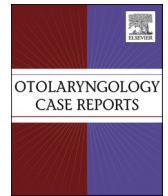




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Coronavirus disease-19 infection and angioedema in African Americans: A case series

Jose Manuel Martinez Manzano^{a,b,*}, Otoniel Ysea-Hill^{a,b}, Brenda Chiang^{a,b},
Simone A. Jarrett^{a,b}, Kevin Bryan Lo^{a,b}, Zurab Azmaiparashvili^{a,b}

^a Department of Medicine, Einstein Medical Center Philadelphia, USA

^b Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, USA

ABSTRACT

Rationale: Few case series have described the simultaneous development of angioedema in patients with coronavirus 19 disease (COVID-19). Most of these reports were described in at-risk patients for developing bradykinin angioedema. Therefore, we aim to describe 5 African American patients who developed simultaneous COVID-19 and angioedema.

Methods: This was a case series of hospitalized patients with simultaneous angioedema and COVID-19 infection in a single center from May 2020 to February 2022. We used descriptive statistics. The study was approved by the institutional review board.

Results: Their median age was 55 years (range 28–66); all patients were African American, and 3/5 were males. All patients developed angioedema within a week of hospitalization. Two subjects had prior history of ACEI-related angioedema but were not exposed to ACEI recently, whereas 1 subject was on chronic lisinopril therapy for the last 3 years. All patients had orofacial involvement; the most common locations were lips (5/5) and tongue (3/5). None had histaminergic features of angioedema (either skin rash or peripheral eosinophilia). 4/5 subjects had respiratory symptoms and chest imaging features of COVID-19 pneumonia, whereas 3/5 subjects developed severe COVID-19 infection. Most patients were treated with standard combination of H1 and H2 blockers, and corticosteroids. A total of 2/5 subjects were intubated; one patient developed refractory tongue swelling, received tracheostomy for extubation, and died due to COVID-19 pneumonia. The median length of angioedema improvement was 44 hours (range 20–168 hours). The median length of hospital stay was 15 days (range 1–49).

Conclusion: We described 5 cases of angioedema in COVID-19 patients that shared risk factors and features of bradykinin-related angioedema.

1. Introduction

Angioedema is the swelling of subcutaneous tissues commonly located in nondependent areas of the body such as the orofacial region and upper airway. In African Americans, bradykinin-related angioedema is the most common mechanism described, especially in the setting of angiotensin converting enzyme inhibitor (ACEI) use.

In the setting of coronavirus disease 19 (COVID-19), the kallikrein-kinin cascade has been postulated as one of several causative mechanisms of pulmonary edema. A retrospective study showed improved oxygenation in patients with COVID-19 pneumonia treated with icatibant - a bradykinin receptor inhibitor [1]. A prior case series reported 4 cases of angioedema in African American patients with COVID-19 infection, and hypothesized an association of COVID-19 infection and angioedema due to bradykinin cascade dysregulation [2]. So far, this association has not been addressed in larger studies.

Therefore, we aim to describe demographics, clinical features, and outcomes of 5 patients with simultaneous angioedema and COVID-19

infection.

2. Methods

This was a case series of hospitalized patients with simultaneous angioedema and COVID-19 infection in a single inner-city tertiary-care community hospital from May 2020 to February 2022. The diagnosis of COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal specimens in every case.

The diagnosis of angioedema was made on clinical basis of swelling localized to either face, lips, tongue, or upper airway. Through electronic medical record review, we gathered data related to demographics, variables related to COVID-19 infection (risk factors, symptoms, severity, and treatment received), and angioedema (prior episodes, location, concurrent urticarial rash, potential triggers, and treatment received), and outcomes of interest (endotracheal intubation, timing of angioedema in length of hospital stay, and mortality).

We used descriptive statistics with frequencies and fractions for

* Corresponding author. Department of Internal Medicine, Einstein Medical Center Philadelphia, 5501 Old York Road, Philadelphia, PA, 19141, USA.

E-mail address: jose.martinezmanzano@jefferson.edu (J.M. Martinez Manzano).

<https://doi.org/10.1016/j.xocr.2022.100457>

Received 10 May 2022; Received in revised form 13 June 2022; Accepted 21 June 2022

