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Case Report

Urticaria in COVID-19 Patient Treated with Lopinavir/ Ritonavir

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Abstract The unknown pneumonia was first found in Wuhan, China in December 2019. A novel corona virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated from lower respiratory tract swab in infected patient. The disease caused by this novel virus was then named as COVID-19 (Coronavirus Disease 2019). We report a male patient with urticarial lesions, varies on size and shape on the both arms and both legs and diagnosed with COVID-19 confirmed case. He was treated with powdered oral medicine containing combination of lopinavir and ritonavir. He developed urticarial lesions in three hours after administration of the drug. The lesions then dissapeared and resolved after 4 days of treatment using cetirizine. The conclusion of this case is still needed to be proven whether the urticarial lesion is related to COVID-19 or drugs used for COVID-19 therapy.

Key words
COVID-19, urticarial drug eruption, lopinavir, ritonavir, infectious disease.

Introduction

A novel coronavirus was first identified in Wuhan, China in December 2019[1]. The virus, later known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19), cause varying degree of illness with cough (67.8%), sputum production (33.7%), dan fever (on admission, 43.8%; during hospitalization, 88.7%) as the main symptoms.[1,2] In few months' time, the virus rapidly affected different parts of the world and was declared as a pandemic by the World Health Organization on March, 11th 2020. Until June 24th, 2020, there were 9.129.146 COVID-19 confirmed cases in the world. There were 47.896 COVID-19 confirmed cases in Indonesia, with 2.525 mortality cases.[3] Studies reported that the symptoms of COVID-19 is no longer limited to respiratory symptoms, but also cutaneous manifestations. A report by Recalcati[4] indicated that 20.4% of 88 patients included to the study in March 2020 had skin manifestations, such as rash (15.9%), urticarial (3.5%), and chicken pox-like lesions (1.1%). Joob *et al*.[5] reported a COVID-19 patient, having petechiae and dengue infection-like symptoms in Thailand. However, none of these studies have clear disease progression. A study by Zhang *et al*.[6] indicated that the skin manifestations might follow COVID-19

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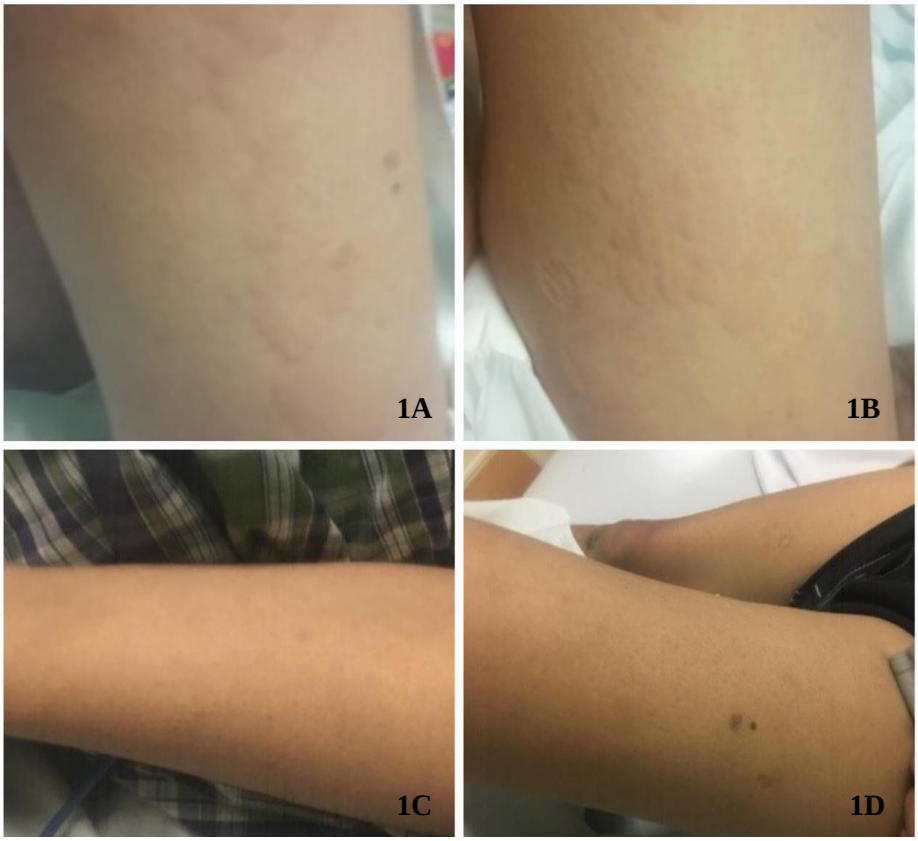

