

# Two Cases of Well Controlled Chronic Spontaneous Urticaria Triggered by the Moderna COVID-19 Vaccine

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## Abstract

Chronic spontaneous urticaria (CSU, chronic idiopathic urticaria) is a clinical diagnosis characterized by recurrent urticaria of unknown origin, with or without angioedema, that occurs for six weeks or longer. Management of CSU includes a second-generation H1 antihistamine and/or elimination of exacerbating factors. If initial treatment is unsuccessful, trials of first generation H1 antihistamine, H2 blocking antihistamine, leukotriene-receptor antagonist, anti-inflammatory or immunosuppressive agents may be administered. Exacerbating factors include stress, environmental conditions, medications, physical stimuli, and infections. We report the first two cases of a COVID-19 vaccine triggered relapse of CSU that was previously well controlled on therapy.

## Keywords

chronic spontaneous urticaria, CSU, COVID-19 vaccine

Chronic spontaneous urticaria (CSU, chronic idiopathic urticaria) is a clinical diagnosis characterized by recurrent urticaria of unknown origin, with or without angioedema, that occurs for six weeks or longer. Management of CSU includes a second-generation H1 antihistamine and/or elimination of exacerbating factors. If initial treatment is unsuccessful, trials of first generation H1 antihistamine, H2 blocking antihistamine, leukotriene-receptor antagonist, anti-inflammatory or immunosuppressive agents may be administered.<sup>1</sup> Exacerbating factors include stress, environmental conditions, medications, physical stimuli, and infections.<sup>1</sup> We report the first two cases of a COVID-19 vaccine triggered relapse of CSU that was previously well controlled on therapy.

The first case was a 49-year-old male who presented with a history of chronic spontaneous urticaria for the past twenty-eight years. The patient's hives presented on the front and back of his body, including his feet and hips. His exacerbating factors include warm temperatures and sunlight, however, there are times that wheals appear spontaneously. Previously, the patient has tried and failed two different high dose first

generation H1 antihistamines (Carbinoxamine and Cyproheptadine), as well as an H2 blocking antihistamine (Ranitidine). Subsequently, the patient was started on omalizumab (Xolair) 300 mg every four weeks, with success experienced after the third dose. The patient had been consistent with his omalizumab injections, and his symptoms were well controlled by pharmacotherapy for about 2 months. After the second dose of the Moderna COVID19 vaccine, the patient had a flare of urticaria identical to previous episodes. The outbreak occurred 16 hours after receiving the vaccination. The patient took cetirizine, and the wheals resolved within 6 hours. Since this flare up, the patient now continues to develop

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hives every 2 to 3 days, and his symptoms are no longer controlled with pharmacotherapy.

The second case was a 74-year-old female who presented with a past medical history of allergic rhinitis and chronic spontaneous urticaria. The patient's CSU symptoms include angioedema of the upper lip. Her last known flare was in 1973. The patient had spontaneous angioedema for multiple years until her symptoms became controlled with a first generation H1 antihistamine. When the patient received her first Moderna Covid-19 vaccine, she experienced the same swelling of her upper lip that she had last experienced in the 1970's. The edema appeared 30 minutes after injection and resolved within 30 minutes without pharmacological intervention.

## Discussion

Chronic spontaneous urticaria is defined by recurrent urticaria (also called hives, wheals, and nettle rash) of unknown origin.<sup>1</sup> The episodes may occur with or without angioedema, or with angioedema alone.<sup>2</sup> A patient will typically have these characteristic lesions most days out of the week for a time period of 6 weeks or longer. One hallmark feature of CSU is that the hives tend to wax and wane rapidly, typically lasting a time period of less than 4 hours.<sup>1</sup> The average duration of CSU is about 2 to 5 years, however, it can last longer than 5 years in 10–25% of people.<sup>3</sup>

