Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

"COVID Arm": Very delayed large injection site reactions to mRNA COVID-19 vaccines

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Clinical Implications

- Atypical very delayed large injection site reactions to the mRNA COVID vaccines appear fairly frequently. They begin about a week after vaccination, persist for several days, resolve without treatment, and have not recurred with second doses.

Novel COVID-19 mRNA vaccines from Pfizer/BioNTech and Moderna were granted Emergency Use Authorization (EUA) in December 2020. The EUA Fact Sheets for Healthcare Providers describe the frequency of injection site reactions within 7 days after each dose for the Pfizer/Moderna vaccines to include pain (84.1%/92.0%), redness (9.5%/10.0%), and swelling (10.5%/14.7%).[1,2] Such injection site reactions are common with most vaccines and attributed to injection technique or immune or inflammatory responses to the antigens or excipients injected. They typically occur within a day or two of vaccination and resolve within a day or two although some can be more prolonged.[3]

We have recently evaluated 12 patients with atypical very delayed injection site reactions to the mRNA COVID-19 vaccines that begin at approximately 1 week after vaccine administration, persist for several days, and can have an overlying dermatitis. In most cases the patients had had the more typical injection site pain, with or without associated redness and swelling, a day or two after vaccination that had resolved before the onset of their very delayed injection site reactions. The average age of the patients was 51 years (range, 27-73 years). The average day of onset for these reactions was 7 days (range, 5-11 days), and they persisted for an average of 5 days (range, 3-8 days). Eleven occurred after the first dose, 11 occurred with the Moderna vaccine, and 11 occurred in women. The one reaction to the Pfizer vaccine occurred only after the second dose. Common symptoms included pain, redness, swelling, and itching at the injection site. One had systemic symptoms of fever and chills. One had mild blistering at the injection site. Some treated these reactions with topical corticosteroids, ice, oral antihistamines, or pain relievers. Figures 1 and 2 depict characteristic reactions in 2 patients with photographs taken on the days indicated after vaccination and used with the patients' permission. We advised the 11 patients whose reactions occurred after the first dose to receive their second dose on time in the usual manner. Although we advised the patients that they may want to receive their second dose in the opposite arm, about half chose to receive it in the same arm as the first dose. All 11 who had the very delayed injection site reaction with their first dose have gone on to receive their second vaccine without a recurrence of this reaction when evaluated at least 2 weeks after the second dose.

While this manuscript was under review, another case series of 12 patients with similar reactions was reported.[4] Similar to our report, their patients had late injection site reactions with a median onset of day 8 and a median duration of 6 days. Their patients were also encouraged to receive second doses and did so in either the same or opposite arm as the first dose. All of their reactions were to the Moderna mRNA COVID-19 vaccine, whereas one of ours was to the Pfizer vaccine and occurred only after the second dose. The vast majority of patients in both reports have been women, although we do not have sufficient comparator data regarding the proportion of female vaccine recipients overall to state with certainty that these reactions occur predominantly in women. Unlike our report, they describe 6 of their 12 patients as having a "recurrence" of their local reactions after the second dose, 3 of the same severity and 3 of lesser severity, although with a median onset of 2 days. In light of this, we requeried our 11 patients who had had late local reactions to their first doses of the Moderna vaccine to determine whether or not they had suffered any earlier onset local reactions after their second doses. Seven reported no local reaction at any time after their second dose, whereas 4 reported that they had local reactions that they described as similar in character to their delayed local reactions after their first doses, but beginning on the day of (2 patients) or day after (2 patients) the second dose. All 11 reconfirmed that they had no recurrence of any late onset local reaction. Thus, it would appear that the 2 reports are quite similar. There have been no recurrences of late onset local reactions, but some patients report a similar, but early onset local reaction to their second dose. The timing of these "recurrences" may make them difficult to distinguish from more common injection site reactions occurring within a day or two of first or second vaccine doses.

The mechanism of these very delayed large injection site reactions is unknown. Arthus reactions would be expected to occur sooner and would also require prior sensitization. The publication cited above speculated that the reactions constitute a delayed type or T cell–mediated hypersensitivity supported by a skin biopsy of one of the late local reactions.[4] Delayed type hypersensitivity reactions would also be expected to occur sooner and typically require prior sensitization, although reactions with primary exposures may also be possible.[5] Unlike conventional vaccines where the immunizing agent is a killed or attenuated component of the infectious agent, these mRNA vaccines require translation of the mRNA to generate endogenously produced viral spike protein to which the immune response is generated. It is possible that the delayed appearance of these reactions is related to this delayed appearance of protein. Also unknown is why the reactions would not recur with the second dose. The humoral or cellular immune response generated by the first dose could presumably moderate any reaction to the second dose.

Although these very delayed large injection site reactions may be of concern to patients and providers, they are self-limited and appear not to recur with second doses, although some patients

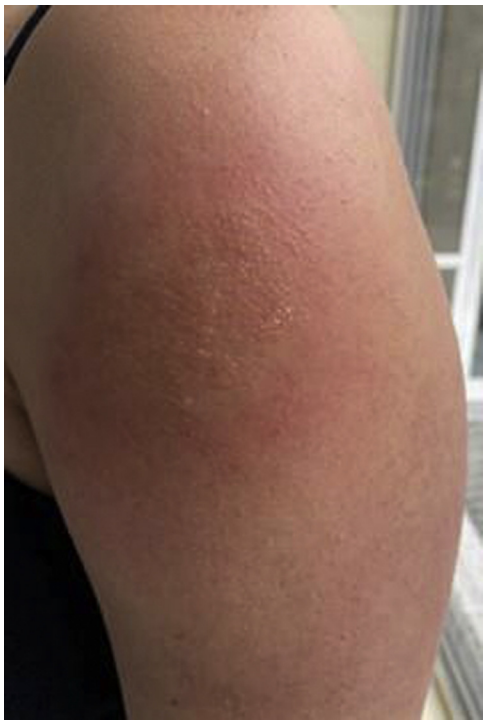

FIGURE 1. Injection site reaction on day 8.

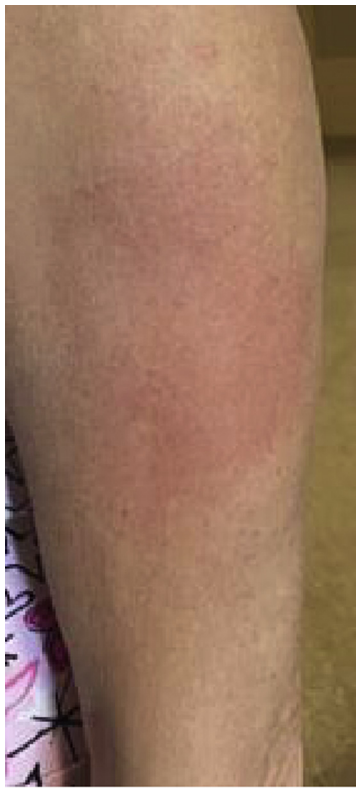

FIGURE 2. Injection site reaction on day 9.

may have reactions similar in appearance but earlier in onset after their second doses. We recommend that patients who have had such reactions receive their second doses on time in the usual manner without any special precautions.

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