Guillain-Barré Syndrome After COVID-19 mRNA Vaccination in a Liver Transplantation Recipient With Favorable Treatment Response

TO THE EDITOR:

In response to the COVID-19 global pandemic, the largest mass vaccination campaign on record was initiated. In the United States, the Pfizer-BioNTech BNT162b2 (https://www.pfizer.com/science/coronavirus/vaccine/manufacturing-and-distribution) and Moderna mRNA-1273 (https://www.wsj.com/articles/moderna-to-build-vaccine-manufacturing-plant-in-africa-11633586400) messenger RNA (mRNA) vaccines received Emergency Use Authorization in December 2020.[1] Because patients who were immunosuppressed, including liver transplantation recipients (LTRs), were excluded from these vaccine trials, the safety and efficacy of COVID-19 vaccination in LTRs are largely unknown. Herein, we report a case of acute inflammatory demyelinating polyneuropathy (AIDP), the most common subtype of Guillain-Barré syndrome (GBS), following an initial dose of an mRNA COVID-19 vaccine in an adult LTR. Case studies such as ours defined as "experiences or observations associated with one or two individuals" are exempt from institutional review board approval at the University of Michigan.

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; HSV, herpes simplex virus; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; LTR, liver transplantation recipient; MRI, magnetic resonance imaging; mRNA, messenger RNA; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal; VAERS, Vaccine Adverse Event Reporting System.

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Patient Case

A 65-year-old Caucasian male with cryptogenic cirrhosis underwent an uncomplicated deceased donor liver transplantation 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 2 days before symptom onset. Pertinent medications included cyclosporine 75 mg 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 infection laboratory tests (Table 1). Brain and spine magnetic resonance imaging (MRI) were normal. Cerebrospinal fluid showed elevated protein without pleocytosis. Electromyography demonstrated prolongation of lower extremity f waves and reduced recruitment of voluntary motor units without active denervation. He was diagnosed clinically and electrodiagnostically with AIDP and treated with intravenous immunoglobulin (IVIg).

TABLE 1. Serum and Infectious and Cerebral Spinal Fluid Studies of Diagnostic Workup

Serum studies	White blood cells, 3500/μL (L) mild monocytosis (17%)
	Platelets, 89,000/μL (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 red blood cells sedimentation rate, 20 mm
	C-reactive protein, 1 mg/dL
	Serum protein electrophoresis with few tiny oligoclonal bands in gamma region
	Vitamin B12, 884 pg/mL
	IgA, 214 mg/dL; IgM, 71 mg/dL; IgG, 1194 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	Severe acute respiratory syndrome coronavirus 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 nonreactive
	QuantiFERON-TB-Gold (University of Michigan, Ann Arbor, MI, USA) 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

Abbreviations: H, High; L, Low.

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

TABLE 2. Timeline of Events in a 65-Year-Old Male LTR 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 paresthesia and weakness
Day 13	Hospitalized; negative evaluation for infectious, inflammatory, or alternative causes of AIDP
Day 17	Postvaccination AIDP diagnosis established; began IVIg × 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

Discussion

AIDP, an acquired autoimmune condition involving injury to myelinated cells on the spinal roots and 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 to 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 the 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.

Postvaccination GBS is the development of GBS within 6 weeks of vaccination. This was established in 1976 when the National Influenza Immunization Program was suspended because of a reported association with postvaccination GBS.[3] However, subsequent studies have not demonstrated an increased risk of GBS after influenza vaccination compared with nonvaccinated individuals. Overall, the incidence of postvaccination GBS is low. A meta-analysis

following the 2009 H1N1 influenza vaccination in the United States reported a GBS incidence rate ratio of 2.35 corresponding to approximately 1.6 excess cases of GBS per million vaccinated compared with nonvaccinated individuals.[4] The onset of GBS has been reported in an LTR following influenza vaccination, but the extremely low incidence of postvaccination GBS is vastly outweighed by the prevention of influenza infection such that consensus guidelines advise annual influenza vaccination among adult and pediatric LTRs.[5]

A review of safety data from both the Pfizer and Moderna mRNA COVID-19 vaccine clinical trials demonstrated no cases of AIDP or GBS in the 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 transplantation or chronic immunosuppression and recovered well after IVIg treatment. The Vaccine Adverse Event Reporting System (VAERS), a national vaccine surveillance reporting program, monitors postmarketing vaccine safety. As of April 1, 2021, a total of 3271 cases of postvaccination GBS have been reported in VAERS among all licensed vaccines within the United States, including 53 reports of GBS following mRNA COVID-19 vaccination.[8] A review of these 53 cases demonstrated that no patients had histories of transplantation. The median age of the 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 Centers for Disease Control and Prevention, American Association for the Study of Liver Diseases, and American Society of Transplantation recommend all LTRs be vaccinated against COVID-19, which should occur either before or at least 3 months after transplantation to promote efficacy.[1] The mRNA COVID-19 vaccines do not contain live or attenuated virus and thus are not contraindicated for LTRs, although the use of this novel vaccine in LTRs warrants further study. With respect to the timing of vaccination, our patient received a COVID-19 vaccination 8 months after transplantation, so his baseline immunosuppression would less likely inhibit immunogenicity.

In conclusion, our report describes a strong temporal relationship between COVID-19 vaccination and the onset of neurological symptoms consistent with postvaccination 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 the onset of GBS.[9,10] However, we feel reporting this potential association is important given the current gaps in the understanding of COVID-19 vaccine safety among LTRs. It is also important to note that the patient demonstrated good response to standard GBS treatment once the diagnosis was established. Because the overall clinical benefit gained from COVID-19 vaccination outweighs the risk of rare adverse events such as postvaccination GBS, we recommend all LTRs undergo COVID-19 vaccination. Finally, transplantation providers should report all potential vaccine-related adverse events to the VAERS registry.

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