



Mini review

Angioedema-post COVID symptoms

Swathi Mukurala*, Jahanavi Bandla, Swetha kappala

Department of pharmaceutical Analysis, Vishnu Institute of pharmaceutical Education and Research, Narsapur, Medak, Telangana, India

* **Correspondence:** Email: swathi.m@viper.ac.in.

Abstract: The non-respiratory symptoms associated with coronavirus disease 2019 (COVID-19) are being reported more frequently as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads throughout the world. Numerous dermatological issues have been connected to this viral infection. Angioedema has been reported by the patients post COVID. In this article, we discuss cases that have been reported in the medical literature and give a case study of angioedema that might be because of COVID-19 infection.

Keywords: cutaneous; angioedema (AE); COVID-19; allergy; immunoglobulin E

1. Introduction

Since it was proclaimed a pandemic, in 2019, the corona virus disease (COVID-19) has resulted in thousands of fatalities and is one of the most closely watched topics globally in terms of its progression and management, as it is a highly contagious viral infection and declared as a big health crisis by WHO in 2020. The origin of COVID-19 was at Wuhan, Hubei province, China in December 2019. There have been 768560727 confirmed cases of COVID-19, including 6952522 deaths, reported to WHO until 12th July, 2023. The disease has an incubation period of 2 to 14 days and is spread through inhalation or direct contact with the contaminated droplets. The symptoms include cough, fever, loss of smell, fatigue, sore throat and breathlessness. The symptoms may be mild to medium that can progress pneumonia, acute respiratory distress syndrome (ARDS) and multiorgan dysfunction, but many of the people are asymptomatic [1].

A new broad-spectrum antiviral medication called favipiravir was developed years ago to treat influenza viruses. RNA-dependent RNA polymerase from the influenza virus is specifically impeded

by this pyrazine carboxamide derivative, which prevents replication. Numerous RNA viruses, including H1N1, Ebola, Arena and bunyavirus, are resistant to the drug [2]. As our country used these agents to treat pneumonia due to COVID viral infections, but developed more side effects like diarrhea. However, later patients with post COVID symptoms developed few cutaneous manifestations [3].

A number of dermatologic eruptions suspected to be connected to COVID-19 have been recorded in the medical literature; however, angioedema has only occasionally been observed. COVID-19 pneumonia with urticaria/angioedema were observed in both genders, as evident in numerous case studies. Patients ranging in age from 30 to 60 years have experienced it [4,5].

According to Memon et al., angioedema is characterized by “*subcutaneous tissues and/or submucosal tissues circumscribed non-pitting edema affecting lips, face, neck and extremities, oral cavity, larynx and gut*”. When it affects the larynx, it can be fatal, but intestinal angioedema is unpleasant and looks like an acute abdomen [6].

The majority of angioedema causes are related to the release of bradykinin or histamine; other vasoactive chemicals may also play a role. On the other hand, definitive information is lacking about prostaglandins, leukotrienes, tryptase, cytokines and chemokines. Naturally, leukotrienes are questionable when cyclooxygenase 1 (COX-1) inhibitor-induced angioedema develops.

Classification of angioedema are allergic/anaphylaxis:

(1) Allergies anaphylaxis:

Foods like shellfish, tree nuts, milk, peanut, eggs especially penicillin, sulfa drugs and their derivatives venoms, fire ants and stinging insects (hornets, wasps, bees and yellow jackets).

(2) NSAID induced:

Idiopathic angioedema:

(a) Histamine, dependent (histaminergic)

(b) Histamine, independent (non histaminergic)

(3) C1 INH deficiency (hereditary, acquired)

ACE inhibitors: Physical processes like exercise-induced anaphylaxis, cold urticaria, cholinergic urticaria, vibratory angioedema

(a) Hereditary angioedema: is an autosomal dominant disorder that is inherited due to mutations in the gene encoding for C1-inhibitor.

