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Non-Histaminergic Angioedema Following Infection with COVID-19

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Abstract

Non-respiratory manifestations of COVID-19, including dermatological manifestations, have been reported, and although urticaria associated with COVID-19 has been reported, there have been no reports of non-histaminergic angioedema following infection with mild COVID-19. Non-histaminergic angioedema has a gradual onset and is characterized by submucosal swelling without accompanying urticaria or pruritus, and poor response to antihistamines and corticosteroids. We report a case of non-histaminergic angioedema in a 29-year-old woman with a history of mild COVID-19 infection. Our case highlights the fact that early diagnosis of non-histaminergic angioedema in mild COVID-19 patients is crucial for effective treatment and requires a high level of suspicion from both general and emergency physicians.

Keywords

Non-histaminergic angioedema, COVID-19, Mild infection

Conflict of Interest Statement

My authors and I declare no conflict of interest except the following: Speaker's bureau: Genentech, GSK< Regeneron/Sanofi, AstraZeneca, Grants: Takeda (S Shahzad Mustafa)

CASE REPORT

Non-histaminergic Angioedema Following Infection with COVID-19

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Abstract

Non-respiratory manifestations of COVID-19, including dermatological manifestations, have been reported, and although urticaria associated with COVID-19 has been reported, there have been no reports of non-histaminergic angioedema following infection with mild COVID-19. Non-histaminergic angioedema has a gradual onset and is characterized by submucosal swelling without accompanying urticaria or pruritus, and poor response to antihistamines and corticosteroids. We report a case of non-histaminergic angioedema in a 29-year-old woman with a history of mild COVID-19 infection. Our case highlights the fact that early diagnosis of non-histaminergic angioedema in mild COVID-19 patients is crucial for effective treatment and requires a high level of suspicion from both general and emergency physicians.

Keywords: Non-histaminergic angioedema, COVID-19, Mild infection

Learning objectives

1. Non-histaminergic angioedema may be triggered by COVID-19- To the best of our knowledge, there have been no publications to date describing non-histaminergic angioedema as a complication of mild Coronavirus 2 (SARS-CoV-2) infection.
2. Suspicion of non-histaminergic angioedema should be high to initiate potentially life-saving treatment if needed.

Background

COVID-19 severity is categorized as mild, moderate, or severe based on symptomatology and respiratory impact. Mild cases present with non-severe symptoms, while moderate cases exhibit noticeable respiratory distress. Severe cases are characterized by significant respiratory distress, often necessitating intensive care unit (ICU) support and advanced respiratory interventions.[1] With the global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), various non-respiratory manifestations of COVID-19, including dermatologic manifestations, have been reported.[2,3] Although urticaria associated with COVID-19 has been documented,[4] there have been no reports worldwide of non-histaminergic angioedema following mild COVID-19 infection. However, non-histaminergic angioedema has been observed in the context of other viral infections.[5,6] Non-histaminergic angioedema has a gradual (hours) onset[3] and is characterized by submucosal swelling without accompanying urticaria or pruritus and poor response to antihistamines and corticosteroids.[3,7] We present a case of non-histaminergic angioedema that occurred in association with mild COVID-19 infection.

Case presentation

A 29-year-old woman with no significant past medical history experienced mild COVID-19 infection and then approximately two months later

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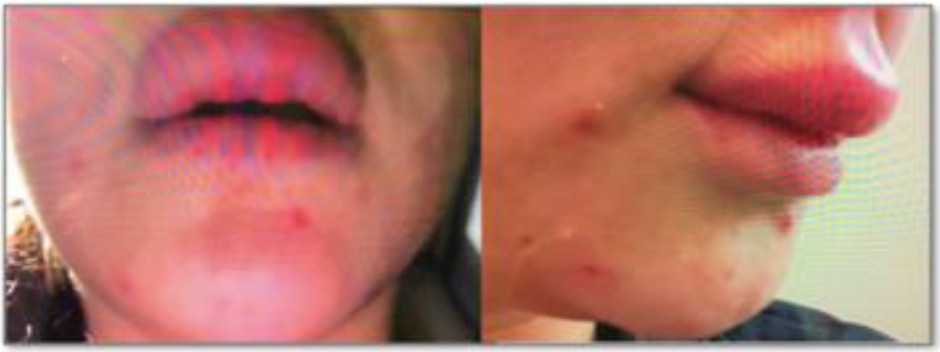

