Hyperinflammatory Syndromes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Messenger RNA vaccination in Individuals With Underlying Immune Dysregulation

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The development of effective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines has been a significant accomplishment. Adverse events are extremely rare, but continued surveillance is important, especially in at-risk populations. In 5 patients with preexisting immune dysregulation, hyperinflammatory syndromes, including hemophagocytic lymphohistiocytosis, developed after SARS-CoV-2 mRNA vaccination. Early recognition of this rare condition is essential.

Keywords. COVID-19; hemophagocytic lymphohistiocytosis; Inflammation; Vaccination.

The rapid generation of safe and effective messenger RNA (mRNA) vaccines has been an unprecedented success of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Adverse events are extremely uncommon, even in large population-database analyses [1]. However, exacerbations of underlying hematologic and autoimmune diseases have been reported after vaccination [2]. Rare cases of possible vaccine-related hemophagocytic lymphohistiocytosis (HLH) have also been published after other SARS-CoV-2 vaccines [3, 4]. Given the widespread administration of these vaccines, it is essential to continue to monitor for rare adverse events and to identify patient populations at risk. We describe 5 cases of hyperinflammatory reactions, including HLH, temporally associated to mRNA vaccination in people with underlying immune dysregulation.

CASE REPORTS

Patient 1
An otherwise healthy 52-year-old man experienced high fever and abdominal pain the day after receiving the first dose of BNT162b2 mRNA vaccine. He reported a viral syndrome 4 months earlier and malaise with low-grade fever the week before vaccination. Ten days after vaccination, he was admitted with fever, acute liver injury, and hypotension requiring vasopressors (additional clinical information in Supplementary Materials). Laboratory results demonstrated increased ferritin (8130 ng/mL) and soluble CD25 levels (Table 1). Antibiotic treatment was initiated, and infectious workup demonstrated only Epstein-Barr virus (EBV) viremia of 11.3 million IU/mL. Dexamethasone and etoposide were initiated for HLH, and the patient’s fever and hemodynamic status initially improved. Bone marrow biopsy demonstrated hemophagocytosis and T-cell lymphoma, and an etoposide-based chemotherapy regimen was started. The patient’s course was complicated by neutropenic fever, Bacteroides bacteremia, and refractory shock, of which he died.

Patient 2
A 53-year-old man had interstitial lung disease with biopsy-proved nonspecific interstitial pneumonia and positive anti-Ro/La and anti–U1-RNP autoantibody results, developing 7 months before presentation. Prednisone and mycophenolate were trialed without improvement and rituximab treatment was planned, so the patient received BNT162b2 mRNA vaccine. Four days after vaccination, he experienced fever and worsening hypoxia. Antibiotics were started, but the patient’s symptoms progressed, requiring mechanical ventilation. Laboratory results demonstrated new pancytopenia, hyperferritinemia (84 848 ng/mL), and increased soluble CD25. Bone marrow biopsy showed hemophagocytosis. Infectious evaluation revealed only EBV viremia (10 275 IU/mL). After treatment was started with dexamethasone, anakinra, and intravenous immunoglobulin, the patient showed improvement. His course was complicated by Pseudomonas bacteremia and autoimmune hemolytic anemia, which responded to rituximab. Ventilatory support was weaned after 3 months, and patient 2 was discharged to a rehabilitation facility.

Patient 3
A 57-year-old man with heart failure and well-controlled human immunodeficiency virus (HIV) infection experienced malaise and nausea 12 days after receiving the mRNA-1273 vaccine. Three days later, he presented with hypothermia (30.2°C) and hypotension. Laboratory results revealed cytopenias with hemolysis, hyperferritinemia (>15 000 ng/mL), and hypofibrinogenemia.
Antibiotics and methylprednisolone were initiated. His hemodynamics and cytopenias stabilized over 72 hours. *Mycobacterium avium* complex (MAC) grew in a sputum culture, without consistent chest computed tomographic findings and with blood cultures negative for mycobacteria. The patient had Kaposi sarcoma herpesvirus viremia (3063 IU/µL). His course was complicated by decompensated heart failure, which improved with diuresis, and he was then discharged. One week later, he presented again with encephalopathy and shock. Despite supportive care and antibiotics, he died 2 days later. No autopsy was performed.

### Patient 4

A 55-year-old woman presented after 4 months of fevers, cytopenia, and hyperferritinemia. She had received steroids for presumed adult-onset Still’s disease, with transient improvement. MAC grew in bone marrow culture, and the patient also had pulmonary aspergillosis. Bone marrow biopsy revealed myelodysplastic syndrome with excess blasts. GATA2 deficiency was diagnosed, based on uniallelic GATA2 expression [6]. The patient’s symptoms stabilized with antibiotics, but intermittent fevers persisted. In preparation for chemotherapy, she received the BNT162b2 mRNA vaccine and experienced high-grade fevers (40.1°C) 3 days after vaccination. Her ferritin level increased from 2642 to 7724 ng/mL, and she had worsening cytopenias. Owing to her pulmonary aspergillosis, steroids were avoided. Anakinra was trialed but not tolerated.