Figure 1 (1A, 1B) Urticarial lesions, variable in size and shape, on the both arms and legs bilateraly (before treatment), (1C, 1D) The urticarial lesions disappeared after 4 days of treatment.

infection as urticarial formation (1.4%) or might be part of drug eruptions (11.4%).

COVID-19 patients are commonly treated with antiretroviral therapy that is also given to other viral infections, such as HIV/AIDS. Koutou *et al.*[7] reported that antiretroviral therapy given to HIV/AIDS patients may develop cutaneous eruptions such as maculopapular exanthema (37%), fixed pigmented erythema (7%), and acute urticaria (5%). However, no study of patients treated with Lopinavir/ Ritonavir, an antiretroviral therapy which can be given to COVID-19 patients, claimed to have acute urticaria drug eruption,[7,8] There was limited data about skin manifestation in COVID-19 cases with no found Lopinavir/ Ritonavir urticarial type eruption. We reported a case of urticaria manifestation in COVID-19 confirmed patient treated with Lopinavir/ Ritonavir in our hospital in Surabaya, Indonesia.

Case report

A male patient was consulted in Department of Dermatology and Venereology with chief complaint of wheals on his arms and legs. He was diagnosed with COVID-19 confirmed case, and treated with powdered oral medicine contained Aluvia® (combination of lopinavir and ritonavir). Hours after powdered oral medicine administration, the wheal appeared on his arms, accompanied with itchy sensation. The wheals then spread on his legs, but no lesions on other skin area. He denied any swelling on both eyes, lips, and genital area. The patient also complained about pain when swallowing, shortness of breath, but there was no complaint of hoarseness.

The patient denied taking any drugs or traditional medication prior to hospitalization. He did not have any history of allergies to drugs, traditional medication and food, both in the patient's and his family's medical history. There were no history of asthma, allergic rhinitis, or atopic dermatitis both in patient's and his family's medical history. The history of hypertension, diabetes mellitus, and coronary heart disease was denied.

Vital signs included a temperature of 36.7 °C, heart rate of 92 beats per minute, blood pressure 114/85 mmHg, respiratory rate of 26 breaths per minutes, and oxygen saturation of 99% with O_2 simple mask. Physical examination revealed bronchovesicular breathing and rhonchi in both lower lungs. There were urticarial lesions, variable in size and shape, on both arms and legs **(Figure 1)**. There was no angioedema on the lips, palpebral area, and genital area. There was no other mucosal or ocular involvement.

The patient was first diagnosed with acute urticaria due to COVID-19 infection with differential diagnosis of drug eruption caused by Aluvia®. The suspected drug was then stopped, and oral cetirizine 10 mg twice daily was administered. After two days of treatment, the itchy sensation got better, and the urticarial lesions faded away. The urticarial lesions then completely disappeared after 4 days treatment. The timeline of interventions and outcome of this patient is shown in **Figure 2**.

Chest radiography revealed bilateral alveolar consolidation with peripheral distribution **(Figure 3)**. The latest laboratory examination showed white blood cells (WBC) count of 9.64 x 10^9/L, lymphopenia, neutrophil-to-lymphocyte Ratio (NLR) of 7, C-reactive protein (CRP) of 19.2 mg/dL. Serum glutamic oxaloacetic transaminase (SGOT) 52 U/L, serum glutamic pyruvic transaminase (SGPT) 74 U/L, serum creatinine 0.9 mg/dL, Blood Urea Nitrogen (BUN) 13 mg/dL, serum electrolyte consist of natrium 131 mEq/L, potassium 4.5 mEq/L, chloride 94 mEq/L, calcium 8.1 mEq/L, magnesium 1.8 mEq/L. Blood gas analysis showed respiratory alkalosis partially compensated metabolic acidosis with mild hypoxemia. A rapid test was positive at second day of hospitalization. PCR/ nasopharyngeal swab examination was positive at second day hospitalization. Four days later, the second PCR examination also revealed positive.

