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Case Report

Severe angioedema requiring airway intervention following evolocumab administration: a case report

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Abstract: Evolocumab is a human monoclonal antibody that effectively reduces low-density lipoprotein (LDL) cholesterol levels by inhibiting proprotein convertase subtilisin-kexin type 9 (PCSK9). Although generally well tolerated, evolocumab may rarely lead to severe hypersensitivity reactions, including angioedema. To the best of our knowledge, severe angioedema requiring airway intervention has not been reported previously in the US population. A 64-year-old woman with hypertension, hypothyroidism, hyperlipidemia, and active tobacco use presented with acute chest pain and was diagnosed with ST-segment elevation myocardial infarction. She underwent percutaneous coronary intervention with two stents placed in the right coronary artery. Despite maximum lipid-lowering therapy, her LDL level remained elevated at 125 mg/dL, prompting the addition of evolocumab (Repatha). Within 24 hours, she experienced progressive tongue and facial swelling, with oropharyngeal edema threatening airway obstruction. Urgent laryngoscopy confirmed early oropharyngeal involvement, which necessitated endotracheal intubation. She received intravenous corticosteroids and antihistamines in the intensive care unit, with symptoms resolving within 48 hours, allowing for extubation and discharge after three days. This case highlights a rare but potentially life-threatening adverse effect of evolocumab.

Keywords: Proprotein convertase subtilisin-kexin type 9, evolocumab, angioedema, intubation, hypersensitivity

Introduction

Low-density lipoprotein (LDL) cholesterol is a recognized and modifiable risk factor for cardiovascular disease. A new category of drugs, monoclonal antibodies that block proprotein convertase subtilisin-kexin type 9 (PCSK9), has been developed to effectively reduce LDL cholesterol levels [1]. The Food and Drug Administration (FDA) of the US has approved two fully humanized monoclonal antibodies, alirocumab and evolocumab, to inhibit or reduce the activity of PCSK9 [2].

Evolocumab is a human monoclonal antibody that effectively reduces LDL cholesterol levels by about 60% [3]. However, evolocumab may lead to common adverse effects, including injection site reactions, nasopharyngitis, headache, upper respiratory tract infection, musculoskeletal pain, back pain, elevated blood pressure, diarrhea, and myalgia [4]. It can also cause severe but infrequent side effects. Recent investigations have reported that evolocumab may lead to severe reactions such as hypersensitivity reactions and angioedema [5].

Although angioedema is listed as a rare adverse effect in the evolocumab product label, severe cases requiring airway management have not been well documented in the US population. To the best of our knowledge, this is the first reported case of evolocumab-induced angioedema requiring endotracheal intubation in the United States. In the current study, we report a case of severe immediate-type hypersensitivity reaction to evolocumab presenting with progressive oropharyngeal angioedema that necessitated urgent airway intervention and intensive care management, highlighting the potentially life-threatening nature of this rare adverse event. The aim of this report is to describe a rare case of severe angioedema requiring airway intervention following the administration of evolocumab, and to highlight the clinical approach to diagnosis and management for this potentially life-threatening adverse effect.

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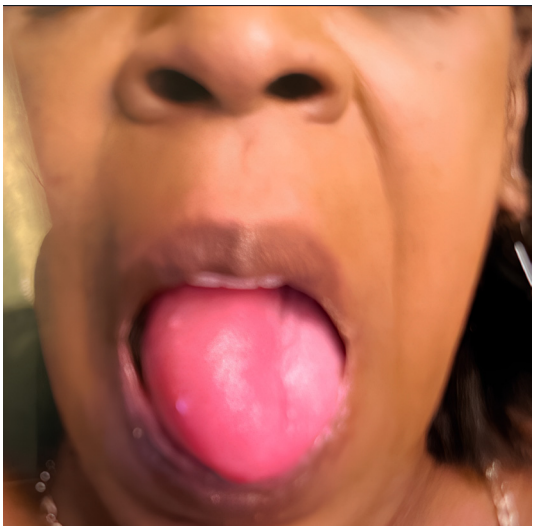

Figure 1. Marked swelling of the right side of the tongue, extending to the soft palate and uvula, was observed approximately 24 hours evolocumab administration (Day 1).

