG) criteria,[13] the patient’s pretreatment score was 18 points (female sex +2, ALP/AST ratio +2, serum IgG > above normal +2, ANA +3, hepatitis viral markers +3, drug history +1, average alcohol intake +2, liver histology +1, other autoimmune diseases +2), which could be classified as a definitive picture of AIH. Thus, prednisolone therapy was initiated at a dose of 0.6mg/kg/day. Following the administration of prednisolone, the patient’s aminotransferase levels returned to the reference range (Table 1). The prednisolone dosage was gradually tapered to a maintenance dosage of 5mg/day, without relapse during 2 years of follow-up.

3. Case report 2

A 47-year-old woman presented to her primary care physician with complaints of upper abdominal pain and nausea. The patient had received an influenza virus vaccine for the first time in her life a month prior to presentation. The vaccine included the A/California/7/2009 (H1N1), A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013, and B/Texas/2/2013 viral strains. Owing to abnormalities observed with liver function tests, the patient was referred to our hospital for further evaluation. She did not use any medication and did not report history of alcohol abuse or of any illness including autoimmune disorders or allergies. Her physical examination showed mild upper abdominal tenderness. Initial laboratory tests revealed mildly elevated liver enzymes: AST 211 U/L, ALT 280 U/L, GGT 70 U/L, and ALP 320 U/L. Other laboratory tests including a complete blood count and serum biochemistry were unremarkable. Viral serologies for hepatitis A, B, C, and E were negative. ANA was positive at a titer of 1:320, and antimitochondrial antibodies were negative. Serum IgG was 1706 mg/dL. The patient’s IAIHG score was 13 points suggesting probable AIH. A liver biopsy was performed revealing histopathological findings that were compatible with AIH: Moderate interface hepatitis with lymphoplasmacytic infiltration and portal tract expansion secondary to fibrosis (Fig. 2) in

Table 1

| Reference range | Before treatment | 6 months after treatment |
|-----------------|------------------|--------------------------|
| AST, U/L        | 13–30            | 115                      | 19                        |
| ALT, U/L        | 20–42            | 61                       | 8                         |
| GGT, U/L        | 13–64            | 237                      | 50                        |
| ALP, U/L        | 106–322          | 399                      | 230                       |
| IgG, mg/dL      | 861–1747         | 3453                     | 1688                      |

Figure 2. A, The portal tract shows heavy lymphocytic infiltration, which extends irregularly into the adjacent tissue. B, Interface hepatitis can be observed with large numbers of lymphocytes and plasma cells (arrows).
addition to rosetting of liver cells in the liver parenchyma. Following the liver biopsy, prednisolone was initiated at a dose of 1.0 mg/kg/day, and following prednisolone therapy, the patient’s aminotransferase levels returned to reference range (Table 2). The patient’s post-treatment IAIHG score was 20 points (female sex +2, ALP/AST ratio +2, ANA +3, hepatitis viral markers +3, drug history +1, average alcohol intake +2, liver histology +5, remission +2), which could be classified as a definitive picture of AIH. The prednisolone dosage was gradually tapered to a maintenance dosage of 3 mg/day, without relapse during 2 years of follow-up.

4. Discussion

This report describes 2 women who presented with AIH after influenza virus vaccinations. In both cases, laboratory test revealed elevated IgG level and aminotransferase levels, and the presence of antinuclear antibodies, suggestive of AIH. In case 1, the histopathological findings showed chronic hepatitis with lymphocytic infiltration without any biliary changes. According to the IAIHG scoring system, the histological score corresponds to be 1 point. In case 2, the histopathological findings showed interface hepatitis, lymphoplasmacytic infiltration, and rosetting of liver cells, which are typical histological features of AIH, corresponding to be 5 points. Both patients were classified as having definite AIH according to the IAIHG scoring system. As the antinuclear antibody was positive, both cases were classified as AIH type 1. Both patients showed an improvement in their liver abnormalities following the initiation of prednisolone therapy. The maintenance prednisolone dosage (5 mg/day) did not significantly differ between the 2 patients.

Several pathogens are known to play a role in the development of AIH. Reported, Epstein–Barr, varicella zoster, and hepatitis A viruses are known triggers for AIH. Of note, a few reports have described the development of AIH associated with vaccination against the hepatitis A virus. Reports suggest that immunization as well as viral infection might precipitate AIH. However, the risk factors of AIH after vaccination have not been elucidated. In both patients described in this report, viral infection did not serve as a trigger for the development of AIH. Moreover, neither patient reported any history of vaccination other than the influenza virus vaccine. A few drugs such as nitrofurantoin and minocycline have been reported to cause AIH. However, both patients reported in this paper did not use any medications until the appearance of subjective symptoms. Previous reports that have described the development of post-vaccination AIH have reported that AIH was known to develop between a week and a month after vaccination. Our observations were in agreement with these reports in that the duration between the administration of the influenza virus vaccine and the onset of AIH was 1 week and 1 month in Case 1 and 2, respectively. Thus, the influenza virus vaccine was presumed to be the trigger for the development of AIH in both cases presented in this report. Five previous case reports have described the development of AIH in patients after vaccination with the hepatitis A virus vaccine, however, a MEDLINE search that examined English-language studies did not reveal any report that has described the development of AIH in patients after influenza virus vaccination. No diagnostic criteria or treatment strategy specialized for AIH induced by virus vaccination has been established. Therefore, in clinical practice, we can only refer to the existing diagnostic criteria and treatment strategy.

Previous reports have demonstrated that influenza vaccination may trigger or exacerbate symptoms of a few autoimmune diseases such as Guillain–Barre syndrome, multiple sclerosis, and myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis. Although a causal link cannot be definitively established between influenza virus vaccination and the development of AIH, because immunization might be a possible cause of other autoimmune diseases, it is reasonable to hypothesize that influenza virus vaccination could trigger the development of AIH.

Influenza virus vaccination is considered safe in patients with chronic liver disease. Although influenza virus vaccination rarely triggers the development of AIH, it is necessary to obtain further data regarding confirmed cases of AIH associated with influenza virus vaccination. In conclusion, clinicians should remain mindful of the fact that AIH can occur after influenza virus vaccination.

Author contributions

Conceptualization: Yuji Suzuki, Yasuhiro Takikawa.
Funding acquisition: Tokio Sasaki, Yuji Suzuki.
Investigation: Yuji Suzuki, Kazuyuki Ishida.
Resources: Yuji Suzuki.
Writing – original draft: Tokio Sasaki, Yuji Suzuki, Kazuyuki Ishida, Keisuke Kakisaka, Hiroaki Abe.
Writing – review & editing: Tamotsu Sugai, Yasuhiro Takikawa.

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