Available online 27 June 2022

2468-5488/© 2022 Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Demographics, clinical features, treatments, and outcomes of patients with COVID-19 and angioedema.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Age (years)	55	28	66	65	54
Race	African American	African American	African American	African American	African American
Sex	Male	Female	Male	Male	Female
Features of COVID-19					
Risk factors for severe COVID-19	ESRD, smoker	Obesity	Obesity	Obesity, T2DM	Obesity, T2DM, heart failure
Respiratory symptoms	Yes	Yes	No	Yes	Yes
Severe COVID-19	No	No	Yes	Yes	Yes
Features of angioedema					
Timing of angioedema onset	Day 4 after admission	Day 1(presenting symptom)	Day 1(presenting symptom)	Day 7 after admission	Day 1 (presenting symptom)
Prior episodes of angioedema	No	Yes. Idiopathic	Yes. Idiopathic	No	No
History of allergies	No	Yes. Lisinopril, aspirin, penicillin	Yes. Lisinopril, penicillin, shellfish	No	Yes. Penicillin, seafood, shellfish
Angioedema location	Lips	Lips, tongue	Lips, tongue	Lips, tongue	Face, lips
Active inpatient medications	Acetaminophen, Aspirin, Atorvastatin, Carvedilol, Cefazolin, Cinacalcet, Dextromethorphan, Heparin, Hydralazine, Levothyroxine, Melatonin, Metoclopramide, Sevelamer	N/A	N/A	Ampicillin-sulbactam, Aspirin, Fentanyl, Fludrocortisone, Furosemide, Heparin, Hydrocortisone, Lansoprazole, Metolazone, Midazolam, Norepinephrine, Propofol, Simvastatin Sodium citrate, Sodium zirconium cyclosilicate, Tamsulosin, Vasopressin, Vecuronium	N/A
Urticarial rash	No	No	No	No	No
Treatment for angioedema	Yes. H1, H2 blockers, steroids	Yes. H1, H2 blockers, steroids, epinephrine	Yes. H1, H2 blockers, steroids	Yes. H1, H2 blockers, steroids	Yes. H1, H2 blockers, steroids
Laboratory analysis					
White blood cell count (x10 ³ /mL)	1.99	8.3	4.7	7.83	14.1
Eosinophil count (x10 ³ /mL)	0	0	70	8	0
Historical C4 levels (mg/dl)	Not available	27.4 (normal 15–57)	Not available	32.1 (normal 15–57)	Not available
Thyroid function testing	Normal	Normal	Not available	Low TSH. Normal FT4	High TSH. Low FT4
Outcomes					
Endotracheal intubation	No	No	No	Yes. For AHRF	Yes. For angioedema and AHRF
Timing of angioedema improvement (hours)	22	44	20	168	60
Length of hospital stay (days)	10	3	1	49	15
Inpatient mortality	No	No	No	Yes	No

COVID-19: coronavirus disease-19. ESRD: end stage renal disease. T2DM: type 2 diabetes mellitus. TSH: thyroid stimulating hormone. FT4: free tetraiodothyronine. H1 blocker: histamine receptor-1 blocker. H2 blocker: histamine receptor-2 blocker. AHRF: acute hypoxic respiratory failure.

categorical variables and medians and ranges for continuous variables. The study was approved by the institutional review board.

3. Results

We described 5 patients who tested positive for COVID-19 on admission and who were diagnosed with angioedema at the time admission or during their hospitalization. Their median age was 55 years (range 28–66); all patients were African American, and 3/5 were males. All patients had risk factors for severe COVID-19 infection, and obesity was the most common risk factor in 4 patients. All patients developed angioedema within a week of hospitalization; 3/5 had angioedema as a presenting symptom on day 1, whereas 2/5 developed angioedema after hospital admission, on day 4 and day 7, respectively.

Two patients had prior history of ACEI-related angioedema but were not exposed to ACEI recently (at least during the past 3 years). Subject 1 was on lisinopril as outpatient for ~3 years and was last exposed to this

medication at least 4 days prior to angioedema onset. None of the subjects with angioedema on day 1 were exposed to their known allergens (documented in Table 1). All patients had orofacial involvement; the most common locations were lips (5/5) and tongue (3/5). None had urticarial rash, nor peripheral eosinophilia (defined as absolute eosinophil count >500 x10³/mL). Only 2 patients had available historical complement C4 levels that were normal.

Four out of 5 patients had respiratory symptoms and chest imaging features of COVID-19 pneumonia, 3/5 patients developed severe COVID-19 infection (defined as the need of oxygen supplementation for management of hypoxia), and 2/5 patients were mechanically ventilated; subject 4 was intubated for acute hypoxic respiratory failure (AHRF) owing to COVID-19, whereas subject 5 was intubated for airway protection owing to angioedema and simultaneous AHRF due to COVID-19.

In terms treatments and outcomes of angioedema, most patients were treated with standard combination of H1 and H2 blockers, and

corticosteroids. The median time to clinical improvement was 44 hours (range 20–168). Subject 4 required tracheostomy on day 26 due to ongoing tongue swelling as a bridge for extubation; this subject died owing to COVID-19 pneumonia on day 49. The median length of hospital stay was 15 days (range 1–49). Further information in [Table 1](#).

