Macrophage Activation Syndrome Complicated by Toxic Epidermal Necrolysis Following SARS-CoV-2 mRNA Vaccination

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To the Editor:

SARS-CoV-2 vaccines have been rapidly deployed worldwide. They have proved to be generally safe and effective at preventing severe disease by eliciting a strong immune response with frequent, albeit usually mild, inflammatory side effects (e.g., fever, myalgias). More serious inflammatory complications have been reported infrequently, such as vaccine-associated myocarditis. Here, we report a case of macrophage activation syndrome (MAS) following SARS-CoV-2 vaccination, which was complicated by toxic epidermal necrolysis (TEN), and provide a tabular review of similar cases of MAS and/or adult-onset Still’s disease (AOSD) occurring in association with SARS-CoV-2 vaccination.

A 23-year-old previously healthy woman developed daily fevers and cervical lymphadenopathy 1 week after receiving her second dose of the Moderna SARS-CoV-2 mRNA vaccine. She was initially seen at an urgent care center and prescribed azithromycin and corticosteroids for a presumed upper respiratory infection. Her symptoms did not abate, and, over the next 10 days, she developed rash, nausea, vomiting, and abdominal pain, leading her to present to the emergency department. On admission (18 days after vaccination), her examination was notable for temperature of 39.1 °C, sinus tachycardia (140 bpm), hypotension (88/66 mmHg), enlarged cervical lymph nodes, and a faint blanchable morbilliform eruption on all extremities.

Initial evaluation demonstrated leukocytosis (18.19 × 10^9/L [4–11 × 10^9/L]) with 93% neutrophils; hemoglobin, 11.4 g/dL (12–15 g/dL); platelets, 93 × 10^9/L (150–450 × 10^9/L), elevated liver enzymes (AST, 130 U/L [10–50 U/L]; ALT, 43 U/L [10–35 U/L]); and CRP, 186.1 mg/L (≤5 mg/L). Computed tomography of her chest, abdomen, and pelvis revealed splenomegaly and diffuse lymphadenopathy. Due to concern for infection, blood cultures were obtained, and broad-spectrum antibiotics were initiated. Her negative cultures and a lack of improvement after multiple courses of antibiotics raised concern for malignancy or autoimmune disease. She underwent excisional lymph node biopsy as well as bone marrow biopsy. Allopurinol was started given concern for lymphoma and risk of tumor lysis syndrome and later discontinued when biopsy pathology and flow cytometry did not show signs of monoclonal expansion/proliferation, therefore ruling out hematolymphoid malignancy. Her biopsies showed no hemophagocytosis and negative bacterial, fungal, and mycobacterial staining and cultures. EBV PCR, IgM, and IgG as well as SARS-CoV-2 PCR and nuclear capsid IgG testing were also negative, arguing against prior infection. Autoimmune serologies were all within normal limits. She met 5 of 8 diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), with fevers; splenomegaly; ferritin, 56,131 ng/mL (5–204 ng/mL); triglycerides, 811 mg/dL (<150 mg/dL); and elevated soluble interleukin (IL) 2-receptor, 6158.5 pg/mL (175.3–858.2 pg/mL). Interestingly, she also met Yamaguchi criteria for AOSD and had marked elevations in both IL-18 (181,803 pg/mL [89–540 pg/mL]) and CXCL9 (548,075 pg/mL [<647 pg/mL]), supporting the diagnosis of MAS [1].

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Her illness course, inflammatory markers, and therapies are shown in Fig. 1A. Dexamethasone and anakinra were initiated on day 36 after vaccination along with prophylactic atovaquone and pantoprazole. Her symptoms and labs improved despite a brief lapse in anakinra, following hospital discharge, until day 64 after vaccination, when she developed a painful, desquamating, and dusky Nikolsky positive eruption, involving 70% of her total body surface area and mucosae consistent with TEN (Fig. 1B). Skin biopsy later confirmed subepidermal vesicular dermatitis with full-thickness epidermal necrosis (Fig. 1C). Potential culprit drugs were held (pantoprazole, atovaquone, and...
cephalosporins), and she received intravenous immunoglobulin (IVIG) 500 mg/kg for 3 days and cyclosporine (CsA) 150 mg BID. Although she no longer had symptoms fulfilling Yamaguchi criteria for AOSD, her IL-18 remained elevated, and, therefore, anakinra was restarted, and steroids were continued to address her underlying MAS. Her rash quickly stopped progressing, and her inflammatory markers trended down. She required prolonged hospitalization for wound care and rehabilitation. Following discharge, she transitioned from anakinra 100 mg daily to canakinumab 300 mg every 28 days, and prednisone was tapered off. She has continued to do well on canakinumab 300 mg every 4 weeks, without recurrence of MAS or TEN symptoms. Testing for HLA-B*5801, which is associated with allopurinol-related Steven Johnson syndrome (SJS)-TEN, was negative. Informed consent was obtained from the patient for publication of this case.

