Autoimmune Hepatitis after AstraZeneca Coronavirus Disease 2019 (COVID-19) vaccine: need for epidemiological study

Hepatitis Autoinmune tras vacunación con la vacuna AstraZeneca contra la COVID-19: necesidad de un estudio epidemiologico

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ABSTRACT

This case-report and brief review of literature were written concerning autoimmune hepatitis potentially triggered by virus vaccines. Soon after the Astrazeneca COVID-19 vaccine, a 70-year-old women presented with jaundice and nausea, with significant hepatic injury (aspartate aminotransferase (AST) 746 U/L; hyperbilirubinemia 9,30 mg/dL (conjugated bilirubin 7,14 mg/dL), elevated immunoglobulin (Ig)G and antinuclear, anti-smooth muscle and anti-actin F antibodies were detected. Considering autoimmune hepatitis (AIH) as a possible cause, a liver biopsy was performed and compatible with AIH. Prednisolone therapy was initiated, with optimal response. This report suggests that immunization against COVID-19 might precipitate or induce AIH. Further data regarding confirmed cases of AIH are mandatory in order to establish a causal link. Therefore, long-term pharmacovigilance surveillance of large cohorts of patients is needed.

Keywords: autoimmune hepatits, SARS-CoV-2, COVID-19 vaccines.

INTRODUCTION

Autoimmune hepatitis (AIH) is a persistent inflammatory disorder which directly affects the liver[1–3]. Clinical presentation is highly variable[3] and the diagnosis is based on clinical, laboratory and histological features[1–3], by using score-systems, such as revised International Autoimmune Hepatitis Group (IAIHG) criteria[4]. The prompt improvement after initiation of corticotherapy confirms the diagnosis of AIH.

No diagnostic criteria or treatment strategy for AIH induced by vaccination have been established, thus diagnosis must be based on the existent state-of-art evidence as in the presented case.

CASE DESCRIPTION

A 70-year-old woman presented to the emergency room of a tertiary-care hospital with jaundice, anorexia and nausea beginning within 72h, without other symptoms, history of drug intake or recent medication changes. She received the first dose of AstraZeneca COVID-19 vaccine 5 days prior to hospital admission. Her physical exam was unremarkable, except for jaundice and tenderness in the upper abdominal regions. Complete blood count was unremarkable, but serum biochemistry revealed aspartate aminotransferase 746 U/L (reference range (RR): 10-30 U/L), alanine aminotransferase (ALT) 682 U/L (RR: 10-36 U/L), gamma-glutamyl transpeptidase 473 U/L (RR: 6-39 U/L), and alkaline phosphatase (ALP) 353 U/L (RR: 35-104 U/L); also total hyperbilirubinemia 9,30 mg/dL (RR: 0.20-1.00mg/dl), conjugated bilirubin 7,14 mg/dL (RR: 0.00-0.30mg/dl) and prolonged partial thromboplastin time (47,2 seconds). An abdominal ultrasound showed no signs of acute disease and computed tomography showed hepatic steatosis, but no stricture nor dilation of the biliary tracts. A predominant hepatocellular hepatitis was assumed and she was admitted to a general medical ward for further investigation: serologic tests for hepatitis A, B, C, D and E, Epstein Barr virus (EBV), Cytomegalovirus were negative; Wilson's disease and toxoplasmosis were also ruled out. Immunology tests revealed elevated immunoglobulin (Ig) G (2486,0 mg/dL; RR: 793,0-1590,0) and positive antinuclear (1:320; RR < 1:160), anti-smooth muscle (1:640; RR < 1:40) and anti-actin F (47,8U/mL; RR > 20U/mL) antibodies. In the first 48h, she developed acute liver failure, with a maximum Model for End-Stage Liver Disease score of 20. Considering AIH as a possible cause, a liver biopsy was performed and the histopathology revealed cholestatic hepatitis with intralobular canalicular cholestasis, interface hepatitis with necroinflammatory activity and ductular reaction, and expansion of portal tracts by a polymorphic inflammatory infiltrate with abundant neutrophils. Based on the revised IAIHG criteria[1], the pre-treatment score was 18 points, which correlates with definite AIH (ALP:ALT ratio < 1.5; IgG 1.56 times above upper limit of normality, high titres of antinuclear antibodies and negative anti-mitochondrial antibodies; no hepatitis viral markers nor use of hepatotoxic drugs, liver histology with interface hepatitis and no other specific changes).

