

CASE REPORT

Uncommon presentation of COVID-19 illness- A concern for delay in diagnosis

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ABSTRACT

Background: COVID-19 illness can present with atypical extra pulmonary manifestations, with cutaneous manifestations being one of them. Dermatological manifestations have been found in around 20.4% of cases, ranging from Urticaria to vesicular rash, livedo reticularis and pseudo-chilblains.

Case Presentation: We present a case of 40 year old female presenting with typical COVID-19 symptoms when she developed an urticarial rash on the 10th day of her illness followed by angioedema involving lips. Drug-induced urticarial rash and other triggering factors known for Urticaria were ruled out; eventual diagnosis of virus-induced urticarial rash was made. She was managed with oral steroids, antihistamine agents and local Lacto calamine lotion. There was complete resolution of rash within 48 hours of RT-PCR negative for COVID-19.

Conclusion and clinical Significance: This highlights that COVID-19 can present with atypical manifestations, and clinicians should be aware not to misdiagnose or delay the diagnosis of the disease, hence reducing the likelihood of transmission of dis-ease.

Keywords: COVID-19, dermatology, Infectious disease

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BACKGROUND

As we are currently engulfed in the global pandemic of COVID-19 caused by the SARS CoV-2 virus, our understanding and learning of its presenting signs and symptoms are changing rapidly. Initially, the most common presenting complaints were fever, dry cough, myalgias, shortness of breath etc., but as we progressed and the number of cases increased, we came across some atypical presenting complaints, including cutaneous manifestations. Cutaneous manifestations have been described from maculopapular rash, urticarial, chilblain-like acral pattern, vesicular lesions, livedo reticularis-livedo racemosa-like pattern, and purpuric "vasculitic" pattern.^{1,2} Although the overall incidence of these dermatological manifestations has been reported to be around 20.4% in a report from Lombardy, Italy,³ but in our institutional experience, we have seen lesser incidence. This might suggest misdiagnosis, delayed diagnosis and/or late presentation of cases, hence underlining the importance of correlating the

dermatological symptoms with COVID-19 illness. Here we present a case of Urticaria and subsequent angioedema in a non-ICU patient with COVID-19 disease from Kashmir, India.

CASE PRESENTATION

A 40-year female presented in COVID clinic with a one-day history of myalgia, fatigue, fever (102°F), chills and rigours, and no associated rash. She reported a loss of appetite but no history of diarrhoea, nausea and vomiting, loss of taste and smell. In view of suspicion of SARS-CoV 2 infection, RT-PCR (Reverse transcriptase-Polymerase chain reaction) test was done, which came out to be positive. The patient was advised home isolation and symptomatically managed. Over the next two days, the patient developed

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Figure 1, 2: Urticarial erythematous rash with central clearing and no discharge was seen on bilateral lower limbs, around knees on both anterior and posterior aspect.



Figure 3: A similar diffuse urticarial rash as seen on extensor surface extending from arms above to forearms below.

new-onset shortness of breath with oxygen saturation around 94% on room air. She consulted a general practitioner and was started on Favipiravir. She continued medication uneventfully for seven days. On the 10th day of illness, the patient developed a rash, which was sudden in onset, associated with chills. She was admitted inpatient for evaluation. On admission, vitals were as follows: Blood pressure 110/70, heart rate 85/min, respiratory rate 20/min, SpO₂ 97% on room air, Temperature 99.4 F.

On examination, a rash was present on bilateral upper and lower extremities sparing palms/soles, face and trunk. It was blanching in character, erythematous with central

clearing, pruritic and non-painful [fig.1,2,3}. No associated discharge was seen. The results of Lab investigations were as follows on admission : low hemoglobin 9.6 g/dl , Total WBC count 3300 cells/mm³, Differential count 63% neutrophils, 28% lymphocytes, 2% eosinophils, Platelets 223,000 cells/mm³ , MCV 66.6 fl/cell, Urea 31mg/dl, Creatinine 0.76 mg/dl, Bilirubin 0.16 mg/dl, ALP 63 IU/L, D dimer 177 ng/ml , IL- 6 9.08 pg/ml, CRP 6.5 mg/dl Ferritin 107 ng/ml. HRCT was done {fig 4.} suggestive of atypical pneumonia with subpleural bilateral ground-glass opacities with CORADS 6 (Covid reporting and data system), CT severity index 10/25. On the very next day, she

Figure 4: High resolution Computed Tomography of chest showing subpleural bilateral Ground glass opacities with right lower zone consolidation, with CT severity index of(CTSI) 10/25.

