

A Case Report of Multiple Intermittent Urticaria After Treatment of COVID-19 Infection

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The authors report a case of a 32-year-old Thai woman with a COVID-19 infection that presented with urticaria and angioedema with a pityriasis rosea (PR)-like rash at a private hospital in Thailand. She presented at the hospital with bloody nasal discharge and diarrhea but without fever, myalgia, or any respiratory symptoms. She complained of angioedema and PR-like lesions on the third day of the treatment. Urticarial rash appeared intermittently for four weeks after all medications were discontinued, during which the patient had no fever, no respiratory symptoms, or any other symptoms. However, the RT-PCR results for COVID-19 RNA were positive during the time that the urticarial symptoms persisted. The COVID-19 RNA became negative on the fourth day after the last urticarial episode. Urticarial rash may be a clue that the inflammatory process is activated by COVID-19 virus after the treatment is completed.

Keywords: Cutaneous; Pityriasis rosea; Angioedema; Urticaria; COVID-19

Received 9 March 2021 | Revised 10 June 2021 | Accepted 15 June 2021

J Med Assoc Thai 2021;104(7):1214-7

Website: <http://www.jmatonline.com>

Cutaneous manifestations in patients with COVID-19 have a wide clinical spectrum with a reported frequency ranging between 1 and 20 percent^(1,2). Urticaria is one of the skin manifestations reported in COVID-19 patients, which usually occurs preceding or concurrently with common COVID-19 symptoms. Additionally, it can be an adverse side-effect of the treatment^(3,4). The authors reported a COVID-19 case with angioedema and pityriasis rosea (PR)-like lesions during the course of treatment. After recession of antiviral treatment, the present patient developed prolonged evanescent urticarial lesions intermittently, which was the only symptom presented until the polymerase chain reaction (PCR) result for COVID-19 RNA was negative. Urticaria may be a

clue that the inflammatory process is still activated by COVID-19 virus after completing the treatment of COVID-19.

Case Report

A previously healthy 32-year-old Thai woman had come to a private hospital in Thailand. She was one of the two cases presenting dermatologic manifestations among the 88 COVID-19 patients in the hospital. She presented with bloody nasal discharge and diarrhea but without fever, myalgia, or any respiratory symptoms. Due to a recent history of returning from abroad, a nasopharyngeal swab testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel assay was performed, and the result was positive. She was treated with chloroquine 250 mg twice daily, ritonavir 100 mg twice daily, and darunavir 600 mg twice daily. On the third day of the treatment, she suddenly developed swollen at the left periorbital area and both upper cheeks without urticarial rash and itchiness (Figure 1). However, her vital signs were normal, and her lungs were clear. She also developed multiple discrete scaly erythematous annular-to-round patches, and some had symmetrical collarette scales at the external upper arm, lower back, and buttock areas, with mild

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How to cite this article:

Bhumiratana N, Supasiri T, Salakshna N, Thanasarnaksorn W. A Case Report of Multiple Intermittent Urticaria After Treatment of COVID-19 Infection. *J Med Assoc Thai* 2021;104:1214-7.

doi.org/10.35755/jmedassocthai.2021.07.12420



Figure 1. Non-pruritic erythematous swollen lesion at left periorbital area and upper cheek.



Figure 2. Mild pruritic multiple discrete scaly erythematous annular-to-round patches with some collarette scales at external upper arm.



Figure 3. Erythematous urticarial lesion at anterior aspect of leg.

itchiness (Figure 2). As a result, angioedema and PR-like lesions were diagnosed, and dexamethasone 5 mg was given every six hours for two days until all lesions subsided. Antiviral medications were given for seven days. The day after discontinuing the antiviral medications, she developed multiple urticarial lesions on the face, arms, and legs without angioedema (Figure 3). All the lesions lasted less than 24 hours. These lesions developed four times over four weeks despite continuous antihistamine treatment, which was desloratadine 5 mg daily in the morning and hydroxyzine 10 mg daily at bedtime. During the fifth week, all urticarial lesions disappeared. Additionally, the SARS-CoV-2 RT-PCR testing was negative. The timeline of symptoms and treatment in this case is shown in Figure 4.

Discussion

The present case is a report of a COVID-19 patient with multiple skin manifestations including urticaria, angioedema, and PR-like lesions. Urticaria manifests as urticarial plaques, typically described as wheals and flares. Sometimes, it can present with angioedema⁽³⁾. The distribution of urticarial lesions in this case did not include the trunk area, while a systematic review and one of the largest series of urticaria in COVID-19 patients reported that the trunk was most commonly involved^(3,5). Moreover, the lesions in the present case did not seem associated with the severity of the disease, even though a previous prospective cohort study reported that the presence of urticaria was associated with more severe COVID-19 infections⁽⁵⁾.

