Angioedema in African American Patients Hospitalized for COVID-19

To the Editor:

We report four angioedema cases in patients admitted to the ICU at Buffalo General Medical Center. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all patients by real-time qRT-PCR. Diagnosis of angioedema was based on clinical presentation, including classical features of acute onset of subcutaneous and submucosal swelling affecting the face, lips, mouth, and tongue without urticaria (1).

All patients were unrelated African American (AA) women from Buffalo, New York (Table 1). Coronavirus disease (COVID-19) symptoms started 2–7 days before diagnosis. Patients were admitted to the ICU for acute respiratory failure and required intubation 1–5 days thereafter. The onset of angioedema, including facial edema and tongue protrusion, occurred 10–14 days after intubation.

Patient 1 required tracheostomy 25 days after intubation because of high-risk extubation. Patient 2 was extubated after 27 days; she previously failed extubation on Day 11 and required reintubation on the same day because of hypoxia and stridor. Anesthesiologists noted laryngeal edema on reintubation. Patient 3 died 14 days after admission because of cardiac arrest, secondary to septic shock and respiratory failure. Patient 4 was intubated on Day 3 and required tracheostomy on Day 22. Our patients showed no evidence of adverse drug reactions or anaphylaxis, including sudden onset of hypotension, bronchospasm, or urticaria. Steroids did not alleviate their symptoms, as angioedema generally does not respond to steroids or β-agonists (2).

We evaluated all medications administered during hospitalization, and none were associated with angioedema except nonsteroidal antiinflammatory drugs, which were continued as needed. No patient received ACE (angiotensin-converting enzyme) inhibitors (ACEIs) or angiotensin receptor blockers during hospitalization, but patient 2 previously received lisinopril at home. None had a past medical history of angioedema. Our patients developed angioedema >10 days after intubation, making oropharyngeal swelling because of traumatic intubation, which occurs early after intubation, unlikely.

The clinical presentation of angioedema is uncommon and is frequently associated with treatment with ACEIs or angiotensin receptor blockers. Idiopathic angioedema and hereditary angioedema (HAE) are rare. Therefore, this unusual cluster of angioedema in AA patients with COVID-19, occurring at the peak of the epidemic, merits further study. Although we cannot demonstrate that SARS-CoV-2 induced angioedema, given the delay in presentation after onset of infection, this may be an unusual post–COVID-19 syndrome.

Pathophysiology of Angioedema

Overexpression or inhibited degradation of vasoactive peptides, BK (bradykinin) and Lys-BK, causes angioedema by binding to epithelial B2 receptors. Similarly, their metabolites des-Arg9-BK (DABK) and Lys-des-Arg9-BK (Lys-DABK) induce angioedema by binding to epithelial B1 receptors, which are upregulated in response to inflammation (3).

Normally, ACE, NEP (neutral endopeptidase), APP (aminopeptidase P), and DPP-4 (dipeptidyl peptidase-4) inactivate BK and Lys-BK, whereas ACE2, APP, and DPP-4 inactivates DABK and Lys-DABK (Figure 1).

When an ACEI blocks ACE, overexpression of NEP, APP, and DPP-4 occurs to compensate for loss of ACE activity and plays a significant role in degradation of BK and Lys-BK, which prevents angioedema (4). Polymorphisms in the genes encoding NEP and APP, leading to lower circulating levels of these enzymes, is more common among AAs, predisposing them to a higher risk of developing ACEI-induced angioedema (4, 5).

A similar mechanism of ACE2 dysregulation by SARS-CoV-2 may underlie the angioedema of our cohort (6). Thus, lower circulating APP levels may not compensate for ACE2 dysregulation, resulting in DAPK and Lys-DABK accumulation, predisposing to angioedema during inflammation that occurs with SARS-CoV-2 infection. As ACE2 is expressed throughout the body, we theorize that the above-described mechanism of injury and epithelial permeability may, in part, be responsible for some of the upper and lower respiratory and gastrointestinal manifestations described with SARS-CoV-2 infection and the angioedema observed in our patients.