(b) Acquired: autoimmune, neoplastic, infectious and drug-induced lympho proliferative diseases [6].

Avner Reshef initially reported angioedema in 1882. Osler then reported hereditary angioedema in 1888, while Donaldson et al. eventually discussed the role of C1 inhibitor in angioedema in 1963 [7].

Few case reports were presented by the author that angioedema may be due to the administration of SARS COV-2 vaccines [8].

Pfizer-BioNTech and Moderna vaccines both include the excipient polyethylene glycol (PEG), which is are cognized potential allergy and is frequently employed because of its stabilizing qualities. Moderna contains an excipient called Trometamol. In various medical preparations, such as vaccines, vitamins and steroids, polysorbate is used as an excipient [9].

A 17-year-old girl who received the polysorbate 80-containing quadrivalent human papillomavirus vaccine (Gardasil®) experienced eyelid edema, urticaria and allergy, dyspnea and wheezing upon administration of her third dosage. A skin test was conducted, and the results demonstrated that polysorbate 80 plays a part in the patient’s allergic reactions [10].

Gurnamvirdi presented a case report where a woman of 55 years old was infected with COVID-19 but did not need to be hospitalized. In July 2020, she received dermal filler treatments for face rejuvenation for five years at several locations, including the cheeks, lips, jawline and chin. The doctor used crosslinked, monophasic hyaluronic acid dermal fillers with a concentration of 20 mg/mL. However, a post-COVID-19 infection delayed hypersensitivity reacted with dermal fillers [11].

As more people throughout the world receive vaccinations, patients experience cutaneous reactions to both the COVID-19 infection and vaccine. However, the vaccine may be an early marker of dermatologic sequelae. The precise cause of delayed reactions to COVID-19 and dermal fillers is unknown, calling for more study and discussion.

Angioedema is defined as an abrupt, non-pitting swelling of mucous membranes, or both, including the upper respiratory and gastrointestinal tracts that last for several hours to three days. The tissues that are affected then recover within few days. Predilection sites include face, hands, feet and genitalia. The most prevalent types of swelling are lip and eye (periorbital). Angioedema may be caused from increases in permeability of submucosal or subcutaneous capillaries and post-capillary venules in the presence of localized plasma extravasation [12].

Mast cell degranulation or stimulation of the kallikrein-kinin cascade can both cause angioedema. The etiology of angioedema caused by an allergic reaction is well recognized as a result of direct mast cell activation. Following allergen-associated IgE binding and cross-linking of the high affinity IgE receptor, the mast cell quickly degranulates, releasing inflammatory mediators such as histamine into the dermis, producing venodilation and intravascular fluid extravasation [13]. Angioedema and other allergic reactions, such as acute urticaria or a more serious anaphylactic reaction, might occur in the former case as a result of immunoglobulin E (IgE)-mediated hypersensitivity to foods or drugs [14].

According to Teresa, leukotrienes may play a unique role in mediating the swelling in angioedema brought by nonsteroidal anti-inflammatory drugs, particularly cyclooxygenase-1 inhibitors [15].

Favipiravir was approved for COVID-19 therapy, with or without hydroxychloroquine, depending on the clinical assessment of the physician and the severity of a patient's disease, following high clinical and radiological improvement rates and quicker viral clearances with this medication in China [15].

Data on favipiravir's side effects are scarce, nevertheless. However, medication used to cure SARS-CoV-2 may also be the reason for angioedema [16].

Contrast-induced reactions can resemble allergies with basophil and mast cell degranulation and be generalized, or anaphylactoid, due to the lack of a specific IgE antibody.

2. Case report

On 4th March, 2023, a 27-year-old female patient with a history of lip swelling for one day arrived at the emergency room. The patient recalled how the swelling in her lip began suddenly throughout the night and remained. Clinically, there was no evidence of a link between eating certain foods or taking certain medications. She denied having taken any recently prescription or purchased over-the-counter, herbal or homemade medicines. She denied having a history of allergies or comparable prior appearances (Figure 1) [17].



