Vildagliptin-Induced Tongue Angioedema: An Uncommon Occurrence

Dear Editor,

Drug-induced angioedema is well documented with angiotensin-converting enzyme inhibitors (ACEIs), estrogen, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin.[1] Recently, dipeptidyl peptidase (DPP-IV) inhibitors or gliptins, a class of oral antidiabetic agents, have been associated with angioedema when used concurrently with ACE inhibitors.[2,3] Herein, we report an uncommon case of angioedema following the administration of vildagliptin without an ACE inhibitor.

A 32-year-old female presented with sudden-onset, persistent tongue swelling for four days [Figures 1 and 2]. There was no associated pruritus, wheals, throat tightness, abdominal pain, syncope, or any other mucosal involvement. Family history was noncontributory. She was a known case of chronic spontaneous urticaria (CSU) controlled with oral bilastine 40 mg and cyclosporine 150 mg daily for the last 2 months. She denied any history of angioedema episode in the past. Detailed drug history revealed initiation of vildagliptin ten days back by her endocrinologist for recently diagnosed diabetes mellitus. There was no other new drug intake. Laboratory investigations including complete blood count, liver and renal function, thyroid profile, serum IgE levels, anti-TPO, CRP, ESR, and C4 levels were within normal limits. Based on the above findings, a diagnosis of gliptin-induced angioedema was made. The patient was switched from gliptin to metformin, resulting in complete resolution in 48 hrs. She is currently under follow-up for CSU and no recurrence of angioedema has been noted.

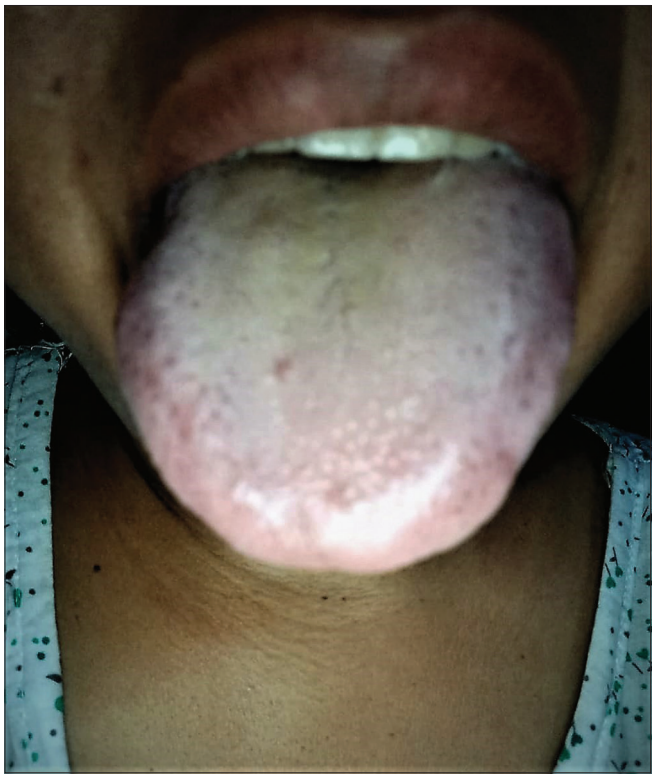

Figure 1: Angioedema affecting the tongue

Angioedema is characterized by sudden-onset, asymmetric, nonpitting, transient-localized swellings due to extravasated fluid into the loose tissues of the body, e.g., eyelids, lips, tongue, and genital mucosa. It can be histaminergic (mast cell mediated), bradykinin mediated, or of unknown cause.[4] These mediators cause arteriolar dilatation, vascular leakage, and swelling. Histaminergic angioedema usually coexists with urticaria and may be a component of anaphylaxis. The absence of urticaria and unresponsiveness to antihistamines hints toward bradykinin-mediated angioedema, which can be hereditary or acquired (drug-induced and acquired C1 inhibitor deficiency).[4] ACE inhibitors are most frequently associated with drug induced angioedema.[5] In almost 50% of cases, it occurs during the first week following exposure, although delayed occurrence several years following drug initiation has been reported. The episodes usually last for two to five days and may resolve even if the drug is not discontinued. However, the subsequent frequency and severity of future episodes may be alarming and life-threatening. Hence, timely recognition and discontinuation of the offending drug is crucial. Other reported causative drugs include NSAIDs, aspirin, statins, fluoxetine, oral contraceptive pills, gliptins, radiocontrast agents, and vaccines.[6]

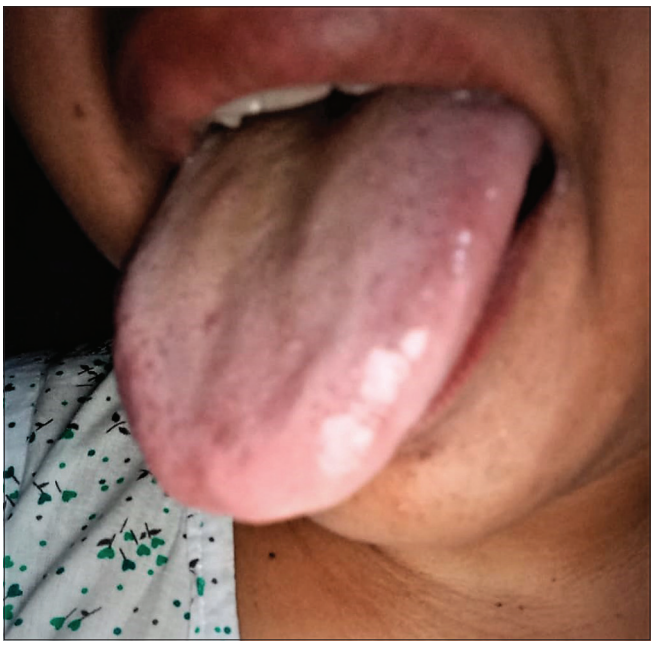

Figure 2: Tongue angioedema (lateral view)

Gliptin-induced angioedema has been occasionally reported in patients who are already receiving concurrent ACE inhibitors or have a prior history of ACEI use.[2,3,7,8] Both ACE and DPP-IV are involved in the catabolism of bradykinin and substance P to inactive metabolites, so their inhibition may result in angioedema by increased serum accumulation of these substances. However, isolated gliptin-induced angioedema has not yet been reported. Our patient, a known case of well-controlled CSU with antihistamines and cyclosporine, developed angioedema following vildagliptin intake, without any ACEI coprescription. Notably, previous reports of gliptin-induced angioedema have implicated sitagliptin, while vildagliptin was the offending drug in our patient.[9,10] The absence of family history and normal C4 levels ruled out hereditary angioedema. Complete resolution following drug discontinuation further strengthened its causative role. An oral drug provocation test could not be done as the patient refused it. Based on the Naranjo Adverse Drug Reaction Probability Scale, it was "possible" that vildagliptin was the causative agent (score = 2).[11] It involved only the tongue and this presentation is also quite uncommon, where the common sites like eyelids and lips are spared. No recurrence has been noted in the follow-up.

Drugs are an important cause of angioedema; however, isolated gliptin-induced angioedema has not been reported previously to our best knowledge. Given the life-threatening nature of this condition, we wish to document and spread awareness among physicians and dermatologists that a commonly used oral antidiabetic agent (vildagliptin) can result in angioedema, even in the absence of ACEIs, the most common culprit drug. This fact should be borne in mind while prescribing gliptins, and we should remain vigilant and counsel our patients accordingly.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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