Case presentation

A 64-year-old woman with a complex medical history, including hypertension, hypothyroidism, hyperlipidemia, and active tobacco use, presented to the emergency department (ED) with acute chest pain. Electrocardiographic findings were indicative of ST-segment elevation myocardial infarction (STEMI), prompting the initiation of immediate percutaneous coronary intervention (PCI) with the deployment of two stents in the right coronary artery. Subsequent evaluation revealed an LDL concentration of 125 mg/dL despite an established regimen of maximally tolerated lipid-lowering therapy (atorvastatin 80 mg daily and ezetimibe 10 mg daily). Echocardiography revealed an ejection fraction of 70% and a normal diastolic function. Given the persistent elevation in LDL levels, evolocumab (Repatha) was added to her therapeutic regimen. At discharge, she was prescribed aspirin, clopidogrel (Plavix), metoprolol, and home medications, including Procardia for hypertension and levothyroxine for hypothyroidism.

Within 24 hours of discharge, the patient returned to the ED, reporting tongue swelling. She described the onset of numbness and absence of taste in the tongue approximately one hour after consuming Repatha, with symptoms exhibiting progressive exacerbation. Notably, there were no accompanying clinical features, such as dyspnea, chest pain, palpitations, wheezing, or dysphagia. Initially evaluated in an urgent care setting, she received 50 mg of oral diphenhydramine before being transferred to the hospital due to suspected angioedema.

Upon re-presentation to the ED, her vital parameters were stable (heart rate 66 bpm, blood pressure 128/65 mmHg, respiratory rate 18 breaths/min, and oxygen saturation 96% on room air). However, physical examination revealed significant right-sided facial swelling and marked edema of the right lateral tongue, extending toward the soft palate and uvula. Despite the absence of rash or periorbital swelling, the progressive nature of the tongue and oropharyngeal edema raised concern for impending airway compromise (**Figure 1**). No evidence of swelling was observed in the extremities, genitalia, or abdominal wall. Chest x-ray imaging was unremarkable, and serial electrocardiograms confirmed sinus bradycardia without new ST-T segment abnormalities compared to prior recordings.

An urgent otolaryngology consultation was obtained. Bedside flexible laryngoscopy revealed early involvement of the oropharyngeal structures but no laryngeal edema (**Figure 2**). Flexible laryngoscopy during clinical assessment revealed early involvement of the oropharynx and absence of laryngeal involvement at that moment; however, a decision was made for preemptive airway protection due to the risk of rapid progression. The patient was sedated with fentanyl and intubated without complications in a controlled setting.

She was treated with intravenous methylprednisolone (125 mg) and diphenhydramine (50 mg), and close airway monitoring was performed in the intensive care unit (ICU). Over the next 48 h, the facial and tongue swelling gradually resolved. She was successfully extubated and discharged home in stable condition after a total of three days of hospitalization.

Discussion

This case report describes a 64-year-old woman who developed severe angioedema of the face, uvula, soft palate, and tongue within 24 hours of receiving evolocumab, requiring emergent intubation. The temporal relationship between drug administration and symptom

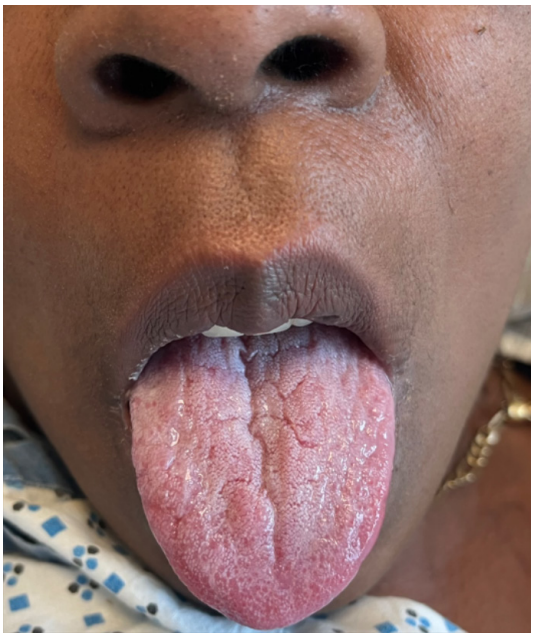

Figure 2. Resolution of right-sided tongue swelling, with normalization of oropharyngeal structures, was observed 48 hours post-treatment with intravenous corticosteroids and antihistamines (Day 3).

