Adverse cutaneous reactions after mRNA SARS-CoV-2 vaccination in 3 patients: a spectrum of severity

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Case 1

A healthy 7-year-old girl received her first dose of Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine in her upper arm. Forty-eight hours later, she developed localized erythema, induration and pruritic papular eruption at the injection site (Figure 1). There were no mucosal lesions, joint pain, fever or systemic involvement. She had no previous history of eczema; asthma; or food, drug or venom allergies.

Her family physician started oral H1-antihistamines. The patient’s symptoms resolved after 5 days without recurrence, and antihistamines were stopped. We subsequently assessed the child and gave a diagnosis of “COVID arm,” a delayed cutaneous hypersensitivity reaction, secondary to the mRNA SARS-CoV-2 vaccination. We advised the family that cutaneous reactions might recur but did not preclude future vaccinations.

Case 2

A 55-year-old man with a history of chronic spontaneous urticaria without angioedema received his third SARS-CoV-2 vaccination. He had had no complications with previous vaccinations, including his first 2 doses of SARS-CoV-2 vaccine (AstraZeneca AZD1222 and Pfizer-BioNTech BNT162b2). Twenty-four hours after his third vaccination, with Moderna mRNA-1273, he developed acute angioedema and urticaria (Figure 2). He had no systemic involvement (gastrointestinal, respiratory, cardiac) suggestive of anaphylaxis, and no involvement of mucosal surfaces, blistering, fevers or arthralgia.

We assessed the patient and diagnosed chronic spontaneous urticaria flare with angioedema secondary to immune activation after mRNA SARS-CoV-2 vaccination. Flares commonly occur after an immune response trigger, such as infections or immunizations. His symptoms were alleviated with oral H1-antihistamines and resolved within a week. He was advised that isolated urticaria with and without angioedema can be managed conservatively and are not contraindications to future vaccinations.

Case 3

A 56-year-old woman with eosinophilic esophagitis, asthma, eczema, allergic rhinitis and hypothyroidism received her third dose of Moderna mRNA-1273 vaccine. She had had no complications after the first 2 doses, but 3 days after her third dose, she developed a painful, raised, erythematous rash on her torso (Figure 3A). She had no urticaria, angioedema, arthralgia, fever or systemic involvement. Two weeks after onset, the rash coalesced to involve most of her body surface area (Figure 3B). She developed skin peeling and desquamation starting on her lower extremities, but no blistering lesions or mucosal involvement. Her family physician started a 7-day course of prednisone (30 mg day 1, tapered by 5 mg/d) and advised H1-antihistamines.

Despite treatment, 3 weeks after onset, the patient’s symptoms progressed to generalized erythroderma (Figure 3C) and she was admitted to inpatient internal medicine. She developed lymphocytosis (12 [normal 4.0–10.0] × 10^9/L), neutrophilia (8.9 [normal 2.0–7.5] × 10^9/L), elevated C-reactive

Key points
• Cutaneous reactions are uncommon adverse effects that can occur after SARS-CoV-2 vaccination as a result of immune activation.
• Delayed local cutaneous reactions (“COVID arm”) and isolated acute urticaria with and without angioedema can be managed conservatively and are not contraindications to future vaccinations.
• Patients with COVID arm or isolated urticaria with and without angioedema should be advised that cutaneous reactions may recur with future doses, but are often milder, of shorter duration and can be mitigated by premedication with oral H1-antihistamines.
• Erythroderma and severe adverse cutaneous reactions after SARS-CoV-2 vaccination are uncommon, but require prompt recognition and treatment and are contraindications to future doses.

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protein level (7.7 [normal ≤ 5] mg/L) and eosinophil count of 0.7 (normal 0.2–0.8) × 10⁹/L). The patient’s eosinophil levels a week before, while on oral corticosteroids, had been 0.0 × 10⁹/L, and previous blood work in 2014 showed a chronically elevated eosinophil count, up to 0.7 × 10⁹/L. Her hemoglobin, platelets, electrolytes, liver enzymes, renal function and autoimmune workup were within normal limits. She had no hemodynamic instability, end organ damage, lymphadenopathy or facial edema.