Fig. 1. Swelling involving face and lips.

experienced recurrent episodes of swelling of the lips, face, neck, and pharynx almost weekly (Fig. 1). The episodes were painful, started gradually, and lasted three to five days each. She denied any itching, rash, joint pain, fever, or chills associated with the swelling. There was no association with exposure to food or medications, including angiotensin-converting enzyme inhibitors, oral contraceptives, over-the-counter medications, or herbal supplements. She also denied any episodes prior to her infection with COVID-19 and had no family history of swelling disorders. Her episodes were so severe that she presented to the emergency department (almost weekly) on multiple occasions. The patient was treated with antihistamines, steroids, and epinephrine during these visits, with no improvement in symptoms. Three times she received plasma-derived C1 esterase inhibitor (Berinert™) in the emergency department, and each time her symptoms improved rapidly within one to 2 h. Laboratory tests, including but not limited to C1 esterase inhibitor level and function, serum tryptase, antinuclear antibodies, complement levels, CRP, and rheumatoid factor (Table 1) were unrevealing. She was also subsequently evaluated by an allergist, who discussed potential therapy with a plasma-derived C1 esterase inhibitor or a bradykinin antagonist (icatibant) to abort future episodes. However, the patient did not experience any additional episodes, and no therapy was initiated.

Table 1. Relevant laboratory findings.

C1 Esterase functional activity	>90% (Normal >67%)
C1 Esterase volume/mass	30 mg/dl (19–37 mg/dl)
Serum Tryptase	2.1 ng/ml (<11.5 ng/mL)
ANA	Negative
C4	28
CRP	0.4 mg/dl (0.0–1.0 mg/dL)

Discussion

Although there are case reports of histaminergic urticaria with angioedema associated with COVID-19 infection,[8] our patient presented with non-histaminergic angioedema, suggesting a different underlying pathophysiology. A plausible explanation for the development of angioedema may lie in the correlation between COVID-19 and angiotensin-converting enzyme 2, a receptor for virus entry into lung epithelial cells. Angiotensin-converting enzyme 2 is known to play a critical role in inhibiting des-Arg9 bradykinin, which is a potent ligand of the bradykinin receptor[9] Therefore, inhibition of angiotensin-converting enzyme 2 leads to excessive activation of the bradykinin pathway and subsequently increases vascular permeability, resulting in non-histaminergic angioedema.[10,11]

We present a case of non-histaminergic angioedema in a young woman with mild COVID-19. She had normal C4, and C1 esterase inhibitor protein levels and function, C1q, and no response to antihistamines or corticosteroids. Because laboratory values were normal and there was no family history, hereditary angioedema could be excluded. Regarding the possibility of a hypersensitivity reaction, she did not have urticaria or other features of an immediate hypersensitivity reaction, such as an elevated tryptase. Because she was not taking any medications, the possibility of a drug reaction can be excluded.[12,13]

Following the guideline for hereditary and acquired angioedema, several treatment options for non-histaminergic angioedema have been proposed. Previous studies have shown that plasma-derived C1 esterase inhibitors, ecallantide,[14,16,17] tranexamic acid,[18,] and omalizumab[15] can be used in the acute phase. However, there is limited therapeutic experience with virally triggered angioedema, owing to the scarcity of literature on this type of angioedema.

Conclusion

Non-histaminergic angioedema can be triggered by even mild COVID-19 infection. Its diagnosis in patients with a history of COVID-19 infection requires a high level of suspicion and attention from both general and emergency physicians. Early diagnosis could help to initiate effective treatment of recurrent COVID-19-related angioedema.

Conflict of interest

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