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REACTIVATION OF HEPATITIS B VIRUS AFTER COVID-19 VACCINATION.

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ABSTRACT

This case presents a possible vaccine adverse event of reactivation (recurrence) of a dormant hepatitis B infection in a young female patient reported after administering the first dose of Pfizer-BioNTech COVID-19 vaccine. This case aims to explore a potential adverse reaction of COVID-19 mRNA vaccine which can reboot the inactive viruses, in this case of hepatitis B infection, due to immunomodulation leading to decreased alloreactivity after vaccination, as no other trigger or cause was found. A young female with history of inactive hepatitis B infection was admitted in the emergency ward of our Hospital with vomiting, fever, and jaundice after receiving the first dose of Pfizer-BioNTech (NY, NY, USA & Mainz, GY) COVID-19 vaccine. Her blood tests confirmed the resurgence of the acute hepatitis B virus infection and accordingly treated with antiviral Tenofovir and other appropriate supportive management. After clinical improvement and regression of liver function test, she was discharged from the hospital.

KEY WORDS: Hepatitis B Infection, COVID-19 Vaccine, COVID-19, Reactivation.

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INTRODUCTION

Since the outbreak of the current pandemic, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the last quarter of 2019, epidemiologists hoped to achieve herd immunity via mass inoculation or infections of 55 to 82% of the population, in order to contain the spread of the pandemic and normalize life to pre-pandemic levels. To achieve this mammoth goal, mass vaccination of billions of the global population would be the only way forward, as the virus has continuously been mutating and resulting in more virulent and infectious variants.

The United Arab Emirates (UAE) approved the COVID-19 vaccine for its population more than 7 months ago. Since that time, 16.9 million doses were administered with more than 55,000 doses being given in a single day: the vaccine has been a breakthrough and probably the most effective way forward to curb the current pandemic. The fast-paced development of COVID-19 vaccine and its emergency authorisation has raised some safety concerns. These concerns are confounded by misinformation campaigns on social media, which seems like a major factor in inertia among certain segments of the population. However, production capacity, supply chain, and logistic constraints are also contributing to inequitable access of effective vaccines to many developing countries. Active reporting, monitoring, and profiling of adverse vaccine events and side effects would help minimise safety concerns and stem conspiracy theories. As these vaccines have been developed and authorised for emergency use due to the extraordinary pandemic situation and exigencies, the medical community and associated experts are streamlining mechanisms to report and analyse the vaccine's adverse events. Recent reports of blood clots attributed to AstraZeneca's (Cambridge, UK) Covid-19 vaccine raised legitimate concerns about their safety. Complete safety profiles of all COVID-19 vaccines, including Pfizer-BioNTech mRNA vaccine, are not yet fully known in those with certain comorbidities and coexisting medical conditions. The introduction of two messenger RNA vaccines [1,2] were a significant milestone in medical science, as they will open new avenues in treating other medical conditions as well. An open, effective, and transparent vaccine adverse event reporting system (VAERS) will enhance vaccines' safety profile and help speed up the drive to dispel

misinformation and conspiracy theories for the COVID-19 vaccine.

CASE PRESENTATION

A healthy 29-year-old expatriate woman approached the emergency department of our Hospital, with a 3-week history of vomiting, loss of appetite, and acute onset of dizziness. Symptoms were associated with passing dark-coloured urine, with a yellowish discoloration of the skin for 3 days. Her history reports having received the first dose of the Pfizer-BioNTech (NY, NY, USA & Mainz, GY) COVID-19 vaccine 18 days prior to symptom onset. She contracted COVID 3 months prior to vaccination, with an uneventful recovery despite no antiviral treatment. The patient reported that she had inactive hepatitis B, which was revealed during a routine medical checkup in her home country 15 years ago. However, she denied any history of symptoms or treatment. She also gave a history of hepatitis B in her father and paternal uncles. There is no other relevant medical history, no recent travel, no contact with sick patients, and no history of illicit drugs. She reports drinking alcohol occasionally. She has a stable relationship with her male partner for many years. Multiple tattoos were noted on different parts of her body, which she said were done around 5 years ago.