An immune-mediated hepatitis possibly secondary to the first dose of AstraZeneca vaccine was assumed and prednisolone (0.5 mg/kg/day) therapy was initiated; afterwards, clinical and laboratory findings improved significantly and she was discharged, under close follow-up. Prednisolone was gradually tapered, without clinical nor laboratory relapse until the present day.

DISCUSSION

This case-report describes a woman who developed AIH after AstraZeneca COVID-19 vaccination. AIH is a persistent inflammatory disorder which directly affects the liver, more commonly in women[1–3]. Due to clinical heterogeneity, diagnosis also relies on laboratory and histological features[1–3]. Laboratory tests were highly suggestive of AIH, revealing elevated IgG and aminotransferase levels and presence of antinuclear antibodies. The histopathological pattern of cholestatic hepatitis has several etiologies (in

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Table 1. Laboratory tests at hospital admission and discharge and in ambulatory re-evaluation after hospitalization. Abbreviations: Alb, serum albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DBil, direct bilirubin; GGT, gamma-glutamil transferase; INR, international normalized ratio; TBil, total bilirubin.

Laboratory test	Admission	Before Discharge	Ambulatory Revaluation
AST (U/L)	746	82	21
ALT (U/L)	682	120	21
ALP (U/L)	353	289	141
GGT (U/L)	473	257	65
TBil (mg/dl)	9,30	6,41	1,07
DBil (mg/dl)	7,14	3,37	0,37
INR	1,41	1,42	1,35
Alb (g/dl)	2,81	3,20	4,61

this case scoring 3 points, according to IAIHG score-system). The sample was immunohistochemically negative for Hepatitis B and C viruses, EBV and Cytomegalovirus; rodanin coloration did not show alterations, excluding Wilson's disease. The prompt improvement in liver parameters following initiation of corticotherapy confirmed the diagnosis of AIH.

Multiple factors contribute to the development of AIH, from infections to an impaired immunoregulatory system[3]. According to previous reports, several pathogens, including EBV, Hepatitis A, B and C viruses can induce AIH[2,3]. There are also reports of AIH induced by Hepatitis A and Influenza virus vaccination[2,3,5]. Molecular mimicry and bystander activation of dormant autoreactive T-helper cells have been nominated as potential mechanisms[6]. COVID-19 has also been associated with the development of autoimmune disorders[6], with at least one case of AIH described by Hong J. et al ([7]). To our knowledge, most of the reported cases of AIH induced by COVID-19 vaccination are related to mRNA-1273 vaccines, such as Pfizer or Moderna vaccines[8,9]. This case-report suggests that COVID-19 immunization based on viral vector may also precipitate or induce AIH.

In our patient, AIH was not triggered by a hepatotoxic virus infection nor drug-induced liver injury. Symptoms started 72h after the first inoculation with the AstraZeneca COVID-19 vaccine. Previous publications stated that the lag-time between vaccination and the onset of symptoms can range from a week to a month after vaccination[2,3]. Our observation is not in agreement with those reports because the latency period was relatively brief, which might question the association between the potential trigger and the autoimmune process. However, brief latency periods after vaccination have been previously described[8,9]. Moreover, and until the present time, as all of COVID-19 vaccines are recent, it is yet not feasible to perform an in-vitro provocation test, to establish a causal link between AstraZeneca vaccine and the development of AIH. Therefore, remains the question whether the vaccine was a direct trigger of an immune injury process or if it awakened a dormant pre-existent and undiagnosed AIH.

CONCLUSIONS

As immunization might be a possible cause of other autoimmune diseases, it is acceptable to hypothesize that COVID-19 vaccine could trigger the development of AIH/hepatotoxic phenomena. COVID-19 vaccination is considered safe and effective[10] and whether there is a causal association with the development of AIH remains to be determined. We have no intention of discouraging the prescription of COVID-19 vaccination, but to shed light over potential serious side effects. Further data regarding confirmed cases of AIH are mandatory in order to establish a causal link. Therefore, long-term pharmacovigilance of large cohorts of patients is needed to detect autoimmune and other rare adverse events of vaccination[5].

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

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