The patient’s fevers continued, but her laboratory values stabilized over 2 weeks, although she continued to need blood transfusions for anemia. She slowly recovered, and her infections improved with treatment.

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**Table 1. Clinical Characteristics and Laboratory Findings During Acute Inflammatory Episode After Receipt of Messenger RNA Vaccine for Severe Acute Respiratory Syndrome Coronavirus 2**

| Patient | Age, y; sex | Underlying condition(s) | mRNA vaccine | Time from vaccine to symptoms, d | Temperature, °C | CRP, mg/L | Ferritin, ng/mL | WBC count, ×10⁷/µL | Hemoglobin, g/dL | Platelets, ×10⁹/µL | Triglycerides, mg/dL | AST, U/L | Organomegaly | Soluble CD25, pg/mL | Hemophagocytosis | H-score* | EBV (blood PCR), IU/mL | Treatment | Vaccine response (anti-spike antibody, IU/mL)* | Outcome | Treatment | Vaccine response (anti-spike antibody, IU/mL)* |  
|---------|-------------|--------------------------|--------------|-------------------------------|-----------------|---------|----------------|-------------------|----------------|----------------|----------------|---------|------------|---------------------|----------------|--------|---------------------|----------|---------------------|----------|----------|---------------------|  
| Patient 1 | 52; Male | Unknown → T-cell lymphoma | BNT162b2 | 1 | 39.5 | 97.7 | 8130 | 5.4 | 11.1 | 172 | 650 | 105 | Splenomegaly | 25 603 | Yes | 239 | 11 300 000 | Dexamethasone, etoposide | ND | Died (Bacteroides bacteremia; refractory shock) |  
| Patient 2 | 53; Male | ILD with autoimmune features | BNT162b2 | 4 | 39.6 | 230.6 | 75 249 | 3.0 | 11.5 | 21 | 263 | 435 | Hepatomegaly | 18 100 | Yes | 213 | 10 275 | Dexamethasone, IVIG, anakinra, methylprednisolone for hypertension | Positive (15.7) | Positive (2.1) | Died (respiratory failure, shock of unknown cause) |  
| Patient 3 | 57; Male | Well-controlled HIV; possible other immune disorder | mRNA-1273 | 12 | 30.2 | 14.6 | >15 000 | 4.7 | <35 | 9 | 142 | <35 | None | 2473 | ND | 185 | 100 | Ketorolac, anakinra (not tolerated) | Positive (15.7) | Positive (2.1) | Died (respiratory failure, shock of unknown cause) |  
| Patient 4 | 55; Female | GATA2 deficiency; MDS (blasts, 6%–8%); MAC; aspergillosis | BNT162b2 | 3 | 40.1 | 198.4 | 7724 | 2.6 | 6.8 | 106 | 106 | 561 | Hepatosplenomegaly | 4907 | ND | 528 | 36 | Methylprednisolone, infliximab | Positive (15.7) | Positive (15.7) | Died (respiratory failure, shock of unknown cause) |  
| Patient 5 | 48; Female | HIV/AIDS; MAC-IRIS | mRNA-1273 | 8 | 39.4 | 134.9 | 285 | 10.6 | 6.6 | 310 | 138 | None | 12.1 | 527 | 48 | ND | ND | ND | Live (remains on treatment for IRIS) |  

**Abbreviations:** AST, aspartate aminotransferase; CRP, C-reactive protein; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; ILD, interstitial lung disease; IRIS, immune reconstitution inflammatory syndrome; IVIG, intravenous immunoglobulin; MAC, *Mycobacterium avium* complex; MDS, myelodysplastic syndrome; mRNA, messenger RNA; ND, not determined; PCR, polymerase chain reaction; WBC, white blood cell.

*The HScore is a unitless score that can be used to estimate the risk of reactive hemophagocytic syndrome developed by Laurence Fardet and colleagues [5].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-spike antibodies were checked with the semiquantitative Elecsys-Roche assay, >2 months after vaccination. SARS-CoV-2 anti-nucleocapsid antibodies were also evaluated in patients 2–5 and results were negative, consistent with the anti-spike antibody response being due to vaccination and not prior coronavirus disease 2019.
Patient 5
A 48-year-old woman with HIV presented with disseminated MAC and immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral therapy. Her course was complicated by HLH with multiorgan failure, which improved with steroids and antimycobacterials. Relapsing pulmonary IRIS flares occurred during weaning from steroids, raising concern for underlying sarcoidosis. Infliximab was initiated, and the patient’s symptoms improved. After 1.5 years, when prednisone was reduced to 10 mg, she received the mRNA-1273 vaccine. Four days after vaccination, she experienced fevers with productive cough and pleuritic chest pain, resembling her previous IRIS flares. Cultures were negative and computed tomography showed worsening mediastinal lymphadenopathy. Results of infectious workup were negative. In view of the patient’s prior severe IRIS, she was treated with high-dose prednisone and infliximab. Her condition improved over 72 hours, and she was rapidly weaned from steroids.

