

Case report

Urticaria and angioedema as a prodromal cutaneous manifestation of SARS-CoV-2 (COVID-19) infection

Khalid Hassan^{1,2}

¹Loch Lomond Surgery, 75 Bank Street, Alexandria, Scotland
²Department of Dermatology, Vale of Leven Hospital, Alexandria, Scotland

Correspondence to
 Dr Khalid Hassan;
 khassan@nhs.net

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SUMMARY

This is a case of a patient who presented with an urticarial rash 48 hours before developing symptoms of fever and a continuous cough. She subsequently developed angioedema of her lips and hands before testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Urticarial rashes occurring 48 hours before other symptoms of COVID-19 infection have been documented. This case demonstrates the importance of heightened awareness that not all urticarial rashes represent spontaneous urticaria and as a consequence, this may result in misdiagnosis and ultimately delayed diagnosis. This is the first reported case in the literature of urticaria with angioedema as a prodromal phenomenon of COVID-19.

BACKGROUND

Cutaneous manifestations of COVID-19 are increasingly being recognised and reported. Urticarial rashes have been identified as being associated with and can occur 48 hours before other symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This case demonstrates the importance of heightened awareness that not all urticarial rashes represent spontaneous urticaria and as a consequence, this may result in misdiagnosis and ultimately delayed diagnosis. This is the first reported case of urticaria with angioedema as a prodromal phenomenon of COVID-19.

CASE PRESENTATION

A 46-year-old staff nurse presented to an emergency doctor on 12 April 2020 with a 24-hour history of a widespread red-raised blanching and itchy rash. Her partner had just recovered from presumed COVID-19 infection; having only had mild symptoms, she was not tested and was back at work. Our patient was on day 13 of self-isolation and was hoping to return to work the following day. She had no fever or continuous cough but did have some nasal congestion. The patient had a history of hay fever, a possible nut allergy and mild asthma. She had not been prescribed any regular medications and had not taken any over-the-counter medications; she had no known allergies to medications. The general practitioner described a classical urticarial rash affecting her upper and lower limbs in addition to her trunk. A diagnosis of probable idiopathic urticaria was suggested and the patient was prescribed fexofenadine hydrochloride 180 mg, to be taken two to four times per day. The following

day the rash worsened and was now associated with swelling of her lips (figure 1) and hands; she now felt feverish and had developed a dry cough. She had a slight wheeze but no tongue or throat swelling. She was subsequently assessed by another general practitioner, her temperature was 36°C, her pulse was 98 beats/min and her oxygen saturation was 98% on room air. She had a widespread urticarial eruption affecting her face, arms, torso, legs and loins. The general practitioner who examined her diagnosed urticaria, but also documented the possibility of an allergic reaction or a viral illness.

INVESTIGATIONS

Reverse transcriptase PCR test on combined nasopharyngeal/oropharyngeal swabs was positive for SARS-CoV-2, 2 days after first presenting to the emergency doctor. A skin biopsy was not carried out.

DIFFERENTIAL DIAGNOSIS

Urticaria is a disease characterised by itchy weals, angioedema or both. It may be spontaneous or inducible, depending on its pattern, and acute or chronic, depending on its duration.¹ Common differential diagnoses would include spontaneous urticaria but this was unlikely as our patient's rash lasted more than 24 hours and proved resistant to treatment.^{2,3} In hindsight, this should have possibly called into question the initial diagnosis. Urticarial-like skin lesions and urticaria can occur with drug eruptions and these can persist for several days.⁴ However, our patient had not taken any new medications in the preceding 14 days. Urticarial vasculitis is a possible differential diagnosis, but the lesions tend to burn and sting rather than an itch.⁵ In addition, the lesions can resolve with bruising or hyperpigmentation, which did not occur with our patient, where the rash resolved completely leaving no residual marks.⁶ Urticarial dermatitis would tend to affect the more elderly and is commonly accompanied by dermatitic lesions.⁷ This did not occur with this patient. Contact dermatitis, which can appear urticarial and contact urticaria, presents with an eruption localised to the site of contact with an irritant or an allergic contact allergens.⁸ Yet, our patient had not come into contact with or used any new substances or products. Occasionally, autoimmune bullous diseases can initially present with an urticarial rash.⁹ These tend to affect the elderly or occur in pregnancy, with a tendency to occur symmetrically on the trunk but also flexures.



