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Guillain-Barré syndrome after COVID-19 mRNA vaccination in a liver transplant recipient with favorable treatment response

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Abbreviations: AASLD, American Association for Study of Liver Disease; AIDP, acute inflammatory demyelinating polyneuropathy; AST, American Society of Transplantation; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; EMG, electromyography; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin; LTR, liver transplant recipient; MRI, magnetic resonance imaging; mRNA, messenger RNA; SOT, solid organ transplant; ULN, upper limit of normal; VAERS, Vaccine Adverse Event Reporting System

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TO THE EDITOR

In response to the COVID-19 global pandemic, the largest mass vaccination campaign on record was initiated. In the U.S., the Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 messenger RNA (mRNA) vaccines received Emergency Use Authorization (EUA) in December 2020.[1] Since immunosuppressed patients including liver transplant recipients (LTR) were excluded from these vaccine trials, safety and efficacy of COVID-19 vaccination in LTR are largely unknown. Herein, we report a case of acute inflammatory demyelinating polyneuropathy (AIDP), the most common subtype of Guillain-Barré syndrome (GBS), following initial dose of mRNA COVID-19 vaccine in an adult LTR.

PATIENT CASE

A 65-year-old Caucasian male with cryptogenic cirrhosis underwent an uncomplicated deceased donor liver transplant in June 2020. In February 2021, he was hospitalized for subacute lower extremity

weakness and paresthesia ascending to bilateral hands over 4 days. He denied fever, cough, diarrhea, rash, sick contacts, surgery, or trauma. He had received his first dose of the Pfizer-BioNTech COVID-19 vaccine two days prior to symptom onset. Pertinent medications included cyclosporine 75mg twice daily. Medical history was notable for coronary artery disease, diabetes mellitus, and hyperlipidemia.

Neurological examination on admission showed bilateral lower extremity weakness, hyporeflexia and loss of pinprick sensation. He could only stand with support and required assistance for ambulation. By hospital day 3, the patient developed bilateral cranial nerve 7 palsies. He had extensive serum and infectious studies (Table 1). Brain and spine MRI were normal. Cerebrospinal fluid showed elevated protein without pleocytosis. Electromyography (EMG) demonstrated prolongation of lower extremity f-waves and reduced recruitment of voluntary motor units without active denervation. He was diagnosed clinically and electrodiagnostically with Acute Inflammatory Demyelinating Neuropathy (AIDP) and treated with intravenous immunoglobulin (IVIG).

Notably, his liver enzymes were newly elevated (Table 1). Liver MRI showed innumerable new bilobar lesions. Liver biopsy demonstrated high grade neuroendocrine tumor of unclear origin plus mild acute rejection in his graft prompting initiation of prednisone. The patient exhibited good response to IVIG including improvement of facial palsies and ambulation. After 2 weeks in rehabilitation, he could walk independently (Table 2).

DISCUSSION

AIDP, an acquired autoimmune condition involving injury to myelinated cells on spinal roots, peripheral and cranial nerves, is the most common subtype of GBS. It classically features monophasic progression of symmetric ascending weakness, sensory loss, and areflexia over 2-4 weeks. GBS can be provoked by gastrointestinal or respiratory infections, trauma, vaccination, or pregnancy. GBS has also been described in association with malignancy including solid tumors of the gastrointestinal tract.[2] Treatment includes IVIG or plasma exchange.

Several etiologies were considered as inciting trigger for this patient's GBS. Infectious etiology was considered given his immunocompromised state, but extensive workup was negative (Table 1). A

rare paraneoplastic-associated GBS was also considered but deemed unlikely given negative serology plus improvement with IVIG alone prior to any treatment of his malignancy. Ultimately, his presentation including temporal association of symptoms and progression appeared most consistent with post-COVID-19-vaccination GBS.

Post-vaccination GBS is development of GBS within 6 weeks of vaccination. This was established in 1976 when the National Influenza Immunization Program was suspended due to reported association with post-vaccination GBS.[3] However, subsequent studies have not demonstrated increased risk of GBS after influenza vaccination compared to non-vaccinated individuals. Overall, incidence of post-vaccination GBS is low. A meta-analysis following the 2009 H1N1 influenza vaccination in the U.S. reported GBS incidence rate ratio of 2.35 corresponding to approximately 1.6 excess cases of GBS per million vaccinated compared to non-vaccinated individuals.[4] Onset of GBS has been reported in a LTR following influenza vaccination, but the extremely low incidence of post-vaccination GBS is vastly outweighed by prevention of influenza infection such that consensus guidelines advise annual influenza vaccination among adult and pediatric LTR.[5]