This patient without history of autoimmune disease developed AOSD with MAS in close proximity to SARS-CoV-2 vaccination. Her course was later complicated by TEN. MAS was diagnosed based on markedly elevated IL-18 and fulfillment of Yamaguchi criteria for AOSD. Marked elevations in IL-18 are a distinguishing feature of both AOSD and MAS. Total IL-18 greater than 24,000 pg/mL differentiates MAS from other types of familial and secondary HLH (sensitivity, 83%; specificity, 94%). Although IL-18 alone cannot differentiate between AOSD and MAS, it tends to be an order of magnitude higher in MAS [1]. Our patient also had unusually high CXCL9, which is a Th1 chemokine induced by interferon gamma production. CXCL9 elevations are seen with MAS, as well as HLH, though typically on the order of 1000–10,000 pg/mL [1].

Both new-onset AOSD and exacerbations of preexisting disease have been reported, following various types of SARS-CoV-2 vaccination (See Supplemental Table 1 and accompanying references). Neither IL-18 nor CXCL9 levels were reported in these publications. Most cases occurred within 1–2 weeks of vaccination, and, as in many other autoimmune conditions, there appears to be a female predominance. Similar to infection, vaccination is a possible trigger for AOSD with or without MAS in predisposed individuals. Both conditions are marked by widespread innate immune activation. Treatment involves IL-1 blockade as well as corticosteroids [2]. Anakinra and canakinumab were used successfully in this case as well as others reported in the literature [3]. Our patient has avoided additional SARS-CoV-2 boosters and, instead, was given tixagevimab and cilgavimab for COVID prophylaxis.

Although our patient responded appropriately to MAS treatment, she was exposed to multiple medications during the early, uncontrolled phase of MAS, which may have increased her risk of developing TEN. The presence of inflammatory disorders, such as autoimmune disease, increases the risk of TEN, particularly in the early stages before the disease is controlled [4]. Inflammation promotes antigen presentation and activation of T cells and NK cells, leading to drug-specific CD8+T cell and NK cell-mediated epidermal damage [5]. In this case, the lapse in anakinra due to delayed insurance coverage following discharge coincided with a resurgence of her inflammatory markers and development of TEN. It is possible that her immunosuppression had masked or prevented TEN and that this gap allowed it to fully manifest. Additionally, certain medications and HLA types are associated with higher risk of SJS-TEN, including allopurinol. The cause of our patient’s TEN remains unknown. Although HLA-B*5801 testing was negative, this does not rule out allopurinol. Treatment of SJS-TEN involves stopping suspected culprit drugs (in this case, allopurinol, atovaquone, pantoprazole, and cephalosporins), wound care, and, typically, immunosuppression. Recent studies have supported the use of cyclosporine and the combination of IVIG plus corticosteroids [5].

The SARS-CoV-2 pandemic led to the rapid development and dissemination of multiple life-saving vaccines. Our report should not dissuade the continued use of these vaccines but provide insight into the presentation of rare inflammatory complications including AOSD and MAS. This case and other reports suggest that these sequelae are responsive to typical immunosuppression, namely IL-1 blockade and corticosteroids. In at least one case, the patient was able to safely receive her 2nd dose once the disease was controlled [3]. Finally, in patients with uncontrolled inflammatory disease, there is an increased risk of SJS/TEN, and development of new mucocutaneous symptoms deserves prompt evaluation and treatment.

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Data Availability All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Conflict of Interest The authors declare no competing interests.

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