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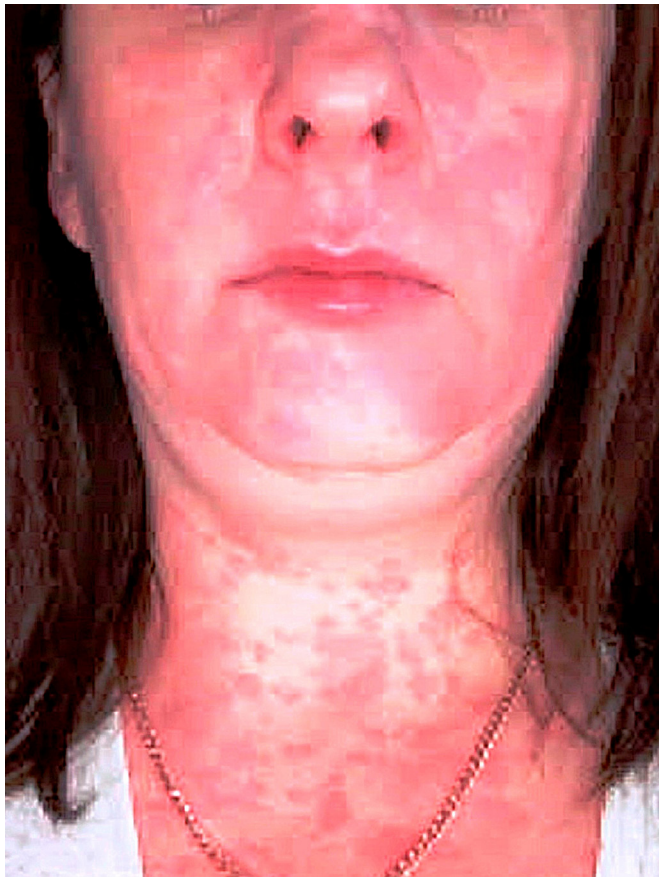


Figure 1 Urticarial erythematous eruption affecting the face, neck and upper chest. In addition, there is mild angioedema of the lower lip, as a result of excess interstitial fluid in the dermis and subcutaneous tissue.

They do not tend to affect the face, which did occur with our patient.^{9 10}

TREATMENT

She was advised to continue taking fexofenadine hydrochloride 180 mg four times per day and she was commenced on prednisolone 40 mg once daily for 3 days. The GP advised self-isolation for 7 days and suggested testing for infection with SARS-CoV-2. Prednisolone helped her lip and hand swelling, but her rash was still itchy and chlorphenamine maleate 4 mg four times per day was subsequently added.

OUTCOME AND FOLLOW-UP

The rash resolved completely over the next few days. The patient made a full clinical recovery and did not undergo further PCR testing before resuming her duties.

DISCUSSION

The prevalence of cutaneous eruptions with COVID-19 has been reported to vary between 0.2% (2/1099) and 20.4% (18/88).^{11 12} In Dr Recalcati's review, the majority of patients had an erythematous rash, one patient had chickenpox-like vesicles and 3% of their cases had an urticarial type rash.¹² Itching as a symptom was reported as being low or absent, which was not the case with our patient, where it was a predominant feature. A case report from France discussed a patient who developed a facial and acral urticarial rash 48 hours before the onset of fever, which was the case with our patient.¹³ With COVID-19, early recognition that

urticaria may be a prodromal sign of infection and early diagnosis would certainly aid prompt testing, tracking and tracing as suggested by the WHO to reduce transmission.¹⁴

Other authors have also identified urticaria and fever, urticaria and drug hypersensitivity, a varicella-like exanthem, a petechial rash, a morbilliform rash, transient livedo reticularis, an eruption similar to symmetrical drug-related intertriginous and flexural exanthema, erythematous-purple pedal papules, vasculitis and chilblains in association with SARS-CoV-2 infection.¹⁵⁻²⁴