The pathophysiology of CSU is still incompletely understood.<sup>2</sup> It involves active and degranulating mast cells within the dermis that release preformed and pre-activated mediators.<sup>2</sup> These include histamine, bradykinin, prostaglandins, leukotrienes, eosinophil and neutrophilic chemotactic factors, platelet-activating factor, and cytokines.<sup>1</sup> This cascade results in vasodilatations and an increase in vascular permeability, consequently leading to the formation of wheals.<sup>1</sup> Autoimmune processes are the main suggested mechanism of action of chronic spontaneous urticaria. Autoantibodies directed against the mast cells high-affinity receptor Fc-epsilon-RI and/or IgE have been found in up to 40% of patients with CSU.<sup>2</sup> When an autoantibody binds to the target, complement activation ensues, resulting in C5a formation that binds to the C5a receptor of mast cells.<sup>2</sup> Mast cell activation and degranulation then follows.

We present the first published cases of an episode of CSU triggered by the Moderna COVID-19 vaccine. In December 2020, the US Food and Drug Administration granted emergency use authorization to 2 mRNA vaccines (Pfizer-BioNTech and Moderna).<sup>4</sup> Several cases of delayed localized hypersensitivity vaccine reactions have been reported with the Moderna vaccine, however, in these cases the patients have no reported history of

CSU. A retrospective case study performed at Yale New Haven Hospital in New Haven, Connecticut identified 16 patients experiencing pruritic and variably painful erythematous reactions near the injection site (dubbed "COVID arm") developed in a median range of 7 days after the first dose of Moderna vaccine administration.<sup>4</sup> Similarly, a registry based study reported 343 unique cutaneous manifestations after the Moderna vaccination, which included 267 reactions after the first dose and 102 after the second dose.<sup>5</sup> The most common cutaneous reactions were delayed large local reactions, local injection site reaction, and urticaria.<sup>5</sup> Local site reactions were defined as occurring within 3 days of first-dose vaccination and delayed large local reactions were defined as occurring 4 or more days after the first vaccination.<sup>5</sup> Urticaria was defined as wheals in a distribution beyond the injection site.<sup>5</sup> No patients were reported to have a history of recurring angioedema or urticaria, making a diagnosis of CSU for these cutaneous reactions after vaccination not valid.

As previously described, chronic spontaneous urticaria is defined as recurrent urticaria, with the hallmark feature of hives that tend to wax and wane rapidly.<sup>1</sup> Patients tend to experience these symptoms for an average time period of two to five years.<sup>3</sup> While previous cases reported do have mention of urticaria and localized hypersensitivity reactions due to the Moderna vaccine, these findings do not include patients with a known history of CSU. Here we describe two cases of CSU triggered by the Moderna COVID-19 vaccine. Our findings are significant because the first step in treatment involves identification and avoidance of potential triggers. Chronic spontaneous urticaria is a mast cell driven disease that can occur spontaneously or induced by exacerbating factors. Triggers of CSU can be identified in 10–20% of cases.<sup>1</sup> These include stress, environmental conditions, medications, physical stimuli, infections, or autoantibodies.<sup>2</sup> If triggers are unavoidable, such as the case of immunization of COVID, then adjustment of pharmacotherapy prior to and post vaccination should be discussed with a physician. This pharmacotherapy includes management with second generation H1 antihistamines.<sup>3</sup> If the patient fails initial management, then trials of increased dose of second generation H1 antihistamine, first generation H1 antihistamine, H2 blocking antihistamine, leukotriene-receptor antagonist, anti-inflammatory or immunosuppressive agents may be administered.<sup>3</sup>

The expedited research and production of the Moderna Covid-19 vaccine has resulted in the potential for adverse effects not yet discovered. Current side effects of the vaccine under investigation include severe systemic inflammatory syndrome, hypersensitivity reactions, and Bell's palsy.<sup>6</sup> Here we describe the first cases of chronic spontaneous urticaria triggered by the

Moderna COVID-19 vaccine. Given the pattern of cases described, the association between the Moderna COVID-19 vaccine and CSU warrants further investigation.

### Ethical Approval

This study was approved by our institutional review board.

### Declaration of Conflicting Interests

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### Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

### Statement of Informed Consent

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