On examination, the patient was found to be a healthy-looking female: conscious, alert, and oriented to person, place, and time. In the ER, she was febrile (temperature 38ºC) and tachycardic, with a heart rate of 109 beats/minute. She was otherwise stable and maintained oxygen saturation with room air. Abdominal examination did not reveal any significant findings. All other examinations were unremarkable, except for mild jaundice of the skin and Icteric sclera. Initial blood tests showed an abnormal liver panel with total bilirubin of 9.7 mg/dL, alkaline phosphatase of 136 U/L, SGPT of 1,156 U/L, SGOT of 1,893 U/L, and Gamma GT of 136. Her INR was 1.53, hepatitis B surface antigen was reactive, and hepatitis B surface antibody was 0.00 mIU/ml. Hepatitis B DNA quantitative PCR was 3,210 IU/ml. with lactate 5.1 mmol/L, procalcitonin 1.03 ng/mL, and C-reactive protein 9.8 mg/L. Routine urine revealed 3+ bilirubin, 1+ protein, and 1+ ketones with WBCs of 30-35. Venous blood gas showed mild respiratory alkalosis with a pH of 7.455 and a decreased pCO2 of 32. Further testing for other viral markers revealed hepatitis BE Antigen positive, while the BE antibody was nonreactive. IgG and IgA were elevated at 18.82 g/L and 4.69 g/L, respectively, HIV serology and tests for other possible causes of hepatitis were also done and reported negative. (Table 1)

Table 1:

Hepatitis A *IgM*	***Non-reative***
Hepatitis D virus	***Negative***
Hepatitis E virus IgG & IgM antibodies	***Negative***
Hepatitis BE Antibodies	***Non- reactive***
Epstein Bar Virus DNA PCR	***Negative***
Cytomegalovirus DNA PCR	***Negative***
Anti Liver-Kidney Microsomal IgG	***Negative***
Smooth muscle antibodies	***Negative <1/40***
Anti-microcondrial M2 Antibodies	***4 RU/ml***
Ceruloplasmin Level	***0.12 g/L***
Anti-Tissue transglutaminase IgG & IgA antibodies	***Negative***
HIV antibody	***Negative***

Table 2: Serial Biochemistry.

Blood Test	Reference Range	09/05/2021	11/05/2021	13/05/2021	15/05/2021
Hemoglobin	12 – 15 g/dL	15	13.5	13.9	12.1
WBC	3.6 - 11 10^3/µL	8.9	9.2	8.1	4.9
Platelets	150 – 410 10^3 /µL	229	172	149	158
Total bilirubin	0 – 1.2 mg/dL	9.7	11.3	10.8	9.5
ALP	35 – 104 U/L	136	127	114	114

SGPT/ ALT	0 – 31 U/L	1156	1528	1689	683
AST / SGOT	0-32 U/L	1893	3189	3464	1301
INR	0.8 – 1.1	1.53	1.94	1.65	1.34
PT	9.7 – 11.4 secs	15.6	19.3	16.6	13.7
Lactate	0.5 – 2.2 mmol/L	5.1	3.5	5.2	2

An abdominal ultrasound demonstrated an average-sized liver with bright echo texture. There were no abnormalities seen in the gall bladder, biliary tree, spleen, and pancreas. Given acute hepatitis, she started on the antiviral tenofovir, 300 mg once daily, with supportive management. As per gastroenterology team advice, she received 2 doses of IV vitamin K 10 mg daily, thiamine 100 mg, N-acetyl cysteine infusion as per protocol, and lactulose once daily. Her progress was monitored with daily liver function tests (Table 2) and she was watched for signs of deterioration or fulminant hepatic failure. Her clinical and biochemical condition improved

OUTCOME AND FOLLOW-UP

Patient was monitored closely, as the liver transplant team was alerted in case she developed unstable liver failure. She received N-acetyl cysteine and antiviral tenofavir on recommendation of the hepatology team. Her condition improved progressively, so she was discharged with advice to continue tenofavir for 6 months and to schedule a hepatology appointment in about 2 months.

DISCUSSION

A history of the vaccine goes back 400 years; Edward Jenner is considered a pioneer of modern vaccines, which are the most powerful armaments with antibiotics to fight infectious diseases. In fact, diseases like small pox were eradicated by mass vaccination campaigns, while polio is on the verge of eradication. Most initial vaccines were developed empirically, with very little immunological insight.[3] Adverse events following immunization (AEFI)[4] appear often, but are still rare and unlikely to be recognised in pre-licensure clinical trials. The vaccine adverse event reporting system (VAERS) was developed globally to establish a causal association between individual vaccines and AEFI.[5]

Currently, several vaccines against SARS CoV-2 are authorised on an emergency basis, around the world, most produced by conventional methods. However, two of them: BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna, Cambridge, MA, USA) COVID-19 vaccines were developed by modern cutting-edge mRNA technology, which encodes SARS-CoV-2 spike (S) protein. Due to the urgency to curb the current pandemic, these vaccines were developed at an unprecedented pace. Hence, we still do not know many of the adverse interactions or side effects of these vaccines.