More recently, Galván Casas *et al* identified five different eruptions in a study of 375 patients: maculopapular eruptions (47%), urticarial lesions (19%), acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%) and livedo or necrosis (6%).²⁵ They further showed that patients with livedo/necrotic lesions were often elderly and had more severe disease, while those with pseudo-chilblains tended to run a milder course. It is not yet certain how different cutaneous

Patient's perspective

I was on day 13 of self-isolation as my partner had just recovered from mild symptoms of COVID-19 and had returned to work on that Monday. However, goalposts changed and I developed urticaria, which accelerated in presentation over the course of that weekend. In the back of my mind, I did question was the urticaria linked to COVID-19? That was dismissed when I presented to out of hours GP who diagnosed urticaria possibly due to an allergic reaction and I was prescribed fexofenadine hydrochloride 180 mg two to four times per day. I felt generally unwell, feverish and had developed a continuous cough. My rash worsened and I developed angioedema of my lips and hands, which caused me great concern. During my illness, I went through a roller coaster of emotions from being scared of the unknown, my anxiety levels were heightened and I physically felt ill and was frightened that my tongue would swell compromising my airway. I was constantly checking this regularly. For about 2 weeks, the exhaustion took hold even going to the bathroom was tiring and took great effort. I spent the majority of my time in bed staring at the ceiling and sleeping. I made sure I was drinking plenty of fluids as my appetite was non-existent. From being diagnosed positive with COVID-19 and going through nearly 3 weeks of illness, this made me reflect on life in general and how lucky I was not to be admitted to hospital. Also, it makes people aware that this COVID-19 virus manifests itself in many different forms in each individual.

Learning points

- ▶ Cutaneous manifestations of COVID-19 are increasingly being reported.
- ▶ Urticarial rashes have been identified as being associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- ▶ It is important to be aware that not all urticarial rashes represent spontaneous urticaria, as this may result in misdiagnosis and delayed testing, tracking and tracing.
- ▶ In this case, the urticarial rash preceded symptoms by 48 hours, which led to delay in diagnosis; this may result in a lost opportunity to prevent transmission.
- ▶ This is the first reported case of urticaria with angioedema as a prodromal phenomenon of COVID-19.

manifestations correlate with disease severity or indeed if the timing of occurrence of the different eruptions has an impact on the clinical course of the illness. Cohen *et al* published a case of a 62-year-old man with a 12-day history of fever, rigours, lassitude, myalgias, anorexia, anosmia, ageusia and a persistent dry cough, who then went on to develop angioedema of the upper lip, which progressed to include swelling of his cheeks and lower face without urticaria.²⁶

The variety of rashes identified does suggest possible different pathophysiologies. Those appearing early may reflect the virological phase, while those occurring later may be indicative of the functional or possibly a dysfunctional immunological response.²⁷ The pathophysiology of this disparate group of presentations has yet to be elucidated but may be made clear by analysis of histopathology samples.²⁰

Angioedema is due to the leakage of plasma from postcapillary venules in the deeper layers of the skin or mucosa and is mediated principally by histamine and bradykinin.^{28–29} Bradykinin-mediated angioedema is less common than histamine-mediated angioedema but is disproportionately associated with greater morbidity and mortality.²⁸ SARS-CoV-2 uses the ACE2 receptor for entry into the cell.³⁰ This results in downregulation of the ACE2 receptor and consequently impaired degradation of bradykinin with late-onset angioedema as highlighted by Cohen *et al*.²⁶ In contrast, in this case report, the patient experienced concomitant urticaria and pruritus suggesting a histaminergic origin.³¹

This patient's urticarial symptoms persisted despite taking fourfold the standard daily dose of fexofenadine hydrochloride and indeed, she went on to develop symptoms of angioedema affecting her lips and hands. The lack of response to treatment should have possibly prompted a re-evaluation of the diagnosis. A search of Google, Google Scholar, PubMed, medRxiv and Trip revealed no published cases to date of COVID-19 presenting initially with urticaria in association with angioedema. It is easy in hindsight, but if the doctor treating her at the time had considered that she may have SARS-CoV-2 infection, would she have been prescribed an oral corticosteroid, with the potential for immunosuppression? Currently, there are no guidelines for the management of angioedema without anaphylaxis during the acute illness in a patient with COVID-19 positive.

Contributors I am a general practitioner and associate specialist working solely with the NHS in Scotland.

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