development (approximately one hour following administration), progression to airway compromise necessitating intubation, and subsequent resolution of symptoms upon drug withdrawal and administration of corticosteroids and antihistamines constitutes strong supportive evidence that evolocumab is the offending agent. This clinical finding underscores an unusual but potentially life-threatening side effect of PCSK9 inhibitors, which are therapeutic drugs that are being used with increasing frequency in patients with refractory hyperlipidemia despite maximal statin and ezetimibe treatment.

Evolocumab is a humanized monoclonal immunoglobulin G2 (IgG2) that selectively targets PCSK9 and inhibits its binding of PCSK9 to LDL receptors on the surface of hepatocytes. This inhibition averts PCSK9-mediated breakdown of LDL receptor, thus elevating LDL receptor density and facilitating hepatic clearance of circulating LDL cholesterol [6]. Although evolocumab has been shown to be extremely effective at lowering LDL cholesterol levels and cardiovascular events in high-risk patient groups, its long-term safety profile remains a work in progress as more extensive patient exposure is accrued in clinical practices. Based on available literature, evolocumab has a generally favorable tolerability profile, and frequently reported adverse effects include injection site reactions, nasopharyngitis, upper respiratory tract infections, musculoskeletal pain, and influenza-like illness [3, 4].

In 2024, Calapai et al. [5] conducted an extensive review of the European database of suspected adverse drug reaction reports. This review demonstrated that cutaneous reactions account for a large percentage of serious suspected adverse reactions to evolocumab, although the exact incidence of angioedema was not specifically emphasized. Indeed, angioedema is listed as a rare adverse effect in the label of the drug. Our case is particularly noteworthy as it demonstrates the potential severity of evolocumab-induced angioedema, with progression to airway compromise requiring intubation and ICU monitoring. The relative infrequency of severe angioedema resulting from the use of evolocumab makes our case all the more extraordinary, especially since, to our knowledge, this may be one of the first US-reported cases of evolocumab-induced angioedema requiring endotracheal intubation.

The pathophysiologic mechanisms of evolocumab-induced angioedema remain incompletely understood but are probably mediated through immunologic cascades. Since evolocumab is a fully humanized monoclonal antibody, it has lower immunogenicity than chimeric or partially humanized antibodies. Nevertheless, hypersensitivity reactions may still occur via several possible immunological mechanisms [7, 8]. The initial confirmed report of evolocumab-induced hypersensitivity mediated by immunoglobulin E (IgE) with proven cross-reactivity to alirocumab in a 61-year-old man who presented with recurrent incidents of urticaria on almost immediate administration was presented by Lam et al. [9]. Their observation of positive cutaneous reactions in both skin prick and intradermal tests affirmed an IgE-mediated process, illustrating that in spite of the completely human nature of these monoclonal antibodies, they still have the ability to cause IgE-mediated immunological reactions in vulnerable subjects. The presentation in our patient could be either IgE- or non-IgE-mediated hypersensitivity reactions. Some monoclonal antibodies can activate the complement cascade or directly activate mast cell degranulation, leading to angioedema without necessarily requiring IgE involvement.

In addition, there is a theoretical possibility that PCSK9 inhibition may interfere with enzymatic pathways in the breakdown of bradykinin and result in bradykinin-mediated angioedema, as occurs with angiotensin-converting enzyme inhibitors [10]. This speculation remains hypothetical, since no specific research clarifies how PCSK9 works in the homeostasis of bradykinin.

The literature also describes other types of hypersensitivity reactions to evolocumab. Porebski et al. [11] reported a case of delayed cutaneous hypersensitivity in a 67-year-old female presenting with erythematous exfoliative lesions following the third injection of evolocumab. In contrast to our immediate-onset angioedema, their patient experienced a delayed reaction with progressive worsening with successive doses and complete resolution following drug withdrawal. This phenotypic and temporal difference between the two reactions suggests that evolocumab hypersensitivity can present with diverse clinical phenotypes and timelines.

