

# Secondary Syphilis Presentation and Urticarial Eruption After Moderna COVID-19 Vaccination

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**ABSTRACT** The diversity of the cutaneous manifestations of syphilis and the ability of the spirochete to evade diagnosis have been well documented by medical literature. However, what triggers the onset of secondary syphilis is not yet clear because of difficulties studying the bacterium. Our case describes the onset of a heterogeneous rash (or coexisting rashes) that presented the day after vaccination with the Moderna mRNA-1273 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. The potential etiologies of the patient's rash: A vaccine reaction, reactivation of chronic spontaneous urticaria, or a physical sign of syphilis itself are then reviewed. The potential for the Moderna coronavirus disease 2019 (COVID-19) vaccine to be the catalyst of this patient's cutaneous manifestations of his immune system responses is also hypothesized.

## INTRODUCTION

Syphilis is a sexually transmitted infection that has been described for centuries and still infects an estimated 6 million people worldwide annually, predominantly in low-income countries.<sup>1</sup> The Center for Disease Control and Prevention (CDC) reported 133,945 cases of all stages of syphilis with 41,655 cases of primary or secondary syphilis in the sexually transmitted disease surveillance data for 2020.<sup>2</sup> Syphilis is especially prevalent among certain populations in the United States, with a significant majority of infections occurring in men, and 53% of infected males being men who have sex with men.<sup>2</sup> The disease is well known to be caused by the spirochete, *Treponema pallidum*, and is primarily spread through sexual contact with infected mucosal surfaces on an infected host. The disease process of syphilis is divided into multiple stages. The first stage, primary syphilis, occurs when the bacterium multiplies and forms a classically painless and non-purulent indurated ulcer or chancre at the site of inoculation and is frequently associated with regional lymphadenopathy.<sup>3</sup> Primary syphilis occurs on average 3 weeks after exposure to the pathogen, and may frequently go unnoticed by the host.<sup>4</sup>

Secondary syphilis occurs in the absence of treatment an average of 8 weeks after resolution of the primary chancre, although not all chancres resolve before disease progression.<sup>4</sup> This stage of the disease is heralded by a rash typically described as a diffuse, maculopapular, erythematous

eruption that frequently involves the palms and soles and resolves spontaneously after several weeks.<sup>4</sup> By this stage, *T. pallidum* has spread throughout the host via hematologic dissemination, leading to systemic symptoms or symptoms of particularly affected organs.<sup>5</sup> These symptoms commonly include sore throat, malaise, low-grade fever, sore throat, headache, anorexia, painless adenopathy, mucous patches, and less frequently jaundice.<sup>4,5</sup> After the resolution of these symptoms, syphilis enters a latent phase of the disease and may progress into tertiary syphilis. Tertiary syphilis generally occurs after years of latent disease and is most frequently manifested as cardiovascular (often aortitis) or neurosyphilis (meningovascular syphilis, paresis, or tabes dorsalis etc.).<sup>4</sup>

We present a patient with multiple dermatologic manifestations almost immediately after administration of the Moderna coronavirus disease 2019 (COVID-19) vaccine that was ultimately diagnosed as a chronic spontaneous urticaria exacerbation and secondary syphilis. Sir William Osler is credited with the description of syphilis as the "Great Masquerader" attributable to its mimicry of the signs and symptoms of many other diseases and the variability of its cutaneous manifestations.<sup>6</sup> Thus, a case of syphilis evading diagnosis due to variability in its presentation is not a novel concept. However, the idea that secondary syphilis and an urticarial exacerbation were both provoked immune responses to the COVID-19 vaccine is a thought-provoking hypothesis.

## CASE

A homosexual young adult male presented to the emergency department (ED) for evaluation of a rash 20 hours after receiving the first dose of the Moderna COVID-19 vaccine. Our patient was found to have a temperature of 100.6 °F, bilateral tender anterior cervical lymphadenopathy, and complained of sore throat and nasal congestion. A physical exam demonstrated a non-pruritic erythematous patch on the chest, erythematous papules on the arms and lower abdomen, and pruritic skin-colored papules on his back. He was prescribed diphenhydramine and ibuprofen for a probable

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**FIGURE 1.** Secondary syphilis manifested as a maculopapular rash on the back of a patient. Reprinted from reference 7 with permission from the publisher.