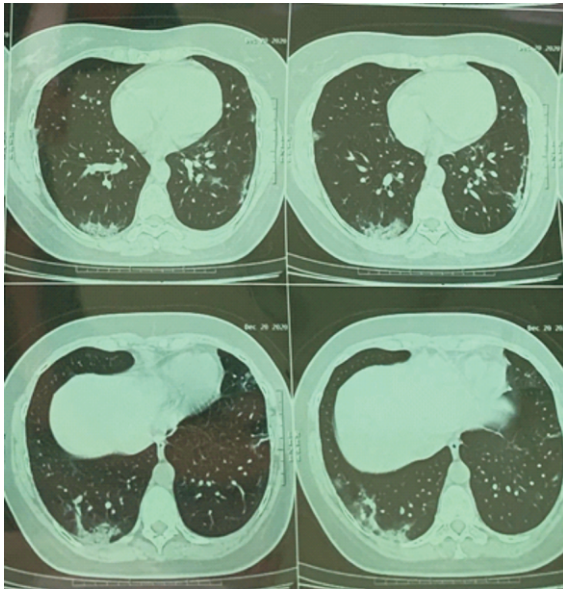


Figure 5: Figure 5: Angioedema involving both upper and lower lips.



also developed swelling and redness of lips one day after rash{fig 5.}. Favipiravir, thought to be one of the triggers, was discontinued on the first day of hospitalization. She was managed with oral steroids, antihistamine agents and local Lacto calamine lotion. She had symptomatic improvement with the medications, but the rash continued to reappear for the next few days as the medication effect weaned off. The patient had no history of a similar rash in the past or any known drug allergies. She was symptomatically managed over the next few days, with the rash weaning on and off in between. Autoimmune causes for drug rash were ruled out, IgE levels were normal, there was no eosinophilia. A skin biopsy was not done due to equipment limitations.

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis included spontaneous Urticaria, but since the rash initially, before hospitalization, persisted for more than 24 hours, making this diagnosis less likely. Another possibility was drug-induced urticarial rash, but other than Favipiravir patient had no history of any additional drug intake in the past 15 days. In our research, various studies have shown that favipiravir has not been associated with any cutaneous adverse events.^{4,5,6} Also, the rash reappeared even after the drug was stopped and

continued to appear till the patient was RT-PCR negative for SARS-CoV-2; hence the possibility of drug-induced Urticaria triggered by favipiravir was unlikely. Urticarial vasculitis was another possible differential diagnosis, but those lesions tend to burn and sting, not itch.⁷ which was not the case in our patient. In addition, the lesions can resolve with discolouration of the skin, either as a bruise or dark pigmentation, which did not occur with our patient, where the rash resolved completely, leaving no residual marks.⁸ Also patient had no history of any recent contact with known skin allergens, any recent change in detergents, soap or any new cosmetics. Considering no urticaria trigger other than a virus could be found, diagnosis of viral(SARS CoV-2) induced urticarial rash with angioedema was considered. A skin biopsy of the same was not possible due to equipment limitations.

TREATMENT

The patient was managed with tablet Prednisone 40 mg once daily, Levocetirizine hydrochloride 5mg twice daily and topical Lacto calamine lotion three to four times daily. She had immediate relief in itch with antihistamines and steroids; the rash continued to appear once the medication

effect weaned off. No change in treatment was sought, as the patient felt subjectively better, and no progression of rash both in severity and spread was observed.

OUTCOME AND FOLLOW-UP

Repeat RT PCR was done on the 4th day of admission corresponding to the 14th day of illness, which came out negative, and the patient had resolution of rash within two days of the negative status of COVID illness. On follow up, the patient has been asymptomatic with no reappearance of rash and has resumed her daily activities.