Similar Cases

Novel clinical findings of COVID-19 are reported daily; some reports showed higher mortality among AAs (7). A report describes a patient who developed angioedema 12 days after developing symptoms of confirmed COVID-19 (8). This patient differs from our patients, as he was a hypertensive, Caucasian male on lisinopril, a major confounder and known cause of angioedema. The authors propose that in the presence of lisinopril, infection with SARS-CoV-2 induces dysregulation of ACE2, producing a "second hit" contributing to angioedema. This proposed two-hit mechanism may also explain what occurred in our patients. AAs have a genetic polymorphism predisposing them to angioedema, thus a second-hit mechanism of ACE2 dysregulation by COVID-19 may underlie the angioedema of our cohort. The authors measured serum levels of functional C1 esterase inhibitor and C4, which paradoxically were elevated. We did not perform these assays, as our patients had no family history suggesting HAE. Another publication described an AA patient with SARS-CoV-2 manifesting histaminergic urticaria and angioedema (7). However, angioedema is a known complication of urticaria and was unlikely due to BK. Although one might expect more reports of angioedema in patients with COVID-19,

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Table 1. Summary of Demographic Data, Clinical Characteristics, and ICU Course in Patients with COVID-19 Developing Angioedema

	Patient 1	Patient 2	Patient 3	Patient 4
Age, yr	56	58	63	69
Sex	Female	Female	Female	Female
Race	African American	African American	African American	African American
Medical history	Hypertension, asthma, depression, former smoker, HSV2	Hypertension, hyperlipidemia, diabetes, obesity, chronic pain	Hypertension, hyperlipidemia, diabetes, stroke, CKDIII, asthma, COPD, obesity, chronic pain	Hypertension, diabetes, HFpEF, CKDIV, depression, CVA
Home medications	Amlodipine, cetirizine, fluticasone/salmeterol, naproxen, paroxetine, prazosin, valacyclovir	Aspirin, glimepiride, insulin degludec, lisinopril, oxycodone-APAP, venlafaxine	Albuterol, aspirin, amitriptyline, amlodipine, celecoxib, cetirizine, dexlansoprazole, furosemide, hydrochlorothiazide, insulin, metformin, montelukast, pregabalin, tiotropium, zolpidem	Acetaminophen, amlodipine, aspirin, ascorbic acid, atorvastatin, clonidine, ferrous sulfate, gabapentin, insulin glargine, pantoprazole, tamsulosin, torsemide, venlafaxine
Medication allergies	None	None	Tetracyclines, macrolides	Prochlorperazine, trimethobenzamide
Angioedema characteristics	Tongue edema and protrusion, upper airway edema	Tongue edema and protrusion, upper airway edema	Tongue edema and protrusion	Tongue edema and protrusion, laryngeal edema
Investigational COVID-19 therapy	Hydroxychloroquine, IL-6 antagonist trial	Hydroxychloroquine, IL-6 antagonist trial	Convalescent plasma	Hydroxychloroquine
Onset milestones, d				
COVID-19 symptoms prior to diagnosis	5	7	2	3
Mechanical ventilation after admission	2	5	1	3
Days of angioedema after intubation	13	10	10	14
Type and dose of steroid received, days after onset of angioedema	Dexamethasone 20 mg × 1 then 10 mg q8h × 3 doses, 4 d	Dexamethasone 10 mg × 1 then 6 mg q8 × 2 d, 7 d	N/A	Methylprednisolone 40 mg × 1; dexamethasone 10 mg q6h × 2 d, 2 d
Tracheostomy after intubation	25	N/A	N/A	22

Definition of abbreviations: APAP = acetaminophen; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CVA = cerebrovascualr accident; HFpEF = heart failure with preserved ejection fraction; HSV2 = herpes simplex virus 2; N/A = not applicable; q6h = every six hours; q8h = every eight hours.

new clinical findings are reported daily, and some described features similar to angioedema but using different descriptors, such as macroglossia, upper airway edema, and laryngeal edema (9, 10).

Future Studies

This report seeks to bring awareness of our unique early observation of angioedema in four AA patients with COVID-19. Correlation of radiographic findings, ventilator settings, autopsy results, and laboratory values from a larger cohort of patients with angioedema and COVID-19 are the next steps to test our hypothesized association between this novel coronavirus and angioedema and to define the pathophysiological mechanisms underlying this serious complication. Molecular and genetic analyses of the BK pathway in patients with COVID-19, especially AAs, could be utilized to estimate the risk of angioedema associated with the disease. We propose a potential therapeutic role for blockade of the activity of β1 and β2 to reduce the morbidity and mortality of angioedema in patients with COVID-19. Consideration should be given to the use of drugs approved to treat exacerbations of HAE, such as ecallantide or icatibant, alone or in combination with antiinflammatory medications as potential therapy (Figure 1).

