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Auto-immune hepatitis following COVID vaccination

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ABSTRACT

Unprecedented loss of life due to the COVID pandemic has necessitated the development of several vaccines in record time. Most of these vaccines have received approval without being extensively whetted for their adverse effect and efficacy profiles. Most adverse effects have been mild, nonetheless, more serious thromboembolic events have also been reported. Autoimmune hepatitis (AIH) can occur in predisposed individuals where an immune mediated reaction against hepatocytes is triggered by environmental factors. Vaccines are a very rare cause of AIH. We report two such cases of AIH triggered by COVID (Covishield) vaccination. While one patient made an uneventful recovery, another succumbed to the liver disease. Ours is the first report of Covishield vaccination related AIH and second ever after any form of COVID vaccination. We hope that our report does not deter COVID vaccination drives. However, we also hope to raise awareness of its potential side effects and the increased role of pharmacovigilance in guiding treatment.

1. Introduction

As the COVID pandemic continues unabated, vaccines remain the only proven defence against this contagion. Vaccines usually take up to a decade to develop. However, the rapidity with which this pandemic has spread around the world causing unprecedented loss of life and the resultant socio-economic impact has necessitated the development of several vaccines in record time [1]. Many of these COVID vaccines quite rightly have received 'emergency' approval for mass vaccination programs without large clinical trials. The reported adverse reactions have predominantly been local injection site reaction and mild systemic events like fever and myalgia [2,3]. Nonetheless, there have also been more serious side effects in the form of thromboembolic events in vaccinated individuals, the cause of which though not full elucidated is purported to be an autoimmune phenomenon [3]. Moreover, due to its molecular mimicry, the antibodies against the severe acute respiratory syndrome coronavirus 2's (SARS-CoV-2) spike protein have affinity for several tissue proteins in the human body and are associated with autoimmune phenomena [4].

Autoimmune hepatitis (AIH) is one such pathology where in predisposed individuals an immune mediated reaction against hepatocytes is triggered by environmental factors [5]. While AIH triggered by viruses has been well reported, AIH after vaccination though described previously, is extremely rare [6,7]. We present two such cases where the Covishield (ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford–AstraZeneca produced Serum Institute of India, India) vaccination showed a temporal correlation and hence, most likely acted as trigger for the development of AIH.

Case-Report 1: A 38-year-old female healthcare worker was admitted with deep jaundice 20 days following administration of the Covishield vaccine. She was apparently well until a week after the vaccination, when she started developing symptoms of fever with fatigue. She was on medication (Levothyroxine) for hypothyroidism for the past 8 years, and had previously been extensively evaluated for the same. An autoimmune etiology was not ascertained as the cause for her hypothyroidism. She had no other comorbidity and gave no history of natural infection with SARS-CoV-2. Apart from medication for hypothyroidism she was not on any other medication. There was no history of alcohol consumption or alternative medication intake. Her symptoms persisted and she noticed pedal edema and her urine turned dark. Her liver function tests at 2 weeks' post-vaccination showed a total bilirubin of 2.86 mg/dL (N: 0.3–1.3 mg/dL), with Alanine transaminase (ALT) of 1025 IU/L (N: 5–40 IU/L) and Aspartate transaminase (AST) of 1101 IU/L (N: 5–40 IU/L).

When the patient presented to the hospital, her liver function tests despite a decreasing trend of the enzymes, showed an elevated total

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bilirubin of 14.9 mg/dL and INR of 2.96. She remained hemodynamically stable with no other signs of decompensation. Tests for Hepatitis A (HAV) (IgM), & Hepatitis E (HEV) (IgM), Hepatitis B (HBV) (Surface antigen) and Hepatitis C (HCV) were negative. ANA was tested using the immunofluorescence assay (IFA) method and had a speckled pattern. Anti-nuclear antibody (ANA) and IgG were mildly elevated (1:80 & 16.5 gm/L respectively). Other autoimmune markers including anti-neutrophil cytoplasmic antibodies (ANCA), anti-soluble liver antigen (SLA) antibodies, smooth muscle antibody (SMA), liver kidney microsome type 1 (LKM-1) antibodies were negative. Her anti-SARS-CoV2 spike protein antibody titres were raised (149.2 U/mL). Her ceruloplasmin and urinary copper levels were normal. Imaging in the form of a contrast enhanced CT scan was unremarkable and blood and urine cultures were negative. A transjugular liver biopsy was done which showed multiacinar hepatic necrosis and diffuse portal/periportal neocholangiolar proliferation (Fig. 1A). Inflammation comprising of lymphocytes, plasma cells and rare eosinophils were also noted (Fig. 1B). Sinusoidal pigment laden histiocytes and central venulitis were noted, and suggestive of AIH. Based on the clinical features, ANA positivity and liver biopsy findings, with a probable diagnosis of AIH (Modified AIH criteria = 15; Hennes score = 6) she was commenced on steroids (30 mg/day of prednisolone) as per the standard AIH treatment protocol [8]. Her liver function tests improved over the next week and she was discharged home on a tapering dose of prednisolone (30 mg/day for 4 weeks followed by a gradual taper of 5 mg every 4 weeks over 6 months) as per the prescribed AIH treatment guidelines [8]. She remains well on 1-month follow-up with normal liver function tests (total bilirubin 0.9 mg/dL. AST: 28 IU/L, ALT 24 IU/L).

