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LETTER

Urticaria in the times of COVID-19

Dear Editor,

Coronavirus disease (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has caused unforeseen mortality, morbidity, and severe economic disruptions in recent times.

Of late, there has been a growing interest regarding the dermatological manifestations in COVID-19. In an early retrospective study among 140 patients, Zhang et al[1] reported 11.4% patients to have drug hypersensitivity and 1.4% to have urticaria. In a report from Italy, 18/88 (20.5%) patients had dermatological manifestations, with 3 patients reporting widespread urticaria.[2] As per one review, 88/256 (34.3%) patients across 16 studies demonstrated skin manifestations, mostly as erythematous maculopapular rash, urticaria, or vesicular rash.[3] On closer look, we find urticaria to be a commonly reported finding among COVID-19 patients. In one of the large prospective studies involving 375 COVID-19 cases, urticaria was present in 19% cases, with mean duration of urticaria being 6.8 days.[4] Although there was a report of one COVID-19 patient presenting with urticaria and dry cough without any fever,[5] the timing of appearance of urticaria was variable, with lesions appearing before, with, as well as >48 hours after onset of fever.[6-9] In most cases, diagnosis of urticaria was made clinically and oral second-generation antihistamines were prescribed with satisfactory results.[6-9] Although skin manifestations did not correlate with disease severity in most case reports,[2,6] the prospective study from Spain suggested that the presence of urticaria and maculopapular lesions was associated with more severe COVID-19 illness and a higher (2%) mortality.[4]

Pathophysiology of urticaria in COVID-19 infection is hypothesized to be multifactorial. Although drug-induced urticaria may be an obvious explanation, urticaria preceded drug therapy or showed spontaneous remission despite continuation of therapy for COVID-19,[6] suggesting that drugs alone may not account for many cases. A direct role of virus-induced mast cell degranulation may be one possibility. SARS-CoV-2 enters cells using angiotensin-converting enzyme-2 protein, which is also present in vascular tissues. Deposition of antigen-antibody complexes leading to complement activation and mast cell degranulation, as well as bradykinin involvement, has been suggested as mechanisms of virus-induced urticaria or urticarial vasculitis. Colocalization of SARS-CoV-2 glycoproteins with complement components in cutaneous blood vessels has been recently demonstrated.[9] Furthermore, patients with COVID-19 infection frequently show elevation in circulating interleukin-6 (IL-6) levels,[10] with the same mediator also having a possible role in urticaria pathogenesis. Finally, COVID-19 patients face significant psychological stress and adverse impact on mental health owing to health issues, financial disruption, anxiety induced by public perception, and effects of isolation and quarantine needed in most patients. Both acute urticaria and chronic urticaria have been shown to be associated with psychological stress. Whether such psychological factors play a role in causing urticaria in COVID-19 remains a subject of future research.

With an ever-rising number of patients, it is too early to determine a precise prevalence of urticaria in COVID-19, and full understanding of pathophysiologic mechanisms may also take time. With an eye on the reported literature, we make a few suggestions regarding urticaria in COVID-19 (Table 1). From management perspective, oral second-generation antihistamines seem to be an initial prudent choice. Omalizumab can be used in refractory patients, with the first two doses being given in a hospital setting as per a recent guidance summary.[11]

We reiterate that data so far are relatively sparse and at times incomparable. As more studies are performed, medical science would be in a better position to elucidate the conundrum of urticaria in COVID-19.

TABLE 1 Suggestions and considerations for urticaria management in COVID-19 patients

1. Any acute-onset urticaria with pyrexia, with or without respiratory symptoms, if having contact with a suspect or patient, to be evaluated for COVID-19 infection.
2. In patients with refractory urticaria and/or atypical morphology, the decision to perform skin biopsy and histopathological examination can be individualized.
3. For symptomatic management of urticaria, standard doses of potent, second-generation, non-sedating H1 antihistamines (eg, fexofenadine/levocetrizine) in twice-daily dosing can be used. In nonresponders, the dose can be increased up to 4-fold the recommended dose (The European Academy of Allergology and Clinical Immunology guidelines).
4. Use of immunosuppressants like cyclosporine should be avoided, including those with refractory, chronic urticaria patients.
5. Use of omalizumab can be considered in severe, nonresponding urticaria. Although specific recommendations regarding urticaria in COVID-19 are still lacking and no relevant data exist, statement from the British Association of Dermatologists on 26 March 2020 allows the use of omalizumab in the pandemic era.[11] First two doses of omalizumab should be administered in hospital and subsequent doses can be self-administered at home.
6. General use of systemic corticosteroids in COVID-19 should be avoided owing to the potential risk of prolonged viral replication. However, the decision to use corticosteroids in urticaria should be individualized and considered only when the potential benefits outweigh the risks involved in usage. If employed, they should be used for shortest possible duration to bring symptoms under control and promptly switched to drugs like omalizumab as soon as feasible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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