4. Discussion

Few case series have described angioedema in the setting of COVID-19 [2,3]. A prior study by Batarseh et al. reported 4 cases of African American patients, who were intubated due to COVID-19 pneumonia, and who developed angioedema at least 10 days after intubation (range 10–14 days) [2]. At the present study, all the patients reported were African American as well, but in contrast to Batarseh et al., we described the clinical presentation of angioedema earlier in the course of COVID-19 infection (range 1–7 days).

The same study by Batarseh et al. hypothesized a “second hit hypothesis” in African American patients and COVID-19 infection; a “first hit” mediated by their ethnic predisposition to develop bradykinin-related angioedema due lower circulating levels of bradykinin degrading enzymes, and a “second hit” mediated by ACE2 dysregulation (a membrane bound receptor required for viral entry to human cells) leading to accumulation of bradykinin products and angioedema [2].

In another study, the samples from bronchoalveolar lavages from COVID-19 patients showed increased levels of bradykinin receptors, and decreased gene expression of C1 inhibitor and ACE, which makes COVID-19 a plausible trigger of bradykinin-mediated angioedema in at risk populations, such as in African Americans, patients on ACEI therapy, or patients with hereditary angioedema [4].

At the present study, none of the subjects displayed histaminergic features of angioedema. Furthermore, 2/5 subjects showed increased susceptibility to bradykinin dysregulation in the past, as these subjects had prior episodes of ACEI-angioedema. In addition, one subject was on ACEI therapy (lisinopril) as outpatient during the last 3 years [5]. Even though ACEI-angioedema is more likely to occur within the first year of ACEI therapy initiation, this subject was still at risk of developing angioedema due to ACEI therapy. In this case, COVID-19 could have served as a trigger of angioedema, as most of patients with ACEI-angioedema are believed to have predisposing conditions leading to bradykinin dysregulation [5].

Of note, one subject died due to COVID-19 pneumonia in this report. This subject had late improvement of lip swelling, and tongue swelling was refractory to medical therapy, which prompted the performance of tracheostomy as a bridge for extubation. In this case, we believe that the refractoriness of tongue swelling was likely related to a strong immune response against COVID-19 infection, as similarly reported in the literature, where massive tongue lymphocytic infiltrates were described in a patient with severe COVID-19 and macroglossia [6].

This cases series had limitations; a causal relationship in between angioedema and COVID-19 infection could not be established from this report, but it represents an incentive for further research in the field. Due to the retrospective nature of the report, we could not assess treatment responsiveness to antiallergic medications. The time of angioedema improvement might be affected by the difference in clinical judgement among physicians.

In conclusion, we described 5 cases of angioedema in COVID-19

patients that shared risk factors and features of bradykinin-related angioedema. Further research exploring the association is needed for improved understanding and management.

Ethical Statement for otolaryngology case reports journal

- 1) This material is the authors' own original work, which has not been previously published elsewhere.
 - 2) The paper is not currently being considered for publication elsewhere.
 - 3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
 - 4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
 - 5) The results are appropriately placed in the context of prior and existing research.
 - 6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
 - 7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.
- The violation of the Ethical Statement rules may result in severe consequences.

Funding source

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] van de Veerdonk FL, Kouijzer LJE, de Nooijer AH, van der Hoeven HG, Maas C, Netea MG, et al. Outcomes associated with use of a kinin B2 receptor antagonist among patients with COVID-19 [Internet] *JAMA Netw Open* 2020 Aug 13;3(8). <https://doi.org/10.1001/jamanetworkopen.2020.17708>. e2017708–e2017708. Available from:
- [2] Batarseh E, Kersten BP, Pinelo AC, Nadler JN, Schwartz SA. Angioedema in African American patients hospitalized for COVID-19. *Am J Respir Crit Care Med* 2020 Dec 1;202(11):1581–3.
- [3] Grewal E, Sutarjono B, Mohammed I. Angioedema, ACE inhibitor and COVID-19 [Internet] *BMJ Case Reports CP* 2020;13(9). Available from: <https://casereports.bmj.com/content/13/9/e237888>.
- [4] Kaplan AP, Ghebrehiwet B. Pathways for bradykinin formation and interrelationship with complement as a cause of edematous lung in COVID-19 patients. *J Allergy Clin Immunol* [Internet] 2021 Feb 1;147(2):507–9. <https://doi.org/10.1016/j.jaci.2020.10.025>. Available from:
- [5] Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE inhibitor angioedema utilizing a large electronic health record. *J Allergy Clin Immunol Pract* [Internet] 2017 May 1;5(3):744–9. <https://doi.org/10.1016/j.jaip.2017.02.018>. Available from:
- [6] Mañón VA, Chubb D, Farach LS, Karam R, Farach-Carson MC, Vigneswaran N, et al. Massive macroglossia, a rare side effect of COVID-19: clinical, histologic, and genomic findings in COVID-19-positive versus COVID-19-negative patients [Internet] *Oral Maxillofac Surg* 2022. <https://doi.org/10.1007/s10006-021-01031-0>. Available from: