Multisystem Inflammation and Organ Dysfunction After BNT162b2 Messenger RNA Coronavirus Disease 2019 Vaccination

BACKGROUND: The U.S. Food and Drug Administration has to date granted approval or emergency use authorization to three vaccines against severe acute respiratory syndrome coronavirus 2 and coronavirus disease 2019. In clinical trials and real-use observational studies, the Pfizer-BioNTech BNT162b2 messenger RNA coronavirus disease 2019 vaccine, as well as the Moderna mRNA-1273 messenger RNA coronavirus disease 2019 vaccine, have demonstrated high efficacy and few adverse events.

CASE SUMMARY: A 20-year-old male college student in good health developed tinnitus and hematuria shortly after vaccination and progressed swiftly to a syndrome of: systemic inflammation; acute kidney injury requiring hemodialysis; acute, bilateral, complete sensorineural hearing loss; radiographic evidence of acute multifocal ischemic strokes; pericardial effusion complicated by tamponade physiology requiring pericardial evacuation; pleural effusions requiring evacuation; and systemic capillary leak. An extensive clinical and research investigation, including cytokine analysis, whole blood cytometry by time of flight, and whole exome sequencing, did not reveal a definitive explanatory mechanism.

CONCLUSION: While the overall safety profile of the BNT162b2 coronavirus disease 2019 vaccine remains excellent for the general population, rare serious events have been reported. In this report, we describe a case of multisystem inflammation and organ dysfunction of unknown mechanism beginning shortly after administration of the first dose of BNT162b2 coronavirus disease 2019 vaccine in a previously healthy recipient.

KEY WORDS: adverse event; coronavirus disease 2019; inflammation; multisystem organ dysfunction; vaccination

The BNT162b2 messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) Vaccine (Pfizer-BioNTech) has demonstrated high efficacy and few adverse events in clinical trials and real-use observational studies (1–7). We describe a case of multisystem inflammation and organ dysfunction of unknown mechanism beginning shortly after administration of the first dose of BNT162b2 COVID-19 vaccine in a previously healthy recipient.

CASE PRESENTATION

A 20-year-old male college student with minimal past medical history received the first dose of the BNT162b2 COVID-19 vaccine in April 2021. He reported feeling well in the days prior to vaccination. Two hours after vaccine administration, he developed new-onset nausea and nonbloody emesis. That night he developed diffuse myalgias and abdominal and suprapubic pain. On postvaccination day 1, he noted fatigue and a pustular rash on his face, chest,
and back. On postvaccination day 2, he developed left-sided tinnitus, gross hematuria, and dysuria, which prompted presentation to the emergency department for evaluation.

The patient’s past medical history was notable only for prior episodes of a similar pustular facial rash that spontaneously resolved. He reported no known past COVID-19 infection, no medications, no recreational drug use or unusual exposures, meals, or ingestions, and no known allergies. He had received childhood vaccinations without prior reactions. Two siblings had received two doses of the BNT162b2 COVID-19 vaccine, and both parents had received two doses of the mRNA-1273 COVID-19 vaccine, all without issue.

His vital signs on presentation were notable for sinus tachycardia but otherwise normal. Physical examination revealed a pustular rash on his face, chest, and back (eFig. 1, http://links.lww.com/CCX/A849), oral plaques, periorbital edema, conjunctival injection, and a diffusely tender abdomen. His initial laboratory evaluation was most notable for leukocytosis, acute kidney injury, and urinalysis with packed RBCs and proteinuria. Comprehensive laboratory results are available in eTable 1 (http://links.lww.com/CCX/A849) and further discussed in Appendix A1–A9 (http://links.lww.com/CCX/A849). The patient was admitted for further management, and his case was reported to the U.S. Vaccine Adverse Event Reporting System and to the manufacturer. The patient provided informed consent for the publication of his case details and images.

DIAGNOSTIC EVALUATION AND HOSPITAL COURSE

Systemic Inflammation

Expanded laboratory diagnostic evaluation was notable for a systemic dysregulated inflammatory process including elevated high-sensitivity C-reactive protein, erythrocyte sedimentation rate, d-dimer, and lactate dehydrogenase, and lymphopenia (eTable 1, http://links.lww.com/CCX/A849 and Appendix A2, http://links.lww.com/CCX/A849). His C-X-C Motif Chemokine Ligand 9 (CXCL9) returned highly elevated at 2,553 pg/mL (reference: ≤ 647 pg/mL) on HD 23, peaked at 6,227 pg/mL (HD 29), and remained highly elevated throughout his 3-month admission, trending down to 1,263 pg/mL on HD 63. The patient’s whole blood was analyzed in a cytometry by time of flight assay demonstrating a significantly expanded granulocytic population and relative lymphopenia (eFig. 2, http://links.lww.com/CCX/A849 and Appendix A5, http://links.lww.com/CCX/A849). Whole exome sequencing revealed two homozygous variants of uncertain significance (Appendix A6, http://links.lww.com/CCX/A849).

Empiric treatment included pulse-dose methylprednisolone for 3 days (HDs 1, 2, and 3) followed by a slow prednisone taper beginning at 1 mg/kg. In response to progressive acute kidney injury and continued systemic inflammation, he received three sessions of plasmapheresis (HDs 10, 13, and 15) and two doses of IV immunoglobulin (IVIG) (HDs 13 and 15). He had a prolonged 3-month hospital course. He remained afebrile throughout, and he had no significant respiratory system involvement at any time. His inflammatory markers improved beginning approximately 2 weeks after admission, rapidly followed by global clinical improvement. Of note, this was greater than 1.5 weeks after his initial treatment with high-dose corticosteroids and in closer proximity to receiving plasmapheresis and IVIG.

Acute Kidney Injury

See Appendix A7 (http://links.lww.com/CCX/A849) for details of his renal evaluation. He progressed to anuric acute kidney injury with peak serum creatinine of 11.6 mg/dL (reference: 0.64–1.27 mg/dL) on HD 7. He underwent percutaneous kidney biopsy (HD 6) that showed hematuria, essentially normal-appearing glomeruli, and only mild tubular injury. He was initiated on renal replacement therapy on HD 6. He remained anuric until HD 20, when he had initial kidney recovery and stopped dialysis. At hospital discharge (HD 89), he remained off dialysis, nonoliguric, and with a normalized creatinine of 0.61 mg/dL.

An expanded cytokine panel on hospital day (HD) 8 demonstrated elevated soluble interleukin (IL)-2 receptor, IL-10, IL-13, and IL-6 (eTable 1, http://links.lww.com/CCX/A849 and Appendix A2, http://links.lww.com/CCX/A849). His C-X-C Motif Chemokine Ligand 9 (CXCL9) returned highly elevated at 2,553 pg/mL (reference: ≤ 647 pg/mL) on HD 23, peaked at 6,227 pg/mL (HD 29), and remained highly elevated throughout his 3-month admission, trending down to 1,263 pg/mL on HD 63. The patient’s whole blood was analyzed in a cytometry by time of flight assay demonstrating a significantly expanded granulocytic population and relative lymphopenia (eFig. 2, http://links.lww.com/CCX/A849 and Appendix A5, http://links.lww.com/CCX/A849). Whole exome sequencing revealed two homozygous variants of uncertain significance (Appendix A6, http://links.lww.com/CCX/A849).

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He had a prolonged 3-month hospital course. He remained afebrile throughout, and he had no significant respiratory system involvement at any time. His inflammatory markers improved beginning approximately 2 weeks after admission, rapidly followed by global clinical improvement. Of note, this was greater than 1.5 weeks after his initial treatment with high-dose corticosteroids and in closer proximity to receiving plasmapheresis and IVIG.
Systemic Capillary Leak Complicated by Pericardial and Pleural Effusions

The patient had systemic capillary leak and persistently low circulating blood volume. He later developed a pericardial effusion (new between transthoracic echocardiograms on HDs 3 and 12) and bilateral pleural effusions thought to be in the setting of this global capillary leak, aggressive volume resuscitation, and possible serositis. Due to concern for impending tamponade, he received a pericardial window and mediastinal drain (HD 12). Chest tubes were placed with exudative pleural fluid. He did not have evidence of overt myocarditis; peak troponin-T was 0.02 ng/mL (reference: 0.00–0.03 ng/mL).

Sensorineural Hearing Loss

The patient had no history of hearing loss. He presented with one day of new-onset left-sided tinnitus. This progressed to bilateral tinnitus (HD1) and acute, complete, bilateral hearing loss (HD2). See Appendix A8 (http://links.lww.com/CCX/A849) for details of his auditory evaluation. He had no auditory recovery and is planned for outpatient cochlear implants.

Multifocal Ischemic Strokes

Brain MRI on HD 5 revealed small punctate strokes in multifocal vascular territories of the bilateral cerebral hemispheres and the left cerebellum (eFig. 3, http://links.lww.com/CCX/A849). These were not apparent on a head CT scan on HD 3 and did not correspond to any examination findings. Additional testing is detailed in Appendix A9 (http://links.lww.com/CCX/A849).