**FIGURE 2.** Urticaria on the lower extremities. Reprinted from reference 8 with permission from the publisher.

allergic reaction to the vaccine. The patient returned on day 3 post-vaccination with spread of the rash to his arms and legs with sparing of his head, palms, and soles, worsened pruritus, and a temperature of 100.0 °F. Well-demarcated pruritic erythematous plaques were also noted over the patient's legs consistent with urticaria as well as an increase in the non-pruritic Erythema papules over his arms, back, and chest. See Figs 1 and 2.<sup>7,8</sup> Point-of-care laboratory evaluation for Influenza A + B, COVID-19, and *Streptococcus pyogenes* was negative, and acetaminophen, prednisone, and famotidine were added for probable allergic urticaria.

Our patient then presented 11 days after vaccination to the COVID-19 testing clinic due to persistent rash and newly reported fever, shortness of breath, fatigue, rhinorrhea, and myalgia. He was noted to have pruritic, erythematous, blanchable papules on his arms and legs consistent with an allergic

etiology and noted interval improvement. No further medications were added and COVID-19 testing again returned negative. On day 15 after vaccination, the patient returned with a temperature of 99.9 °F and paroxysms of increased pruritus. The physician noted improvement of the maculopapular rash on the forearms, abdomen, and chest and resolution of the eruption on his thighs. The patient denied recent or current genital lesions, urinary symptoms, or recent unprotected intercourse. Laboratory evaluation from this visit demonstrated antibodies to the rapid plasma reagin test with a titer of 1:128. He was treated with 2.4 million units of benzathine penicillin G. A treponemal antibody test obtained before the penicillin administration was positive. The patient then recalled unprotected homosexual sexual encounters a few months prior and public health was notified. He later confirmed resolution of his rash after treatment with penicillin and recounted a history of stress-induced chronic spontaneous urticaria (CSU). The patient's possible CSU eruption was also successfully treated with the regimen of antihistamines and systemic glucocorticoids described above. Ultimately, the patient elected not to receive the second dose of the COVID-19 vaccine.

## DISCUSSION

Our case describes likely secondary syphilis that initially evaded diagnosis attributable to the uncharacteristic urticarial rash and the temporal association with the Moderna COVID-19 vaccine administration. Although fever and lymphadenopathy in the setting of a diffuse rash (as seen in this case) are clues pointing towards syphilis, these signs are also possible reactions after the Moderna COVID-19 vaccination. Later, the patient's more systemic symptoms were consistent with possible COVID-19 at follow-up, which further delayed this patient's diagnosis as he was being evaluated for this and was quarantined despite a negative test. The diagnosis was likely further complicated by the atypical presentation of this rash, which was likely because of a combination of simultaneously occurring disease processes. The archetypal rash of secondary syphilis consists of an erythematous macular or papular eruption that is generalized, symmetric, and involves the palms and soles.<sup>9</sup> However, it is well known to take many forms and has even been previously described as urticarial.<sup>6,10</sup> Therefore, the heterogenous rash presented in this case may be attributable to the unifying diagnosis of syphilis. Another possibility is that the urticaria occurred via a different mechanism at the time of the onset of syphilis. Psychologic stress, recent vaccination, and bacterial infection may have caused the urticaria onset as all are known triggers of urticaria.<sup>11-13</sup> These triggers are therefore a likely cause or contributing factor to the urticarial portion of the rash. The patient's later elucidated personal history of CSU induced by stress makes this disease another likely cause or contributing factor to the urticarial portion of the rash.