Case-Report 2: A 62-year-old diabetic male presented with fever, anorexia and jaundice of 3 days' duration. He had been vaccinated with Covishield 16 days prior to his admission. He gave no history of drug or native medication intake. His past history was remarkable for two episodes of jaundice in the past decade which had resolved with native medication. At admission, his liver function tests were elevated with a total bilirubin of 19.2 mg/dL (direct 10.2 mg/dL), AST of 1361 IU/L and ALT of 1094 IU/L. Imaging in the form of a contrast enhanced CT scan was unremarkable apart from an enlarged liver and minimal interbowel free fluid. Tests for HAV (IgM), & HEV (IgM), and HCV were negative. Though he was HBV core-antibody positive, his HBV surface antigen and DNA (quantification) were negative. His autoimmune work-up panel (ANA, ANCA, SMA, LKM-1), was also negative. His anti-SARS-CoV2 spike protein antibody titres were elevated (167.5 U/mL). The patient developed altered sensorium over the next few days. Three days following the admission, his total bilirubin increased to 25.6 mg/dL (direct:14.1 mg/dL), while the enzymes showed a decreasing trend (AST: 548 IU/L and ALT: 607 IU/L. Furthermore, his INR progressively worsened to a peak of 4.08.

He underwent a *trans*-jugular liver biopsy which demonstrated porto-central bridging necrosis (Fig. 1C). There was portal/periportal neocholangiolar proliferation and mild to moderate inflammation comprising of lymphocytes along with plasma cells, eosinophils and polymorphs. Focal rosetting and emperipolesis was noted. Patchy hepatocanalicular bilirubinostasis and central venulitis were identified. There was mild portal fibrosis (Ishak stage 2/6) (Fig. 1D). A likely diagnosis of AIH was made. He was started on steroids (prednisolone 30 mg/day), despite which there was only a transient improvement in his liver function tests (total bilirubin:18.6 mg/dL). Further, he underwent 5 cycles of therapeutic plasma exchange. Nonetheless, he remained cholestatic (total bilirubin: 14.6 mg/dL) and his INR remained elevated with a peak of 6.7. Given the above clinical picture he