Discussion

Urticaria is a local, transient skin or mucosal edema (wheal) on erythematous macule that is usually pruritic.[9] Rapid and transient vasodilation of plasma into cutaneous or

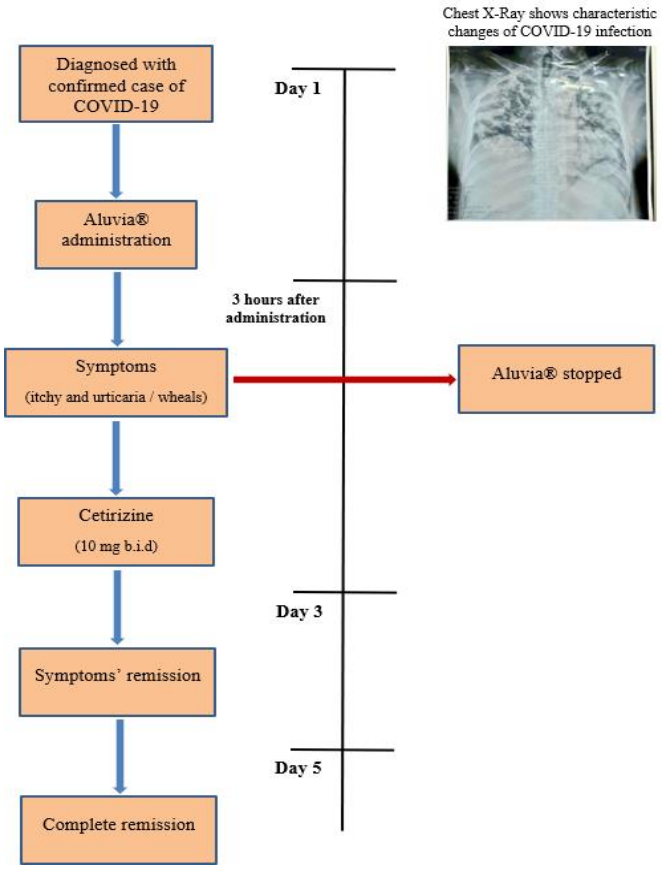

Figure 2 Timeline of interventions and outcomes.

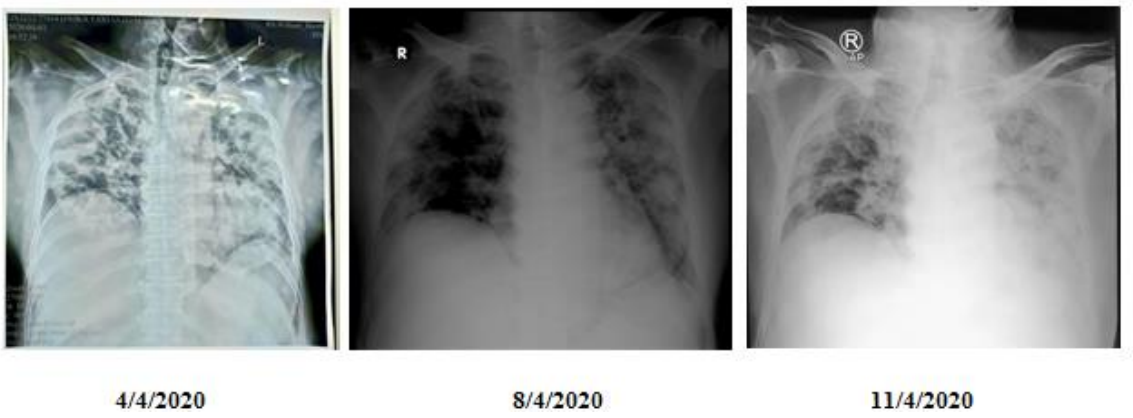

Figure 3 Chest radiography revealed bilateral alveolar consolidation with peripheral distribution.