The differential diagnosis of angioedema covers a broad etiology, including hereditary angioedema (HAE), acquired C1 esterase inhibitor deficiency, food ingredient-or concomitant medication-induced allergic reactions, and idiopathic angioedema [12]. In this case, the timing of evolocumab treatment, absence of prior episodes, and therapeutic response to corticosteroids and antihistamines all significantly supported a drug-induced angioedema diagnosis. The severe presentation requiring intubation underscores the potentially life-threatening nature of this reaction. The anatomically localized presentation of angioedema to the oropharyngeal tissues, without concomitant cutaneous involvement elsewhere, are a somewhat atypical presentation for IgE-mediated processes, which more typically present with generalized urticaria. Isolated angioedema without urticarial symptoms can occur in drug-induced reactions; however, the absence of a family history and acute onset without preceding episodes markedly decrease the probability of HAE [13].

This clinical finding has important implications for clinicians who prescribe PCSK9 inhibitors to patients with diabetes. Although severe angioedema requiring intubation is a rare side effect, clinicians should be aware of hypersensitivity reactions, especially with the first dose of medication. Patients should be educated about potentially concerning signs that require urgent medical assessment, particularly symptoms involving facial or oropharyngeal swelling, which may rapidly progress to airway compromise. As demonstrated in our case, even initially stable patients can progress to requiring airway intervention, highlighting the need for close monitoring and early involvement of specialists when evolocumab-induced angioedema is suspected.

As science and clinical practice demonstrate, the course of hypersensitivity to evolocumab may range from immediate to delayed onset and from mild to severe, requiring diligent follow-up and vigilant monitoring following initiation of therapy.

Treatment involves immediate cessation of evolocumab and supportive care consisting of systemic corticosteroids and H1 antihistamines. Epinephrine administration should be considered if there are signs of systemic anaphylaxis. Because of the risk of airway compromise, close monitoring in an intensive care environment is warranted, with a low threshold for securing the airway through endotracheal intubation, as demonstrated in our patient. Additionally, alternative lipid-altering treatments should be considered if hypersensitivity is confirmed [13].

This case adds to the limited literature on severe hypersensitivity reactions induced by evolocumab, emphasizing critical aspects of diagnosis and management. Diagnosis is primarily clinical, supported by temporal correlation with drug exposure and exclusion of alternative etiologies. Early otolaryngological evaluation through laryngoscopy can assist in assessing airway involvement and determining the need for intubation. Management should be multidisciplinary and prompt to prevent fatal airway obstruction. If hypersensitivity is confirmed, alternative lipid-lowering therapies should be considered. Awareness of such potentially severe reactions is essential for the safe use of PCSK9 inhibitors.

In patients with severe hypercholesterolemia who require therapeutic options in addition to ezetimibe and statins, other strategies are indicated. But as shown by Lam et al. [9], immunologic cross-reactivity between alirocumab and evolocumab can result, likely secondary to

structural homology between these monoclonal antibodies. Therefore, Switching between PCSK9 inhibitors after a hypersensitivity reaction is cautioned.

New lipid-lowering medications, such as bempedoic acid and inclisiran (a small interfering RNA for PCSK9 messenger RNA), may be viable alternatives; however, their long-term safety is still being studied. In summary, the current case report presents a rare but clinically relevant side effect of evolocumab [14]. With the increased use of PCSK9 inhibitors in wider clinical practice, familiarity with the risk and severity spectrum of hypersensitivity reactions, including angioedema requiring intubation, is needed to facilitate early diagnosis and manage it appropriately [5, 9]. Ongoing pharmacovigilance and mechanism-based studies of these hypersensitivity reactions will inform and shape safer prescribing. The benefit-to-risk profile of evolocumab remains favorable for most patients with severe hypercholesterolemia; however, individualized consideration and monitoring are necessary, particularly in patients with a history of drug allergy or hypersensitivity reactions.

Conclusion

In conclusion, this case highlights a rare but significant adverse effect of evolocumab therapy. As PCSK9 inhibitors are increasingly used in clinical practice, awareness of potential hypersensitivity reactions, including angioedema, is essential for prompt recognition and management. Further pharmacovigilance and research into the mechanisms of these reactions will enhance our understanding and inform safer prescription practices.

Disclosure of conflict of interest

None.

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