Figure 1. (a) Mild angioedema on the lips on day 1. (b) Lip angioedema disappeared five days later [17].

When the doctor asked about her health background, she revealed that a few weeks ago she was infected with the SARS-CoV-2 virus. Additionally, she had appendicitis and peritonitis during her postpartum period prior to the COVID attack. Later, in following investigations, the patient's vital signs at admission appeared like this: 37.4 °C temperature, 119/67 mm Hg blood pressure, 20/min respiratory rate, and 98% oxygen saturation at room temperature. No other skin abnormalities were found. A chest examination was done, but no wheezing sound or crackles were revealed.

Then, the doctors suggested her to undergo a RT-PCR test and a few blood tests. No test was done to identify the histamine levels.

Everything was normal in the reports. She was advised to take steroids (prednisolone dispersible 40 mg tablets once for 3 days). After taking medication, the lips' swelling subsided in a day. After 5 days, she was reported with the same condition again, and the doctors confirmed that the angioedema might be a post-COVID symptom.

3. Treatment

She was instructed to keep taking the antihistamines or anti-allergy medication levocetirizine + montelukast 5 mg twice daily, as it relieves hay fever (a seasonal allergy) and other allergies that include sneezing, runny noses and allergic skin disorders.

4. Outcome and follow-up

Over the following few days, angioedema totally subsided, the patient underwent a full clinical recovery, and no further PCR testing was necessary before they resumed their jobs.

According to Kesh et al., a woman at the age of 46, who recently woke up with AE of lips and tongue, arrived at the emergency room. H1-antihistamines and intravenous corticosteroids were unsuccessfully used to relieve the edema. She was taken to the intensive care unit because the swelling in her lips persisted and reached other areas of her body. This allowed for continuing monitoring and potential airway protection. Fortunately, the swelling started to decrease after 12 hours and disappeared entirely after 24 hours [18].

As stated by Nanda et al., they collected data from the past 10 years at a children hospital and identified median age of 13.2 (Inter quartile range (IQR), 9.1–18.8), for 21 children. While their study's median age for symptoms of HAE attacks was 5.7 years, the mean age of symptom onset

frequently mentioned in practice and the literature is 11.2 years. This finding is consistent with other studies [19].

The first or second decade of life is when clinical symptoms of HAE typically initially appear. Only a small percentage of people experience years without symptoms in between recurring attacks during the ensuing years. In this study, we established a swelling pattern with frequent and uncommon swelling sites and the associated episode frequencies. This pattern, which is unique to HAE, enables an educated guess at a diagnosis based on clinical symptoms discussed by Bork et al. [20].

According to Batarseh et al., four cases of African American patients who suffered from COVID-19 pneumonia were incubated; these patients all developed angioedema at least 10 days (range 10–14 days) after their incubation [21].

According to Graziani et al., an 86-year-old man visited the emergency room after developing worsening facial, lip, neck and uvula edema following the administration of the fourth dosage of the SARS-CoV-2 vaccination COVID-19 Moderna mRNA-1273 72 hours earlier. Previous SARS-CoV-2 vaccinations had been Pfizer-BioNTech. Upon observation, no urticaria was observed and the physical examination was unremarkable. He experienced repeated episodes of swelling for 3 days. Parenteral corticosteroids, antihistamines and epinephrine aerosol were administered as the condition was worsening and developed respiratory failure. Upon undergoing fibro bronchoscopy. The oropharynx and glottis showed edemas, and immediate orotracheal intubation were performed. Blood tests revealed normal tryptase and histamine levels, as well as deficiencies in C4 and C1 esterase inhibitors (C4 0.02g/l (0.1–0.4g/l) and C1 29% (70–130%)) and treated with tranexamic acid (1500 mg/day). Alessandro Graziani et al. concluded that the incidence of AAE may be a Trigger due to administration of Moderna vaccination [22].

