

Severe Angioedema Associated With Angiotensin-Converting Enzyme Inhibitor Therapy in Two Patients With Pollen-Food Allergy Syndrome

Angiotensin-converting enzyme (ACE) inhibitor therapy can be associated with bradykinin-mediated angioedema, which may occur at any time during the course of therapy.^{1,2} Pollen-food allergy syndrome (PFAS) represents an immunoglobulin E (IgE)-mediated hypersensitivity reaction recognized in patients with birch pollen allergy and is characterized by mouth and throat itching following the ingestion of certain fruits, nuts, and vegetables. PFAS occurs as a result of the structural homology between major allergens from certain fruits and the birch pollen major allergen Bet v 1. In rare cases, PFAS may present with angioedema and/or anaphylaxis.^{3,4} We present the first report of two cases of severe PFAS in patients with concomitant use of ACE inhibitor therapy.

Patient 1 was a 65-year-old man with history of hypertension (taking lisinopril 10 mg daily for the previous 10 years) and seasonal allergic rhinoconjunctivitis who experienced two episodes (1 week apart) of tongue and lip angioedema and mouth itching within 10 minutes after apple consumption. During the second episode, he required treatment with epinephrine, corticosteroids, and antihistamine. Laboratory testing demonstrated increased serum-specific IgE levels to apple (3.01 kU/L; class 2) and birch (47.70 kU/L; class 4) and normal serum levels of C1-esterase inhibitor and eosinophils. Given the high suspicion for severe PFAS in the setting of ACE inhibitor therapy, lisinopril was changed to losartan. Three years after this event, no further episodes of angioedema have occurred.

Patient 2 was a 45-year-old man with a history of hypertension (taking lisinopril 10 mg daily for the previous year) and seasonal allergic rhinoconjunctivitis who developed three episodes of tongue angioedema

and mouth itching within several minutes after the ingestion of jackfruit and cashew nuts. The third episode required treatment with oral prednisone and antihistamine. Laboratory testing demonstrated increased serum levels of birch-specific IgE (8.19 kU/L; class 3), normal serum levels of specific IgE levels to jackfruit (0.13 kU/L; class 0), and C1-esterase inhibitor and eosinophils. Severe PFAS in the setting of concurrent ACE inhibitor therapy was suspected and lisinopril was changed to losartan. No further episodes of angioedema have occurred within 1 year after the ACE inhibitor was changed (Table).

ACE inhibitor-related angioedema is bradykinin-mediated and is distinguished from IgE-mediated angioedema by a slower onset of action, longer duration, lack of urticaria/pruritus, and failure to respond to antihistamines, corticosteroids, or epinephrine. However, our patients most likely did not experience typical bradykinin-induced angioedema, despite being on ACE inhibitor therapy, but rather an IgE-mediated reaction for the following reasons. Both patients were sensitized to birch pollen and developed oral symptoms within minutes after ingestion of foods containing allergens homologous to birch Bet v 1,⁵ thereby suggesting a diagnosis of severe PFAS. Moreover, the symptoms responded promptly to the administration of epinephrine, antihistamine, and corticosteroids.

Data from *in vitro* studies demonstrate that a bradykinin analog was a potent inducer of skin mast cell histamine release.⁶ Therefore, we believe that the concomitant ACE inhibitor therapy may have been responsible for the severe clinical symptoms.

The usual PFAS treatment involves avoiding the raw forms of culprit foods.⁷ Developing severe PFAS in the

TABLE. Patients' Characteristics

	Patient 1	Patient 2
Symptoms	Two episodes of tongue and lip angioedema, mouth itching, shortness of breath (within 1 week) that resolved after subcutaneous epinephrine, antihistamine, and corticosteroid administration	Three episodes of tongue angioedema, mouth itching, and shortness of breath (within 1 month) that resolved after antihistamine and corticosteroids administration
Time frame/culprit	Ten minutes after apple ingestion	Several minutes after eating jackfruit and cashews
Use of angiotensin-converting enzyme inhibitor prior to symptoms	Lisinopril 10 mg daily for 10 years	Lisinopril 10 mg daily for 1 year
Specific IgE	Positive for apple and birch	Positive for birch
Other labs	Both patients had normal levels of C4, C1-esterase inhibitor, serum total IgE, and serum eosinophil count	
Outcomes	Patients were diagnosed with pollen-food allergy syndrome. No further episodes of angioedema have occurred after changing lisinopril to losartan	

setting of concomitant ACE inhibitor therapy may warrant the following: (1) evaluation by a cardiologist, primary care physician, or nephrologist regarding the presence of PFAS and safety of initiating ACE inhibitor therapy in those patients; (2) whether to stop ACE inhibitor use in patients with PFAS; and (3) investigating the proper recommendations regarding precautions (eg, epinephrine autoinjectors) in such cases. Further research is necessary in order to characterize the association between severe PFAS and concurrent ACE inhibitor therapy.

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