DISCUSSION

Viral infections are known to have cutaneous manifestations. Urticaria, specifically, is linked with several viral infectious agents.⁹ A recent prospective study from Spain¹⁰ reported different eruptions in 375 COVID-19 patients with urticarial lesions consisting of 19% of them, the rest being maculopapular eruptions, acral areas of erythema with vesicles or pustules (pseudo-chilblain), other vesicular eruptions and livedo or necrosis. Urticarial signs have been seen to appear concurrently with different symptoms and last for an average duration of 6.8 days. Our patient developed signs on the 10th day of her illness, lagging slightly behind the average. Apart from the one study by Galván Casas et al.¹⁰ which showed an association between acute urticaria and increased mortality (2% mortality in the sample), multiple other studies which have failed to show a correlation of Urticaria in COVID-19 with disease's severity, which can be seen in our case as the patient was in stable condition and has fully recovered.

Various hypotheses regarding the development of urticarial rash in COVID-19 patients have been postulated, which is believed to be multifactorial in origin. Viral-induced complement activation leading to mast cell activation with degranulation and histamine release can give Urticaria.⁹ Second, Angiotensin-converting enzyme 2 (ACE2), the protein which SARS-CoV-2 uses to enter cells, is found abundantly in the vasculature, particularly vascular endothelium. This mode of entry disrupts the regular ACE2 activity, leading to increased activity of Angiotensin II, forming reactive oxygen species, leading to complement activation and hence mast cell degranulation.^{11,12} Third, Angioedema has been known to be caused by leakage of plasma from postcapillary venules, mediated principally by histamine and bradykinin. SARS-CoV-2 mediated

downregulation of ACE2 receptor results in impaired degradation of bradykinin with late-onset angioedema. However, Bradykinin-mediated angioedema is less common than histamine-mediated angioedema.^{13,14} Our patient with Urticaria with pruritis could suggest histaminergic mediated origins which resolved with antihistaminics, and subsequent angioedema could suggest both histaminergic and bradykinin mediated origins.

LEARNING POINTS/CLINICAL SIGNIFICANCE

- COVID-19 is presenting with varied atypical presentations, including dermatological manifestations.
- Urticaria is one of the most common cutaneous manifestations in COVID-19
- Primary care physicians are most likely to miss Urticaria as a manifestation of COVID-19, delaying diagnosis or leading to misdiagnosis.
- In this case, Urticaria with angioedema was a delayed presentation, which was confusing at first, treated with oral steroids, disappeared after viral clearance from the body.
- This was the first reported case of dermatological manifestation of COVID-19 in our setup.

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REFERENCES

1. Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. *Br J Dermatol*. 2020;183(3):431-442.
2. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: An international registry of 716 patients from 31 countries. *J Am Acad Dermatol*. 2020;83(4):1118-1129.
3. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34(5):e212-e213.
4. Costanzo M., De Giglio M.A.R., Roviello G.N. SARS CoV-2: recent reports on antiviral therapies based on

- lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. *Curr Med Chem.* 2020;27:45364541.
5. PREVAIL II Writing Group. Multi-National PREVAIL II Study Team. Davey R.T., Jr. A randomized, controlled trial of ZMapp for Ebola virus infection. *N Engl J Med.* 2016;375(15):14481456.
 6. Sissoko D., Laouenan C., Folkesson E. Experimental treatment with favipiravir for Ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med.* 2016;13(3):E1001967.
 7. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992;26:441488
 8. Dincy CVP, George R, Jacob M, et al. Clinicopathologic profile of normocomplementemic and hypocomplementemic urticarial vasculitis: a study from South India. *J Eur Acad Dermatol Venereol* 2008;22:789794
 9. Wedi B., Raap U., Wiczorek D. Urticaria and infections. *Allergy Asthma Clin Immunol.* 2009;5:10.
 10. Galván Casas C., Català A., Carretero Hernández G. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol.* 2020;183:7177.
 11. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203: 631637.
 12. Vaduganathan M., Vardeny O., Michel T. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med.* 2020;382:1653-1659.
 13. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract* 2018;6:113241
 14. Cohen AJ, DiFrancesco MF, Solomon SD, et al. Angioedema in COVID-19. *Eur Heart J* 2020; 34: 3283-3284
 15. Hoffman M, Kleine-Weber H, Schroder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271280.