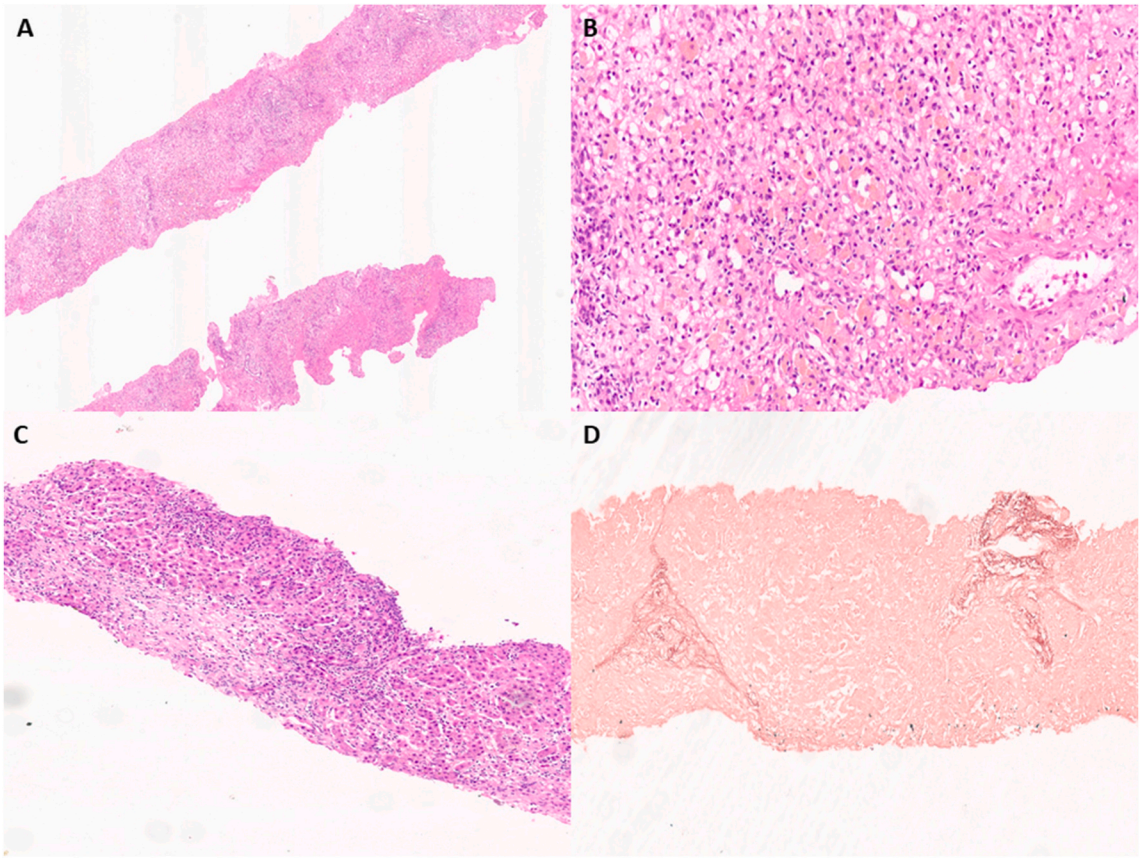

Fig. 1. First patient's liver biopsy showing multiacinar hepatic necrosis and periportal neocholangiolar proliferation (A, H&E, 2.5x). First patient's liver biopsy demonstrating lymphoplasmacytic inflammation and pigment laden macrophages (B, H&E, 15x). Second patient's liver biopsy showing porto-central bridging necrosis (C, H&E, 7.5x). Second patient's liver biopsy with mild portal fibrosis (D, Orcein, 10x).

was offered liver transplantation. However, due to socio-economic constraints the patient and his family declined the offer. Following a protracted course of supportive therapy, the patient died three weeks following the admission.

2. Discussion

Autoimmune reactions after vaccination are rare and occur in less than 0.01% of all those who are vaccinated [5–7]. Nonetheless, there could be an under-reporting bias as most cases are likely to be mild or asymptomatic. These reactions are due to an immune intolerance to self-antigens combined with a failure of intrinsic homeostatic systems that prevent a promiscuous immune response to these antigens. Purported mechanisms for this reaction include molecular mimicry between the antigenic determinants of the vaccine and human proteins, leading to autoantibody formation. Other theories include, immune complex formations effecting a T lymphocyte imbalance and a bystander activation as a result of an exuberant innate immune response to the adjuvants added to most vaccines [5–7].

Most previous reports involve the influenza vaccine. Apart from AIH, other autoimmune disease like Guillain–Barre syndrome and multiple sclerosis have also been reported with it [5–7]. Similarly, COVID vaccinations have been implicated in several thromboembolic events, labelled as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). These vaccine-induced antibodies cause platelet activation, resulting in thrombosis and consequently thrombocytopenia akin to idiopathic thrombocytopenic purpura or heparin-induced thrombocytopenia [9].

There is a recent report of AIH associated with an mRNA COVID-19 vaccine (Pfizer-BioNTech) [10]. This was a 35-year-old postpartum woman who developed symptoms including choluria 6 days following the mRNA vaccine administration, her peak bilirubin was 4.8 mg/dL and she had an uneventful recovery with steroids. There were however, several atypical features regarding this patent's presentation including low immunoglobulin levels, presence of eosinophils on liver histology, more commonly seen in drug induced liver injury and that the interval between vaccination and disease onset was remarkably short, raising concerns that the association could indeed be coincidental [11]. Our first patient too had a relatively short interval of 7 days between vaccination and onset of symptoms (fever), however jaundice was noticed only in the second week. She had a relatively uneventful course, with a recovery following a course of steroids. There was a history of hypothyroidism in this patient, which had previously been evaluated and deemed not to be of autoimmune etiology. The second patient on the other hand, was older, with a possibility of pre-existing liver disease. He had a more protracted course and died despite supportive therapy and steroids.

Covishield is a viral vector vaccine using a modified chimpanzee adenovirus ChAdOx1, and to the best of our knowledge, ours is the first report of Covishield vaccine induced AIH. Although an objective causality cannot be proven, the temporal correlation of both these patients raise concerns of a strong link between the vaccine and AIH. In the second patient, there could also be an element of reactivation of a subclinical liver disease due to the immune boost provided by the vaccine. This insult most likely upset the tenuous balance the liver was in. Given that he fulfilled the King's college criteria for urgent liver transplantation he was offered supra-urgent listing, which he declined.

We concede that there were no clear clinical or biochemical features apart from a chronological association to differentiate our patients' vaccine-related AIH from idiopathic AIH. Nevertheless, we surmise that the COVID vaccine served as a trigger for AIH in our patients. We hope that our report does not deter COVID vaccination drives. However, we also hope to raise awareness of its potential side effects and the increased role of pharmacovigilance in guiding treatment. Only large, multicentre, longitudinal studies enrolling patients from across the globe can truly validate the findings of our report. In the meantime, it is important to continue therapy ensuring that the benefits still outweigh the risks.

Author contributions

Dr.Ashwin Rammohan, Dr. Akila Rajakumar & Dr. Mukul Vij contributed to conception and design. Dr. Ashwin Rammohan, Dr. Dinesh Jothimani & Prof. Mohamed Rela contributed to the acquisition, analysis and interpretation of data, drafted the article and revised it critically for important intellectual content. Prof. Mohamed Rela gave the final approval of the version to be published.

Declaration of competing interest

The above doctor has no conflicts of interest or financial ties to disclose.

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