DISCUSSION

While the safety profile of the mRNA COVID-19 vaccines remains excellent (1, 2), rare serious adverse events have been reported, including allergic reactions, myocarditis, thrombocytopenia with or without thrombosis, hematuria, and exacerbations of systemic capillary leak syndrome (1, 2, 6, 8–15). We report a case of multisystem inflammation and organ dysfunction of unknown mechanism beginning shortly after administration of the first dose of BNT162b2 COVID-19 vaccine in a previously healthy recipient. The patient experienced systemic inflammation, hematuria, progressive acute kidney injury requiring hemodialysis, acute complete sensorineural hearing loss, discovery of acute multifocal ischemic strokes, pericardial effusion complicated by tamponade physiology requiring pericardial evacuation, pleural effusions requiring evacuation, and systemic capillary leak. To our knowledge, a similar syndrome has not been reported elsewhere.

While difficult to fully establish a direct causative link between the BNT162b2 COVID-19 vaccine and the syndrome presented, the patient was previously healthy, there were no other known potential triggers, and the time course is compatible: healthy at the time of vaccination, symptom onset began 2 hours after vaccine administration, and multiple organ dysfunction within 2 days.

The clinical team considered a broad differential diagnosis including autoimmune, malignant, infectious, and genetic syndromes. Despite an extensive evaluation, a clear diagnosis or mechanistic explanation remains unknown. Broad possibilities include a coincidental onset of an unrelated syndrome, a preexisting preclinical syndrome that was unmasked by the vaccine administration or the immune response to the vaccine, or a de novo adverse effect syndrome.

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mRNA vaccines induce an mRNA-mediated type I interferon (IFN) innate immune response, which in most hosts remains local and transient, and helps to induce an antigen-specific immune response (16–21). A dysregulated and prolonged type I IFN-mediated, innate immune response could explain the patient’s lymphopenia, expanded population of immature neutrophils, and systemic inflammatory state. CXCL9 is a chemokine directly induced by IFN-gamma, a type II IFN, and is a biomarker of IFN activity (22). The patient was found to have markedly elevated levels of CXCL9, indicating IFN-gamma–mediated immune activation. The patient’s serum CXCL9 remained elevated 2 months into his course despite clinical and laboratory evidence of improvement suggesting that his inflammatory state had resolved, which could be consistent with an underlying interferonopathy (23). His whole exome sequencing revealed the presence of homozygous variants of uncertain significance in the C1S and SCNN1A genes, neither of which correlated with a compatible clinical syndrome (Appendix A6, http://links.lww.com/CCX/A849).

Recent evidence has emerged of a risk of myocarditis following mRNA COVID-19 vaccine administration, especially in young men (8, 10, 12). The patient had a new pericardial effusion with concern for serositis as one of multiple potential drivers, but he had no biochemical evidence for myocarditis. The reported cases of myocarditis...
also do not include the other elements of this patient's multisystem syndrome. Exacerbations of rare systemic capillary leak syndromes have been reported (15), but the patient had no evidence of a prior leak. A similar pustular rash was reported in two patients after following mRNA COVID-19 vaccine administration but were not accompanied by any other features (24). Preliminary reports of hearing loss after COVID-19 vaccination have not been confirmed in large observational studies (25).

CONCLUSIONS

While the overall efficacy and safety profile of the BNT162b2 COVID-19 vaccine remains excellent for the general population, rare serious events have been reported. We report one unique case of multisystem inflammation and organ dysfunction of unknown mechanism beginning shortly after administration of the first dose of BNT162b2 COVID-19 vaccine in a previously healthy recipient. It is important to identify, report, and study these rare events for the purposes of safety monitoring and advances in mechanistic understanding, especially as the threat of severe acute respiratory syndrome coronavirus 2 and COVID-19 continues and with an unknown need for future vaccine formulations and administrations.

ACKNOWLEDGMENTS

Foremost, we thank the patient and his family for their willingness to contribute to general scientific and medical advancement by consenting to the publication of this report. We wish to thank the long list of frontline clinicians, including primary medical teams including medical residents and medical students, ICU teams, and consulting subspecialty services for their dedication to the care of the patient. We acknowledge the critical input from the Immune Dysregulation Program Team at the Children's Hospital of Philadelphia, including Edward M. Behrens, MD, Kathleen E. Sullivan, MD, PhD, and Neil D. Romberg, MD, and from the U.S. Centers for Disease Control and Prevention Clinical Immunization Safety Assessment Project.

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