CLINICAL VIGNETTE

To Vaccinate or Not to Vaccinate: PMR Relapse Following COVID-19 Booster Vaccination

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Clinical Vignette

An 80-year-old female with a polymyalgia rheumatica (PMR) in full remission for five years presented to the emergency room (ER) with two-weeks of pain involving the posterior aspect of her right shoulder and right dorsal lateral neck with radiation to the cervical spine and left shoulder. She reports that she received her COVID Moderna second monovalent booster vaccine (mRNA – 1273 monovalent 100 µg/0.5 ML) two weeks prior, and initially developed mild erythema, swelling and pain at the injection site on the right triceps area. She has multiple medical problems including Hashimoto's thyroiditis, primary hyperparathyroidism, and osteoporosis. Her PMR was in remission after successful corticosteroid taper. She had moderately severe COVID-19 infection not requiring hospitalization approximately 11 weeks prior to receiving her COVID booster. At that time, she was treated with nirmatrelvir 150 mg – ritonavir 100 mg for infection management, and guaifenesin and benzonatate for symptomatic care. She had fully recovered from acute disease at the time she received her booster vaccine.

Basic labs were within normal range, and right upper extremity dopplers in the ER were negative for deep venous thrombosis (DVT). She was discharged with recommendations to follow up with her rheumatologist. When she presented to her rheumatologist a few days after the ER visit, she reported fatigue, myalgias, and progression of pain in the neck, bilateral shoulder, hip and thighs.

Laboratory findings included elevated C-reactive protein (CRP) level of 17 mg/dL (0.3 to 1.0 mg/dL), erythrocyte sedimentation rate (ESR) of 68 mm/h (0 to 20 mm/h) and Interleukin-6 (IL-6) level of 56.5 pg/ml (0 and 43.5 pg/ml). Her white cell count and hemoglobin were mildly decreased to 3.6×10^9/L and 10.9 g/dL, respectively. Bilateral shoulder ultrasound showed bilateral subacromial bursitis, and right biceps tenosynovitis. Other laboratory and imaging studies were negative.

Based on clinical and laboratory findings her prior history of PMR and co-morbidities, the patient met criteria for PMR flare and relapse. She was restarted on prednisone 15 mg per day with good efficacy and improvement in symptoms within seven days. However, gradual dose taper failed after 30 days, and the patient remained on treatment for six months. She subsequently, she asked us for recommendations regarding future booster immunizations.

Discussion

Background Information and Vaccine Mechanism of Action

The global COVID-19 pandemic health crisis revolutionized vaccine generation and production, placing messenger RNA (mRNA) vaccine technology in the spotlight. COVID-19 is caused by the SARS – CoV-2 virus, which impacted millions across the globe, causing infections and deaths worldwide over the last three years. The rapid development of two mRNA vaccines in less than a year, raised great hopes for the fight against the pandemic, and in particular protecting immunocompromised individuals from developing severe disease. On the flip side, the rapid production also led to a great deal of controversy and concern for severe adverse effects.

Essentially mRNA vaccines are composed of synthetic mRNA encapsulated in lipid particles.[1] COVID-19 mRNA vaccines encode for the spike protein S of SARS CoV-2. Host cells start making the spike protein S upon delivery of the vaccine.[1,2] This has the potential to elicit a highly S protein specific antiviral response in the vaccinated individual.[1,2] Both COVID-19 mRNA vaccines (Moderna and Pfizer) produced in the United States have been highly effective in preventing COVID-19 in large clinical trials.[1-3] Additionally, follow up studies show these vaccines are effective at reducing severe illness and hospitalization in subsequent SARS-CoV-2 variants.[3]

Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is an immunologic abnormality in which, unlike what the name implies myopathic process, muscle cells are often histopathologically normal and uninvolved in the disease process. Instead, peri-articular structures, such as the bursa and tendons, are the most affected in PMR. The cause of PMR is unknown, but what we know that Interleukin-6 (IL-6) is the main cytokine involved in PMR relapses and flares, and is key in the pathogenesis of the disease.

IL-6 is a soluble mediator with pleiotropic effects on inflammation, immune response and hematopoiesis. It is promptly and transiently produced in response to infections and tissue injuries, contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reaction.[4] Additionally, IL-6 has been shown to be involved in a number of rheumatological diseases, and blocking the activity of IL-6

is a feasible, new therapeutic approach to chronic inflammatory diseases.[5]

Some studies that have linked PMR to Giant Cell Arteritis (GCA), and there is suggestion of a cyclic pattern in incidence and seasonal variation, implying possible environmental and infectious triggers.[6,7] Candidate infection triggers of PMR include Varicella-Zoster Virus, Epstein Barr Virus, Parvovirus B19 and Chlamydia pneumoniae;[6] and more recently, the role of SARS-CoV-2 is also under investigation.[7,8]

PMR is almost exclusively a disease of older adults with peak incidence between the ages of 70 and 80. It is a relatively common disease, and the lifetime risk of developing PMR has been estimated at 2.43% for women and 1.66% for men.[9] Serum levels of inflammatory markers are often mildly elevated in PMR. The most common is circulating IL-6 levels, in which its expression in elderly may be associated with underlying disease.[10,11]

COVID Vaccine and Infection as Triggers for Polymyalgia Rheumatica

A few studies and case reports document new onset or relapsed PMR following initial COVID-19 vaccine series. However, there are no clear data following booster vaccines and limited data following acute infection. There is also limited published data in the literature regarding risk of any rheumatological disease or relapse in patients with underlying acute infection and/or recent history of COVID-19 infection.[12] Mettler at al. reported that 1,295,482 COVID-19 vaccinations resulted in 147 cases of GCA (0.01%), 290 cases of PMR (0.02%) and 9 (0.0006%) cases of GCA with PMR.[12] Further, 61.9% of the reported cases occurred after mRNA vaccines and 37.4% after viral vector vaccines.[13]

Manzo et all suggest that rheumatological relapse after COVD-19 infection is underreported because the rheumatological symptoms are masked by other manifestations of the infection, and these patients are usually managed by non- rheumatologists, who may miss the diagnosis. Additionally, they suggest that in diseases, such as PMR, in which IL-6 plays a more prominent role, the altered regulation of immunity induced by SARS CoV-2 might represent a specific trigger.[9]

Conclusion

It is possible that mRNA vaccines trigger an autoimmune response and cause flares of chronic inflammatory conditions and rheumatological diseases in some susceptible individuals. This may occur not only after the COVID-19 initial vaccine series, but also after booster shots. Moreover, a prior COVID-19 infection, especially if severe and accompanied by a cytokine storm, may make individuals with history of autoimmune and rheumatological disease more susceptible to subsequent vaccine-induced flares.

In our patient with a known history of PMR, we suspect that synergy between immunological stimulation by prior COVID-19 infection and the subsequent immunological stimulation by mRNA COVID booster vaccine contributed to the PMR relapse. The benefits of the COVID-19 immunization certainly outweigh the risks from contracting the disease, especially in older, immunocompromised individuals. However, when considering future booster vaccinations, we recommend an individualized risk-benefit assessment, taking into consideration not only the patient's own comorbidities and immunocompromised status, but also the patient's level of exposure to the virus in the community.

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