mucosal tissue might happen spontaneously or triggered by multiple factors.[9,10] Amongst the most common causes of acute urticaria besides being spontaneous are infections (29%), drugs (5%), insect bite reaction (2%), and foods (1%).[10] It is more likely to be associated with respiratory tract infection (21%), including coronavirus infection, than other kind of infections.[10,11]

The first cutaneous observation in COVID-19 patients in Italia indicated that out of 20.4% COVID-19 patients develop cutaneous manifestations. To which, only 3,4% had urticarial rash.[4] Urticarial rash can present together with or before the onset of common COVID-19 symptoms such as cough and fever.[12-14] A 27-year-old woman was reported to have urticarial rash 48 hours before the onset of fever up to 39.2ºC.[13] Another study reported a 39-year-old nurse with urticarial rash, also 48 hours before the onset of pyrexia (38.3ºC).[14] The urticarial rash occurred almost simultaneously with COVID-19 disease onset in a report of 71-year-old man.[14]

Urticaria may occur as the disease progresses. A 60-year-old woman initially admitted to the hospital for dry cough and pyrexia with no history of taking any medication developed urticarial eruption after 3 weeks.[15] A 64-year-old female was initially admitted with difficult breathing, fever, and cough and treated with hydroxychloroquine, azithromycin, and oseltamivir before the onset of urticarial.[16] A 32-year-old woman was reported to have urticarial rash 6 days after the initial symptoms. She received hydroxychloroquine and azithromycin for 4 days before the rash occurred.[17] A 51-year-old COVID-19 patient developed urticarial rash 5 days after the onset of symptoms while receiving a combination of azithromycin, hydroxychloroquine, and cefoperazone-sulbactam medications[18]. None of the 3 cases above stopped the medication yet the urticarial rash was resolved after treatment with anti-histamines.

Although not impossible, the relationship between urticaria and infection is difficult to establish. It is hypothesized that COVID-19 may cause urticaria through complement activation and mast cell granulation, although it is also possible that the binding of COVID-19 to ACE2 receptor to activate bradykinin pathway[18,19] may be a contributing factor. These reports present evidence regarding a possible association between urticaria and COVID-19, especially when presented with pyrexia.

Nevertheless, urticarial drug eruption is a major differential diagnosis. COVID-19 is often treated with hydroxychloroquine and azithromycin, medications which can lead to an

urticarial rash.[20] Aluvia® was one of the HIV medicines, consisting of Lopinavir and Ritonavir with positive evidence against COVID-19. However, the highly active antiretroviral therapy (HAART) including this drug was reported to have a marked increase in the incidence of adverse drug reactions. HAART may cause mild to severe adverse drug reaction, such as maculopapular reaction, urticarial reaction, morbilliform reaction, Stevens-Johnsons' syndrome/ toxic epidermal necrolysis (SJS/TEN). The most common adverse drug reaction caused by Lopinavir/ Ritonavir was maculopapular rash.[8] Despite all the reports regarding the adverse events and the phase II-IV study to the drug, no data was indicative that the drug may cause urticarial rash.

Conclusion

To conclude; urticarial rash, especially when accompanied with pyrexia, is indicative of COVID-19 disease. Aluvia® may not be the causative agent of urticaria found in this case, however further examinations are needed to confirm the diagnosis,

(there seems to be no significance of reporting it then) which is the one of the limitations in this case report. Urticarial drug eruption is a differential diagnosis that still cannot be eliminated from this study.

The patient stated that he was satisfied enough with the therapy for both the COVID-19 and the urticarial lesions. The patient denied any side effect or anything that is uncomfortable. He understood that COVID-19 is a new disease with many symptoms and factors involved and hoped that this disease will have proper medication guidelines. He also gave his consent for his photos to be published in this case report.

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