It is already known that urticarial lesions in the majority of reported cases occurred concurrently with other COVID symptoms⁽³⁾ and subsided within one to two weeks⁽³⁾, with the reported mean duration of urticaria being 6.8 days⁽⁵⁾. A few case reports showed urticaria without other symptoms in COVID-19 patients, which also improved within one week^(6,7). The present case developed acute urticarial lesions intermittently throughout four weeks after treatment, even when the patient experienced no fever, no respiratory symptoms, or other COVID-19 symptoms. Only the COVID-19 RT-PCR were continuously positive during the course of intermittent urticaria. Notably, the pathophysiology of urticaria in COVID-19 is hypothesized by either the virus itself or drug eruption⁽³⁾. In the present patient, drug-induced urticaria was not likely to be taken into account due to the uncorrelated onset and prolonged intermittent urticarial eruptions. Therefore, her

32 year old Thai woman

- Came back from London
- Self quarantine

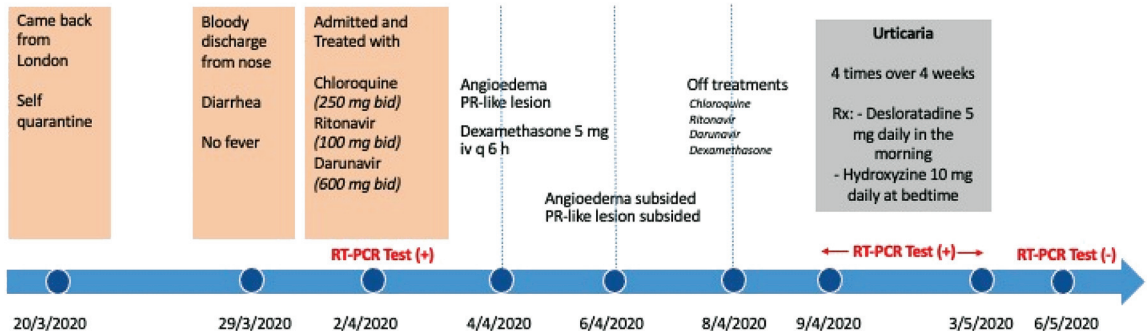


Figure 4. The timeline of symptoms and treatment in this case.

rashes most likely arose from the hypersensitivity reaction to SARS-CoV-2. This can be explained by the hypothesis that COVID-19 infections cause mast cell degranulation and activate inflammatory system-attributed urticaria⁽⁸⁾.

The present case also demonstrated other forms of skin eruption simultaneously with urticaria. She had PR-like lesions along with angioedema during the COVID-19 treatment period. While the cause of PR in general is still unclear, it is thought to be a viral trigger, which can occur in COVID-19 patients^(9,10). Similarly to the urticaria in the present case, the angioedema was likely triggered by SARS-CoV-2⁽¹¹⁾ since it developed on the third day of treatment, making it less likely to be caused by the drug. Additionally, there is a hypothesis that inhibition of angiotensin converting enzyme-2 (ACE2), which is a receptor of the virus in respiratory epithelial cells, causes bradykinin accumulation, leading to angioedema in COVID-19 patients⁽¹¹⁾. Interestingly, the present patient developed urticaria and angioedema without respiratory symptoms, which is different from many previous reports⁽¹¹⁾.

In terms of treatment, in the reported cases of SARS-CoV-2 infection with urticaria, improvement was achieved with antihistamine treatment⁽¹²⁾, while the present case still had multiple onsets of urticaria despite continuous treatment with antihistamines. Systemic corticosteroid along with oral antihistamines may be promising for urticaria, but may also increase the risk of prolonged viral replication⁽³⁾. In the present case, high dose corticosteroids were given for only two days, however, the viruses were detected for the following four weeks. Therefore, the authors propose

that low-dose systemic steroids may be more suitable for urticaria management, which is supported by a recent report demonstrating that low-dose systemic steroids with oral antihistamines can control urticarial attacks in COVID-19 patients⁽¹³⁾.

Interestingly, urticaria was the only sign present post-treatment other than the positive RT-PCR for COVID-19 for the duration of four weeks. Among other symptoms and signs in COVID-19 infection, urticaria is the objective symptom that can be easily detected. In addition, it is known that there is a causal relationship between viral infection and urticaria⁽⁸⁾. The present case report emphasizes that urticaria may be a clue that there is still having an inflammatory process activated by COVID-19 virus and the COVID test would still be positive. Accordingly, the present case report suggests that if urticaria still occurred, the COVID test after treatment to check the status of the virus may be postponed until the urticaria resolved.

Conclusion

To the best of the authors' knowledge, the present case is the first reported observation of multiple intermittent urticaria for four weeks despite full recovery of all COVID-19 symptoms, whereas the RT-PCRs for COVID-19 were positive during this time. As being known that viral infections are a known trigger for urticaria, urticaria may be a clue that there is still viral activity after treatment of COVID-19.

What is already known on this topic?

Urticaria can be seen in the COVID-19 patients. Most of the reported cases occurred concurrently with other COVID symptoms and normally subsided

within one to two weeks.

What this study adds?

This case developed intermittent urticaria for several weeks after treatment of COVID-19 infection. Furthermore, the COVID-19 RT-PCR was continuously positive, even when the patient experienced no other COVID-19 symptoms. The authors propose that urticarial symptom can be a clue that there still is viral activation after treatment of COVID-19.

Ethical approval and consent to participate

The present case was conducted ethically in accordance with the World Medical Association Declaration of Helsinki (COE 2021-01). The patient in this manuscript had given written informed consent to publish her case details and photos.

Authors' contributions

All authors listed have significantly contributed to the investigation, development, and writing of the case presentation.

Funding disclosure

The authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

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