This study supports the severity of AAE associated with C1INH deficiency, which needs to be well controlled to avoid attacks that could be fatal or incapacitating. Icatibant and pdC1INH could be utilized in severe attacks due to their effective response and low side effects. Acquired C1INH deficiency is closely related to B-cell lymphoid malignancies, particularly SMZL and MGUS. AAE manifestations are under the control of the related disease's treatment. Rituximab could be suggested; however, we need to do prospective trials to pinpoint the exact therapeutic approach [23].

5. Discussion

Using the terms COVID-19, coronavirus 2019, SARS-CoV-2, urticaria, angioedema, skin symptoms and dermatology, we searched the PubMed and Scopus databases for papers, including case reports, published between, March 30, 2020 and March 30, 2023. We found that in case 1, a 61-year-old hypertensive man with COVID-19 presented with lip and face edema after 12 days of fever, chills and dry cough. Neither skin lesions nor itching returned. Following two days of taking methylprednisolone and diphenhydramine, all symptoms except cough improved [24].

A 34-year-old man who had neither erythema nor pruritus, had a labial angioedema appear. For three hours, this symptom lingered before gradually going away. After sixteen hours, he was fully recovered [25]. A profound urticaria is angioedema [26]. The COVID-19 infection is another example of a virus or bacterial infection that can cause urticaria and angioedema, expanding the list of cutaneous signs and symptoms of this puzzling sickness. Therefore, in the context of this

pandemic, when clinically relevant, these lesions ought to trigger early viral testing and infection control measures [27].

Skin signs of diverse morphological characteristics, such as vesicles, acral chilblain lesions, petechiae exanthems and urticaria, are among the distinguishing symptoms of COVID-19 infection [28].

Inflammatory mediators like cytokines cause capillary vasodilatation and increased permeability, which is how the pathophysiology is explained [29]. The known relationship between SARS-CoV-2 and angiotensin-converting enzyme 2, a receptor for the virus to enter lung epithelial cells, provide a hypothesis that explains how angioedema started [30].

The skin manifestations of the enigmatic virus now include a new member in the form of angioedema, which is usually caused by various viral or bacterial illnesses. In spite of this, these lesions, in the context of this pandemic, ought to trigger early viral testing and infection control measures when clinically appropriate [31].

With over 45 clinical antihistamines available globally, antihistamines are currently the largest class of medications used in the treatment of allergic diseases. The first antihistamine was licensed for use in humans in 1942. They were once categorized as histamine H1 receptor (H1R) antagonists, but after stabilizing the H1R's inactive state, they were reclassified as inverse agonists [20–22]. These drugs interfere with the allergic-inflammatory processes by their mode of action and by opposing the actions of HA at the H1R. As a result, they are preferred therapies for individuals suffering from allergic rhinitis (AR), conjunctivitis and urticaria. They are classified as second-generation antihistamines.

Antihistamines are also prescribed for conditions such as atopic dermatitis (AD), anaphylaxis, nonallergic angioedema, otitis media, sinusitis, sleeplessness, anxiety, migraines and other vestibular disorders for which there is insufficient clinical proof of their effectiveness [23]. They are not utilized in people with asthma, even if they are recommended for those with allergic rhinitis and concurrent asthma [32].

A physiologically active chemical molecule is called a steroid. In order to treat allergic reactions, steroids like corticosteroids act by reducing the inflammation caused by allergies. They prevent and cure runny or itchy noses caused by seasonal or year-round allergies, as well as nasal stuffiness and sneezing. Additionally, they can lessen swelling and inflammation brought on by other kinds of allergic reactions.

6. Conclusions

Angioedema may be caused from the different medical conditions like medication taken during COVID or COVID vaccination or it may be due long-term COVID symptoms. Reslizumab or antihistamines would be the treatment options to the angioedema patients who have not responded to the steroid therapy. Moreover, building immunity also plays a major role to alleviate these symptoms.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflicts of interest.

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