Given our observational report's limitations, we cannot conclude a causal relationship between COVID-19 and angioedema. We hope our unusual findings will raise awareness of this complication and motivate further investigation. ■

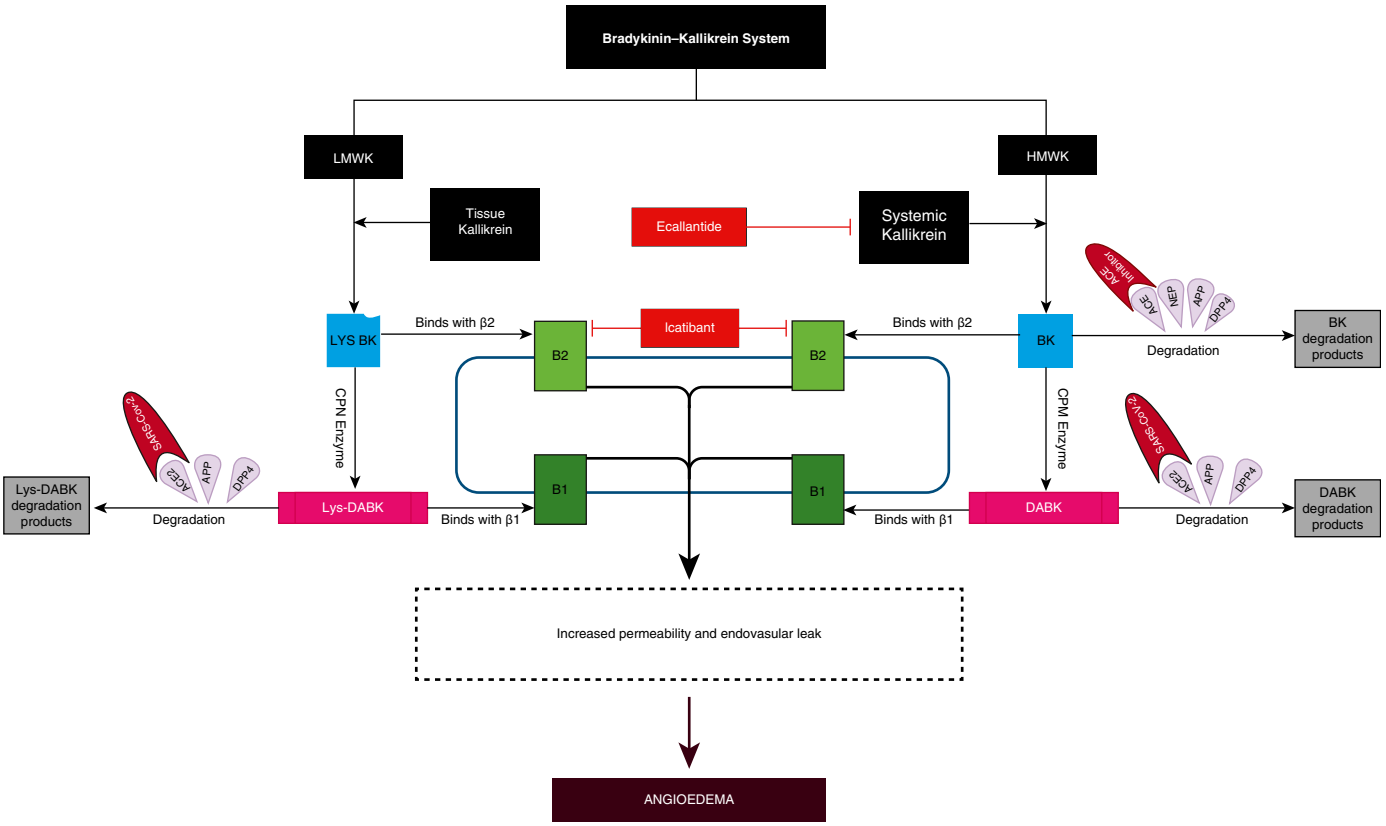

Figure 1. Systemic and tissue kallikrein–kinin system pathways with potential therapeutic targets for angioedema. BK = bradykinin; CPM = carboxypeptidase M; CPN = carboxypeptidase N; DABK = des-Arg9-BK; HMWK = high-molecular-weight kininogen; LMWK = low-molecular-weight kininogen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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