Prelaunch efficacy and safety phase 3 trials of BNT162b2 and mRNA-1273 COVID-19 vaccine demonstrated efficacy > 94% for both vaccines, and an excellent safety profile.[6,7] In terms of adverse effects, all studies reported mild local and fewer nonfatal systemic self-limiting side effects. Local adverse effects reported were injection site pain (84.1-92%), swelling (10.5-70%), and erythema (9.5-14.6%). Systemic adverse effects of major concern were anaphylaxis in susceptible individuals; however, only two cases were linked to COVID-19 vaccine, as it is extremely rare. Other systemic effects reported were headache (55.1-64.7%), fatigue (62.9-70%), myalgia (38.3-61.5%), fever (14.2-15.5%), chills (31.9-45.4%), nausea/vomiting (1.1-23.0%), and arthralgia (23.6-46.4%).[3.]

Inactivated vaccines, such as influenza, hepatitis A, Japanese encephalitis, and rabies have been incriminating in the resurfacing of silent infections. Recently, few studies reported reactivation of Herpes simplex or Herpes zoster viruses after receiving inactivated COVID-19 vaccines.[8]

COVID-19 mRNA vaccine is a novel experience for everyone, establishing a link between mRNA vaccine and reactivation of hepatitis B infection, which is still elusive to many in the medical field.

That said, many studies reported activation of HBV in carriers of HBV (undetectable blood HBV load and negative Hbe Ag) or aggravation of liver injury with SARS-CoV infection.[9] One UAE study reported the first case of COVID-19-induced reactivation of hepatitis B virus (HBV) in a healthy 36-year-old man.[10] Previous evidence suggested that underlying liver conditions, such as hepatitis and cirrhosis, could worsen, thereby elevating liver enzymes, frequently seen in COVID-19. [11,12]

Reactivation of silent HBV infection has not been reported in the literature after receiving novel mRNA-based COVID-19 vaccine. The underlying pathogenesis of transient reactivation of HBV could be immunomodulation; leading to decreased alloreactivity after vaccination against hepatitis B virus [13], as no other trigger was found. As for as patient's clinical presentation, several typical HBV infection features, such as serum-sickness-like illness, fever, vomiting, and other constitutional symptoms did occur after vaccination. Clinical manifestations may have coincided with abnormal laboratory tests.

There is a rising concern about the possibility of vaccine-induced autoimmunity, as one previous study reported similar findings.[9] The probable cause is that the vaccine induces high concentrations of anti-spike IgG antibodies and CD4+ and CD8+ T cells.[9,10] A recent case report described autoimmune hepatitis developing in a healthy 35-year-old female in her third month postpartum, after receiving her first dose of Pfizer-BioNTech COVID-19 vaccine; she presented with generalised pruritus, then choluria, and jaundice.[9] Another proposed hypothesis is that both hepatocytes and bile duct epithelial cells might express the angiotensin-converting enzyme 2 receptor (known as the COVID-19 enzyme entry receptor), in which COVID-19 may damage both of these cells.[14,15]

It must be noted that recent studies reported the reactivation of HBV infection, post COVID-19 therapy, including IL-6 receptor antagonists, IL-1 receptor antagonists, and high-dose corticosteroids, emphasising the necessity for HBV screening with consideration of prophylaxis in cases of high transaminase levels.[16,17] As a result, a retrospective study showed that COVID-19 cases with chronic HBV infection have a higher risk of hepatitis B reactivation, despite the use of corticosteroids.[18]

Lately, many authors have addressed questions related to specific liver disease phenotypes, such as transplantation and immunosuppression, and their contribution to COVID-19 susceptibility and outcome. Yet, the hepatology researchers focussed on COVID-19 vaccine responses in these cases, as well as in healthy individuals. Long-term follow-up of large cohorts are needed to define the precise laboratory correlates of vaccine protection, post-vaccination. As the vaccine induces a high viral spike protein, we must evaluate patient responsiveness by assessing humoral and cellular responses.

To our knowledge, this is the first reported case of acute hepatitis B reactivation in a healthy young woman, following COVID-19 mRNA vaccine. However, the causality of this association cannot be corroborated, and as such, coincidence might be possible.

LEARNING POINTS

Covid-19 vaccine was authorised for emergency use, so any side effect attributed to the vaccine can be reported and then investigated thoroughly.

•Until clarifying the hypothesis, it is important to evaluate patient responsiveness by assessing both humoral and cellular responses.

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