A review of safety data from both Pfizer and Moderna mRNA COVID-19 vaccine clinical trials demonstrated no cases of AIDP or GBS in vaccinated or placebo arms.[6] In February 2021, the first peer-reviewed case report describing post-COVID-19 vaccination GBS was published.[7] The patient had no history of transplant or chronic immunosuppression, and recovered well after IVIG treatment. The Vaccine Adverse Event Reporting System (VAERS), a national vaccine surveillance reporting program, monitors post-marketing vaccine safety. As of 4/1/21, a total of 3271 cases of post-vaccination GBS have been reported in VAERS among all licensed vaccines within the U.S, including 53 reports of GBS following mRNA COVID-19 vaccination.[8] Review of these 53 cases demonstrated that no patients had history of transplant. The median age of patients was 56 years and the median time to symptom onset was 5 days (range 0-33 days). The larger number of cases associated with the Pfizer versus Moderna vaccine may relate to the total number of doses administered to date.

The CDC, American Association for the Study of Liver Diseases (AASLD) and American Society of Transplantation (AST) recommend all LTR be vaccinated against COVID-19, which should occur either before or at least 3 months after transplant to promote efficacy.[1] The mRNA COVID-19 vaccines do not contain live or attenuated virus and thus are not contraindicated for LTR, though use of this novel

vaccine in LTR warrants further study. With respect to timing of vaccination, our patient received COVID-19 vaccination 8 months after transplant so his baseline immunosuppression would less likely inhibit immunogenicity.

In conclusion, our report describes a strong temporal relationship between COVID-19 vaccination and onset of neurological symptoms consistent with post-vaccination GBS. An extensive medical evaluation failed to demonstrate any infectious, malignant, or alternative precipitant. We recognize that the patient's GBS following COVID-19 vaccination is strictly correlative, and appreciate the very real challenges of defining causality of vaccination with onset of GBS.[9,10] However, we feel reporting this potential association is important given current gaps in understanding of COVID-19 vaccine safety among LTR. It is also important to note the patient demonstrated good response to standard GBS treatment once the diagnosis was established. Since the overall clinical benefit gained from COVID-19 vaccination outweighs the risk of rare adverse events like post-vaccination GBS, we recommend all LTR undergo COVID-19 vaccination. Finally, transplant providers should report all potential vaccine-related adverse events to the VAERS registry.

Table 1: Serum, infectious and cerebral spinal fluid studies of diagnostic workup

Serum studies	White blood cells 3,500/uL (L) mild monocytosis (17%)
	Platelets 89,000/uL (L)
	Aspartate transaminase 149 IU/L (H)
	Alanine aminotransferase 294 IU/L (H)
	Alkaline phosphatase 233 IU/L (H)
	Total bilirubin 2.1 mg/dL (H)
	Westergren RBC sedimentation rate 20 mm
	C-reactive protein 1 mg/dL
	SPEP with few tiny oligoclonal bands in gamma region
	Vitamin B12 884 pg/mL
	IgA 214 mg/dL, IgM 71 mg/dL, IgG 1,194 mg/dL
	Thyroid stimulating hormone 1.83 mIU/L
	Paraneoplastic autoantibody panel negative
	Chromogranin-A 403 ng/mL (ULN <93 ng/mL)
	Carcinoembryonic antigen 36 ng/mL (ULN <3 ng/mL
Infectious studies	SARS-CoV-2 negative by nasopharyngeal swab PCR
	Human immunodeficiency virus negative

	Epstein-Barr virus negative
	Cytomegalovirus negative
	Fungal cultures negative
	Aerobic cultures negative
	Rapid plasma reagin non-reactive
	QuantiFERON-TB-Gold negative
	Blood culture negative
	Gastrointestinal pathogen panel stool PCR negative
	Urine culture
Cerebral spinal fluid studies	Red blood cells 2 cells/cmm
	White blood cells 1 cell/cmm
	Protein 107 mg/dL (H)
	Glucose 87 mg/dL (H)
	HSV DNA by PCR negative
	Cryptococcus Ag negative
	Fungal cultures negative
	Aerobic cultures negative
	Acid-fast bacteria culture negative
	Flow cytometry negative for atypical or malignant cells
	Cytology negative for carcinoma

Table 2. Timeline of events in a 65-year-old male liver transplant recipient with GBS after first dose of COVID-19 mRNA vaccine

Day 1	First dose of Pfizer-BioNTech BNT162b2 mRNA vaccine
Day 3	Onset of ascending paresthesias and weakness
Day 13	Hospitalized; negative evaluation for infectious, inflammatory or alternative causes of AIDP
Day 17	Post-vaccination AIDP diagnosis established; began IVIG x 5 days
Day 23	Prednisone 60 mg per day for mild rejection
Day 26	Discharged home with improvement
Day 50	Minimal residual neurologic symptoms and ambulating without assistance

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IRB Statement: Case studies such as ours defined as "experiences or observations associated with one or two individuals" are exempt from IRB approval at University of Michigan.

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