The elicited inflammatory milieu and immune response to the disseminated syphilis infection and COVID-19 vaccination are alternative mechanisms that could have triggered

this patient's CSU. Four cases of CSU onset or recurrences in previously well-controlled diseases after COVID-19 vaccination have already been described in literature (Moderna: 2, Pfizer: 1, AstraZeneca/Oxford: 1).<sup>12,13</sup> 157 additional COVID-19 vaccine reactions had symptoms reported as CSU based on a search of reactions caused by all COVID-19 vaccines using the CDC's Vaccine Adverse Event Reporting System (VAERS).<sup>14</sup> The vaccination alone is thus another plausible trigger of this case's urticarial rash. Infection is another factor that is known to exacerbate CSU and is another possible etiology or contributing factor to this patient's urticarial rash in the setting of his ongoing syphilis infection.<sup>15,16</sup> Yet, as the pathophysiology of CSU is not currently known and what triggers it is only identified in 10-20% of cases, the exact mechanism which catalyzed our patient's urticarial reaction in this patient remains uncertain.<sup>16,17</sup>

Another possible consequence of the Moderna COVID-19 vaccination in this patient is the possibility that the immunization could have instigated the onset of secondary syphilis. This hypothesis would be difficult to prove as routine progression of the patient's syphilis from primary to secondary stages from the natural course of disease without catalyzation from immunization was likely to occur. There is a paucity of data regarding host response to *Treponema pallidum* and the corresponding pathophysiology. This is attributable to both the difficulty in culturing the organism in vitro and the lack of a good inbred animal model for study, which also makes this theory harder to investigate.<sup>18</sup> However, the temporal association between the Moderna COVID-19 vaccine administration and the onset of the patient's rash allows the theory that secondary syphilis was precipitated by immunological response to the vaccine. Notably, Syphilis has been reported as a symptom after any vaccination 17 times and after COVID-19 vaccination from all COVID-19 vaccines given in the United States 13 times per the CDC's VAERS.<sup>14</sup> Furthering this hypothesis, the inflammatory response from the vaccine may share an immune pathway in common with the immune response to secondary syphilis.

Vaccination with the mRNA COVID-19 vaccines, including Moderna's mRNA-1273, has demonstrated the production of T helper type 1 (Th1) cytokines and Th1 polarized CD4+ T cells likely via the inherent immunostimulatory effect of the mRNA.<sup>19-21</sup> While Th1 cells are usually associated with the host response to viruses and intracellular bacteria, they have also been found to play a significant role in the immune response to *Treponema pallidum*, an extracellular bacterium.<sup>6,22,23</sup> The Th1 cytokine release induced by the administration of the vaccine therefore could have played a role in the immune response to the patient's ongoing syphilis infection and triggered the onset of the patient's rash and secondary syphilis.

*T. pallidum* persists in the human body after immunologic clearance of the primary chancre and despite the presence of pathogen-specific antibodies, high burdens of the bacteria can be found in intradermal lesions of secondary syphilis.<sup>23</sup>

The ability of the bacteria to evade clearance in the skin is thought to be as a result of antigenic variation of cell surface proteins, the lack of transmembrane proteins on the outer membranes of syphilis, and the bacterial density in the skin.<sup>5,23,24</sup> With the bacterium already in place in the cutaneous tissues of infected patients and *T. pallidum*-specific antibodies already circulating in the patient, the host seems primed to initiate an immune response at any moment with a small stimulus to the immune system. It is thus possible that along with the Th1 immune response from the Moderna COVID-19 vaccine a threshold to progress to secondary syphilis was reached.

## CONCLUSION

The inflammatory milieu caused by the COVID-19 vaccine is demonstrated here to be a possible trigger for the recurrence of CSU and the precipitation of the onset of secondary syphilis. Although the temporal association between these occurrences does not prove a causal relationship, it does demonstrate the possibility of the existence of such a mechanism. The possibility of CSU to be triggered by the patient's syphilis reaction or stress are alternative explanations. As the exact pathophysiologic mechanisms for CSU and the onset of secondary syphilis remain unknown, these hypotheses cannot be proven currently but present enticing directions for post-vaccination surveillance and future research. Continued use of VAERS to identify more cases of immune reactions such as this will undoubtedly aid in the identification of further cases and research. A note of importance for such future cases is that false-positive rapid plasma reagin tests after COVID-19 vaccination have been described and acknowledged by the Food and Drug Administration.<sup>25</sup> Thus, we recommend continued confirmatory treponemal testing of positive rapid plasma reagin tests in the setting of rashes that present after COVID-19 vaccination, as done in this case. The discovery of a more ideal inbred animal model allowing for improved in vivo research of syphilis would also provide a crucial step towards furthering our understanding of this spirochete's pathophysiology and interplay with the human immune system.

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None declared.

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