We started the patient on hydrocortisone valerate ointment 0.2% twice daily, topical emollients, oral H₁- and H₂-antihistamines and analgesics. Healthy skin developed under areas of peeling and she was discharged from hospital after 5 days.

The patient was transitioned to topical fluocinonide 0.05% and desonide 0.05% ointment. A month later, she was assessed by dermatology, who supported the diagnosis of erythroderma. Because her symptoms improved with therapy, no biopsy was performed. Her erythroderma was presumed secondary to mRNA SARS-CoV-2 vaccination. We subsequently assessed her and advised that future doses of mRNA SARS-CoV-2 vaccination are contraindicated.

Discussion

About 11.3 billion SARS-CoV-2 vaccinations have been administered worldwide, 81.5 million of which have been given in Canada.¹ With emergent reports of a wide range of cutaneous reactions after vaccination, clinical uncertainty and patient apprehension regarding subsequent doses have arisen.²

A study of health care workers who received mRNA SARS-CoV-2 vaccinations reported a 1.9% incidence rate of
cutaneous symptoms after the first dose. Of these, 17% reported recurrence of cutaneous reactions after the second dose. Other studies have estimated a recurrence rate of 8.5%-43% with subsequent doses. As of Apr. 24, 2022, in Ontario, adverse events after SARS-CoV-2 vaccination (mRNA and non-mRNA) occurred following 63.3/100,000 of doses administered. Allergic skin reactions comprised 22.7% of events. However, this rate is likely an underestimate, particularly for mild events, which are more likely to remain unreported to a health care professional.

Delayed local cutaneous reaction

Delayed local cutaneous reaction, colloquially called “COVID arm,” is a delayed injection-site reaction characterized by tenderness, erythema, pruritus and induration. It is differentiated from common acute injection-site reactions, which have immediate onset (<1 d), quicker resolution and decreased severity, as can be seen with other vaccinations or injections. In the Moderna mRNA-1273 Phase III trial, 0.8% and 0.2% of patients developed delayed injection-site reactions after the first and second doses, respectively. Symptoms can begin 2 days after vaccination, but typically develop within 6–8 days, lasting about 4–6 days, as in Case 1. Reactions after a second dose usually occur within 2 days, last a median of 3 days and are typically milder.

Observational studies have noted that more than 80% of patients reporting COVID arm are women. This may be because of reporting bias or increased vaccination status of women at the time of studies, or related to gender-specific differences in immunologic response to vaccination. In these studies, delayed local cutaneous reactions were more common after Moderna mRNA-1273 than Pfizer-BioNTech BNT162b2 or AstraZeneca AZD1222. Although exact incidence and recurrence rates are unknown, case series have noted that 50.0%-73.3% of patients who react after their first dose developed symptoms after their second dose. The severity of most second reactions was the same as or milder than initial symptoms.

Why some patients develop delayed local cutaneous reactions remains unknown, but T-cell responses to a vaccine excipient, mRNA component or lipid nanoparticle are thought to play a role. From those who have had biopsies, findings showed superficial perivascular and perifollicular lymphocytic infiltrates with rare eosinophils and scattered mast cells, in keeping with a delayed T cell–mediated hypersensitivity reaction.

Treatment includes supportive measures, cold compresses, H1-antihistamines, analgesics and topical corticosteroids. Delayed local cutaneous reactions are benign and self-limiting and are not contraindications to future vaccination. Patients should be advised that symptoms can recur with future doses, but are typically milder, with quicker onset and resolution.

Urticaria with and without angioedema

Urticaria with and without angioedema can flare after any immune activation, including vaccination or infection. In recipients of mRNA SARS-CoV-2 vaccinations, 1 study reported that...
0.4% and 0.3% of people developed urticaria and angioedema after their first dose, respectively. For people who reacted to the first dose, the recurrence of urticaria and angioedema was 3.3% and 2.6%, respectively. Of those who did not react to their first dose, 0.6% developed urticaria and 0.4% reported angioedema after their second dose.