Ethical Approval
All patients evaluated at the National Institutes of Health provided written informed consent and were enrolled in 1 of 3 clinical protocols (NCT00404560, NCT00018044, or NCT02147405). These protocols were approved by the National Institutes of Health Institutional Review Board.

DISCUSSION
We describe 5 cases of hyperinflammation occurring after SARS-CoV-2 mRNA vaccination in people with preexisting immune dysregulation. All patients had negative results of SARS-CoV-2 polymerase chain reaction testing and no clinical evidence of prior coronavirus disease 2019 (COVID-19). Symptoms began 1–12 days after vaccination, and everyone received immune suppression. Two of the 5 patients in whom HLH developed died within 6 weeks of presentation. In adults, HLH is a diverse hyperinflammatory syndrome characterized by immune-mediated pathology. Although typically classified as primary or secondary, its pathogenesis is complex and multifactorial [7]. Jordan and colleagues proposed categorizing HLH by underlying immune predisposition into subgroups, including cancer, rheumatologic disease, immunocompromise, and treatment-associated [7]. Infection-associated HLH was not considered a separate entity, because patients with any of these conditions may have an infectious trigger [8, 9].

Our case series highlights the utility of this system, as each individual had a unique underlying immunologic disease. Owing to the temporal association, it is possible that mRNA vaccination served as a trigger for the subsequent hyperinflammatory state. The pathophysiology of HLH is driven by enhanced T-cell activation and interferon γ production leading to severe macrophage activation, hypercytokinemia, and life-threatening inflammation [7, 8]. mRNA vaccines have been shown to drive an acute expansion of activated CD4+ T cells after the first injection [10]. Given the importance of T cells in HLH pathophysiology, it is possible that this expansion could lead to increased interferon γ production and bystander activation, triggering pathologic inflammation in at-risk individuals.

It is important to emphasize that these patients had significant preexisting immune dysregulation, which was an independent predisposition to hyperinflammation. Patient 1 had T-cell lymphoma, which is known to increase susceptibility to HLH. EBV can drive this pathogenesis by infecting both B and T cells [11]. Autoimmune diseases, such as adult-onset Still’s disease, can predispose to HLH (referred to as macrophage activation syndrome [MAS]) [8]. HLH/MAS has also occurred with other rheumatologic diseases associated with interstitial lung disease, including Sjogren syndrome and dermatomyositis [12].

Patient 3 had well-controlled HIV infection and a sputum culture in which MAC grew, without clinical evidence of mycobacterial infection. He had Kaposi sarcoma herpesvirus viremia, which has been implicated in hyperinflammatory syndromes in people with HIV [13], but a definitive diagnosis was not established. Despite the suspicion of additional immunodeficiency, no other immune disorder was identified and the etiology of HLH in this patient remains unknown. Patients 4 and 5 had histories of HLH-like inflammation associated with disseminated mycobacterial infections in the setting of GATA2 deficiency and AIDS, respectively. Interestingly, less fulminant inflammatory symptoms developed, highlighting the spectrum of clinical severity that can occur with different causes of hyperinflammation.

All patients in this case series experienced hyperinflammatory responses after the first injection of an mRNA-based vaccine, but causality cannot be ascertained. More than 200 million people have been vaccinated against SARS-CoV-2 in the United States, and unrelated disease processes may be detected in the perivaccination period. Unfortunately, the baseline population rate of HLH in adults is difficult to estimate owing to clinical heterogeneity and variability in preexisting immune disorders [14]. This is further complicated by the absence of widely accepted and validated diagnostic criteria in adults, making large database analyses unreliable [14]. However, vaccines are potential triggers of HLH in infants with genetic predispositions [15]. Although this is not a well-described phenomenon in adults, the mechanism of mRNA vaccines is novel, and their impact on T-cell responses is not fully known.

This is the first case series describing hyperinflammatory syndromes following SARS-CoV-2 mRNA vaccination in individuals with preexisting immune dysregulation. Review of the Vaccine Adverse Event Reporting System (VAERS) database identified an additional 36 reports from across the United States of hyperferritinemic inflammatory syndromes described as HLH, MAS, or new-onset Still’s disease occurring after mRNA
vaccinations [16]. Owing to the limitations of the database with variability in recognition and reporting, complete clinical data and outcomes could not be confirmed for each case.

These rare observations should not change current vaccine recommendation guidelines. The risk of hyperinflammation and death from COVID-19 far outweighs the extremely low risk of severe vaccine-related adverse events [1]. Acute SARS-CoV-2 can also cause an HLH-like syndrome, and although its incidence is debated, it has been reported in up to 5% of severe cases of COVID-19 [17]. Therefore, the odds of HLH developing from SARS-CoV-2 infection remains markedly greater than any potential small perivaccination risk. In those without COVID-19, vaccination should be explored among the possible provocations of hyperinflammatory responses, including HLH. Individuals with persistent, severe inflammatory symptoms after vaccination should be evaluated for underlying immune dysregulation. They should have close follow-up, and immune suppression, if required, should always be directed at the underlying disease process. Further study of the genetic and immunologic mechanisms predisposing to HLH is needed to improve diagnosis and treatment of this increasingly recognized hyperinflammatory syndrome.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyright and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
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