Life-threatening Idiopathic Nonhistaminergic Acquired Angioedema With Response to Lanadelumab

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Idiopathic nonhistaminergic acquired angioedema (InhAAE) comprises forms of recurrent angioedema that are not familial or hereditary and that recur persistently upon antihistamine treatment, after exclusion of known causes of acquired angioedema, such as idiopathic histaminergic angioedema, angiotensin inhibitor–induced angioedema, and acquired angioedema with low C1 inhibitor [1]. This type of presumably bradykinin-mediated angioedema is more severe than mast cell–mediated angioedema, with an estimated 45-fold higher risk of death [2].

We report the case of a 43-year-old woman with life-threatening InhAAE that has required several orotracheal intubations owing to laryngeal edema. Her history was remarkable only for bronchial asthma and allergy to dust mites, and she was taking inhaled salmeterol/fluticasone 50/500 µg every 12 hours. Her parents and sister had no history of angioedema. She was asymptomatic until March 2015 (age 34 years), when she presented with angioedema affecting her hands and feet, dyspnea, stridor, and dysphonia. Her condition did not respond to H1 antihistamines (dexchlorpheniramine 5 mg/6 h), corticosteroids (hydrocortisone 300 mg bid), or epinephrine and eventually required orotracheal intubation. The symptoms subsided with subcutaneous administration of icatibant 30 mg (Firazyr, Shire Pharmaceuticals). Treatment was started with intravenous C1 inhibitor 1000 IU/48 h (Cinryze, Shire Pharmaceuticals). However, 3 days after discharge from the intensive care unit and after two 1000-IU doses of C1 inhibitor, she was reintubated owing to laryngeal angioedema.

After her second intubation, the patient presented weekly angioedema of the hands and, about once a month, angioedema of the lips, cheeks, and/or eyelids, as well as bloating and abdominal pain (usually perimenstrual). These attacks required additional doses of C1 inhibitor (Cinryze 1000 IU) or icatibant (30 mg), which resolved the peripheral angioedema in about 2 hours; abdominal symptoms took 12-24 hours to resolve. Since 2015, the patient has been taking tranexamic

acid 1000 mg/8 h and C1 inhibitor as long-term, off-label prophylaxis at variable doses (from 500 IU/48 h up to 1000 IU/24 h IV), depending on the intensity and frequency of the attacks. Other therapies tried included stanozolol, progestogenic anovulatory drugs, and omalizumab (300 mg/15 d for 6 months), which were withdrawn because of poor tolerance or lack of efficacy. Including the last intubation in August 2020, the patient has required 6 additional orotracheal intubations, some of which were combined with 6000 U of C1 inhibitor/24 h and 2 doses of icatibant 30 mg/24 h, to control her symptoms.

Throughout the course of the disease, levels of C4, C1 inhibitor (functional and antigenic), C1q, tryptase, D-dimer, high-molecular-weight kininogen, and plasma prekallikrein (coagulation method) remained normal both during and outside the attacks (Table). Common mutations causing hereditary angioedema (C1 inhibitor, factor XII, plasminogen, angiopoietin, myoferlin) were ruled out by a genetic study. Whole-exome sequencing was unremarkable. Available analytical data for cleaved high-molecular-weight kininogen (HKa ELISA) did not differ from those of the control sera.

InhAAE responded to albumin plasma exchange in a similar case reported by Cohn et al [3] in 2018. Given the patient's indolent course, we decided to start this treatment, with 4 sessions in 2019; this reduced the frequency and intensity of the angioedema. However, when the central venous access was changed for plasmapheresis, the patient developed bacteremia and experienced an attack requiring further intubation. This circumstance led us to definitively withdraw plasma exchange.

The absence of adequate control led us to start off-label treatment with lanadelumab (Takhzyro, Takeda Pharmaceuticals) at a dose of 300 mg every 2 weeks in November 2020. Since initiating this therapy, the patient has not required new admissions to the intensive care unit or new orotracheal intubations. During the first 3 months of treatment, the doses of C1 inhibitor and tranexamic acid were gradually reduced until they were withdrawn. The patient continues to take lanadelumab 300 mg monthly. During these 2 years of treatment, she has required rescue treatment with C1 inhibitor or icatibant on 4 occasions owing to peripheral angioedema with abdominal symptoms: 2 coinciding with concomitant infections (post-COVID respiratory illness, and urinary tract infection) and another 2 in the context of stressful situations.

Table. Laboratory Data

Parameter	Minimum values		Maximum values	
	During attacks	Off attacks	During attacks	Off attacks
C1 inhibitor (antigenic) NR, 20-34 mg/dL	42.6	43.2	46.8	49.2
C1 inhibitor (functional) NR, 70%-150%	107	150	120	150
C4 NR, 10-40 mg/dL	14	15	18	21
C3 NR, 82-180 mg/dL	106	107	115	125
C1q NR, 10-25 mg/dL	14.3	22	16.1	21.5
D-Dimer NR, 0-500 ng/mL	< 150	230	420	390
Plasma prekallikrein (activity) NR, 70%-120%	99	95	128	132
High-molecular-weight kininogen (activity) NR, 70%-120%	73	91	120	120

Abbreviation: NR, normal range.

Prior to treatment, the mean values on the Angioedema Quality of Life Scale and Angioedema Activity Score were 70 and 100, respectively. Three months after starting treatment with lanadelumab, the mean values on these scales were 22 and 28, respectively.

We report the case of a patient with idiopathic angioedema who experienced extremely severe symptoms. We consider her disease to be nonhistaminergic, given the lack of response to antihistamines, corticosteroids, adrenaline, and omalizumab. Although all the biochemical biomarkers of bradykinin release were normal or negative throughout the process, the only treatments that achieved partial control of her symptoms were those that regulate the action of bradykinin, namely, C1 inhibitor, icatibant, and lanadelumab. Consequently, we think that in the present case, the patient experienced angioedema that is probably mediated by bradykinin, with no mutations in C1 inhibitor, factor XII, plasminogen, angiopoietin, or myoferlin genes.

Recent studies showed that in InhAAE, several—and in part unknown—genetic mutations might be responsible for impairment of various factors in the contact activation system, resulting in a lack of control of the kallikrein system with bradykinin as a key mediator [4].

In previous cases, patients with InhAAE responded to therapy with C1 inhibitor or icatibant [5-7]. To our knowledge, this is the first reported case of nonresponsive InhAAE to be controlled with lanadelumab, a monoclonal antibody that inhibits plasma kallikrein. Lanadelumab prevents cleavage of high-molecular-weight kininogen and, consequently, the formation of bradykinin [8]. Nonhistaminergic angioedema might be caused in part by unknown defects that cause an alteration of the contact activation system and with it, a deficit in the control exercised by the kallikrein system leading to an increase in production of bradykinin [4,5,9].

In conclusion, lanadelumab may be an effective therapy in patients with InhAAE that does not respond to antihistamines, corticosteroids, epinephrine, or omalizumab. In this type of angioedema, which is probably induced by contact activation and bradykinin release (albeit without proven alterations in biomarkers for bradykinin-mediated angioedema), lanadelumab may be an effective alternative, since it can inhibit production of bradykinin and, as such, has demonstrated its efficacy in other forms of bradykinergic angioedema, such as hereditary angioedema due to C1 inhibitor deficiency.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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