However, in 1 United States–wide registry with clinician-reported reactions after SARS-CoV-2 vaccination, reported rates were higher; 13% of reactions consisted of urticaria with and without angioedema, three-quarters of which occurred after the first dose. Similar incidence rates of urticaria have been reported in Spain, with 18.6% of these patients having a previous history of urticaria with and without angioedema. In this Spanish cohort, 41% of reactions occurred with Pfizer-BioNTech, 25% with Moderna and 34% with AstraZeneca vaccines.

Isolated urticaria with and without angioedema can occur days after SARS-CoV-2 vaccination and is presumed secondary to host immune response or complement activation-related pseudoallergy. It should be distinguished from rare, immediate, life-threatening, immunoglobulin E (IgE)–mediated anaphylactic reactions. Anaphylaxis occurs within minutes after vaccine administration and is associated with other end-organ involvement. Urticaria and angioedema are both cutaneous symptoms, and in isolation, without involvement of cardiac, respiratory or gastrointestinal systems, do not meet criteria for anaphylaxis. Physician concern regarding vaccine allergy should prompt referral for further evaluation by an allergist.

Treatment includes H₁-antihistamines or, in more severe cases, oral corticosteroids. Urticaria is not a contraindication to future vaccine doses and does not require further subspecialist evaluation. Patients should be counselled about the possibility of recurrence due to immune activation with future vaccinations, and premedication with oral H₁-antihistamines is advised. In patients with a known predisposition for cutaneous eruptions with stressors, such as the patient in Case 2 with a history of chronic spontaneous urticaria, premedication with oral H₁-antihistamines can be considered, even if there is no previous history of cutaneous reactions after vaccination.

Any second-generation, nonsedating H₁-antihistamine — over the counter (cetirizine, loratadine, desloratadine, fexofenadine) or prescribed (bilastine, rupatadine) — can be used for premedication or treatment. Physicians may advise taking as much as 4 times the standard dosage (such as cetirizine 40 mg/d or bilastine 80 mg/d). H₁-antihistamines can be continued until symptom resolution.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions include delayed onset; T cell–mediated reactions, including acute generalized exanthematous pustulosis; drug reactions with eosinophilia and systemic symptoms; Stevens–Johnson syndrome; and toxic epidermal necrolysis. Although rare after SARS-CoV-2 vaccination, severe cutaneous adverse reactions must be promptly identified and treated, as reactions can be life threatening. Català and colleagues graded 20% of reported cutaneous adverse reactions after SARS-CoV-2 vaccination as severe and 1% as very severe (generalized erythrodemic, exfoliative, ulcerative or bullous rash).

Erythroderma, or exfoliative dermatitis, is characterized by skin erythema and desquamation compromising 90% or more of the total body surface area. It has a broad differential. It occurs most commonly secondary to an exacerbation of pre-existing dermatoses, such as psoriasis or spongiotic dermatitis, but can also be caused by T-cell lymphomas and paraneoplastic disorders. Immune-mediated skin conditions like atopic dermatitis and psoriasis may flare with vaccines, and pre-emptive optimization is advised.

Erythroderma can occur as an isolated adverse drug reaction, but may also occur with severe cutaneous adverse reactions. As in Case 3, onset typically begins with small patches of erythema that coalesce to involve most of the body surface area, progressing to scaling and skin peeling. Histopathologic findings include spongiosis, acanthosis, hyperkeratosis and perivascular inflammatory infiltrates. Drug-induced erythroderma can be associated with colloid bodies, lymphocytes and hydropic degeneration of the epidermal basal layer. Laboratory investigations may include elevated erythrocyte sedimentation rate, leukocytosis, eosinophilia, elevated IgE and anemia.

Treatment includes identifying and stopping contributory medications or causes, and supportive measures. Temperature regulation, proper nutrition, skin barrier protection, fluid status monitoring, H₁-antihistamines and topical corticosteroids are suggested. For severe symptoms, systemic corticosteroids can be started, such as prednisone 1 mg/kg/day with taper. For drug-induced reactions, symptoms typically resolve 2–6 weeks after the drug is stopped. For patients who developed erythroderma or severe cutaneous adverse reactions after mRNA SARS-CoV-2 vaccination, future doses with similar vaccine excipients, mRNA component or lipid nanoparticles are contraindicated.

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

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