# Life-threatening idiopathic nonhistaminergic acquired angioedema with response to lanadelumab

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**Palabras clave**: Angioedema bradicininérgico idiopático. Lanadelumab. C1 inhibidor.

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

We report a 43 year-old woman who suffers from a life-threatening idiopathic, nonhistaminergic acquired angioedema that has required several orotracheal intubations due to laryngeal edema. As the only significant antecedent she had a history of bronchial asthma and allergy to dust mites, and she was on inhaled treatment with salmeterol/fluticasone 50/500 every 12 hours. Her parents and sister had no history of angioedema. She was asymptomatic until March 2015 (34 years old), when she presented with angioedema of hands and feet, dyspnea, stridor, and dysphonia. From the onset, she was unresponsive to H1-antihistamines (dexchlorpheniramine 5mg/6 hours), corticosteroids (hydrocortisone 300 mg bid,), or epinephrine, and finally required orotracheal intubation. The symptoms subsided with subcutaneous administration of icatibant 30 mg (Firazyr®, Shire Pharmaceuticals). Treatment with intravenous C1-inhibitor (Cinryze®, Shire Pharmaceuticals) 1000 IU/48 hours was started, but three days after discharge from the intensive care unit and after two 1000-IU dosis of C1-inhibitor, she required a new intubation due to laryngeal angioedema.

Since her second intubation, the patient presented weekly angioedema of the hands, and about once a month, angioedema of lips, cheeks and/or eyelids, as well as bloating and

 
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abdominal pain (usually perimenstrual). These attacks required additional doses of C1-inhibitor (Cinryze® 1000 IU) or icatibant (30mg), which achieved resolution of peripheral angioedema in about two hours, while abdominal symptoms took 12-24 hours to resolve. Since 2015, the patient has been on sustained treatment with tranexamic acid 1000 mg/8 hours, and C1-inhibitor in long-term, off-label prophylaxis with variable doses (from 500 IU/48 hours up to 1000 U/24 hours IV), depending on the intensity and frequency of her angioedema. Other therapies were tried, such as stanazolol, progestagenic anovulatory drugs, and omalizumab (300 mg/15 days during six months), which were withdrawn due to poor tolerance or lack of efficacy. Including the last intubation in august 2020, the patient has required six additional orotracheal intubations, in some of them demanding up to 6000 U of C1-inhibitor/24 hours and two doses of icatibant 30 mg/24 hours to control her symptoms.

Throughout her evolution, the levels of C4, C1-inhibitor (functional and antigenic), C1q, tryptase, D-dimers, high-molecular-weight kininogen, and plasma prekallikrein (coagulating methodology), have been normal inside and outside the attacks (Table 1). 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 (cHMWK) (HKa ELISA) were not different from the control sera.

Cohn et al. reported a similar case responding to albumin plasma exchange in 2018 [3]. Given the torpid evolution of our patient, we decided to start this treatment, performing up to four sessions in 2019 that resulted in a drop in the frequency and intensity of the angioedema. However, after changing her central venous access for plasmapheresis, our patient developed a bacteraemia and suffered from a subsequent attack requiring a new intubation. This circumstance led to withdraw plasma exchange definitely.



doi: 10.18176/jiaci.0926

The lack of adequate control in our patient led us to start an off-label treatment with Lanadelumab (Takhzyro®, Takeda Pharmaceuticals) at a dose of 300 mg every two weeks in November 2020. After beginning this therapy, the patient has not required new admissions to the Intensive Care Unit or new orotracheal intubations so far. Along the first three months of treatment, the doses of C1 inhibitor and tranexamic acid were gradually reduced until withdrawn. Now, she is following Lanadelumab 300 mg monthly. During these two years of treatment, she has required rescue treatment with C1-inhibitor or icatibant on four occasions due to peripheral angioedema with abdominal symptoms: two of them coinciding with concomitant infections (post-Covid respiratory illness, and urinary tract infection), and another two in the context of stress situations.

Prior to treatment, the mean values of angioedema quality of life scale (AE-QoL) and angioedema activity score (AAS28) were 70 and 100 respectively. Three months after starting treatment with Lanadelumab, the mean values of these scales were 22 and 28 respectively.

We report a patient suffering from idiopathic angioedema with extremely severe symptoms. We consider her disease as non-histaminergic, given the lack of response to antihistamines, corticosteroids, adrenaline or omalizumab. On the other hand, all biochemical biomarkers of bradykinin release have been normal or negative throughout the process. However, the only treatments that achieved partial control of her symptoms were those that regulate bradykinin's action: C1 inhibitor, icatibant, and lanadelumab. Consequently, we think that our patient suffers from an angioedema probably mediated by bradykinin, without mutations in the genes C1-inhibitor, factor XII, plasminogen, angiopoietin and myoferlin.

Nonetheless, recent studies showed that in InhAAE, various, and in part unknown genetic mutations might be responsible for impairment of different factors of the contact system, resulting in a lack of control of the kallikrein system with the result of bradykinin as a main mediator [4].



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In previous cases, patients with idiopathic non-histaminergic angioedema responded to therapy with C1-inhibitor or icatibant [5-7]**.** To the best of our knowledge, this is the first reported case of unresponsive InhAAE that can 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]. Part of the non-histaminergic angioedema might be caused by unknown defects that cause an alteration of the contact system and with it, a deficit in the kallikrein system's control determining an increase in bradkynin's production [4,5,9].

In conclusion, lanadelumab may be an effective therapy in patients with non-histaminergic idiopathic angioedema unresponsive to antihistamines, corticosteroids, epinephrine, or omalizumab. In this type of angioedema probably induced by contact activation and bradykinin release (although without assessment of biomarkers for bradykinin-mediated angioedema) lanadelumab may be an effective alternative, since it can inhibit bradykinin's production; and as such, has demonstrated its efficacy in other forms of bradykinergic angioedema, as hereditary angioedema due to C1-inhibitor deficiency.

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**FIGURE LEGENDS**

**Table**. Laboratory data.

| PARAMETER | MINIMAL VALUES | | MAXIMUM VALUES | |
|---|---|---|---|---|
| | IN ATTACKS | OFF ATTACKS | IN ATTACKS | OFF ATTACKS |
| C1 INHIBITOR (ANTIGENIC) N. R. 20-34 mg/dl | 42.6 | 43.2 | 46.8 | 49.2 |
| C1 INHIBITOR (FUNCTIONAL) N. R. 70-150% | 107 | 150 | 120 | 150 |
| C4 N. R.10-40 mg/dl | 14 | 15 | 18 | 21 |
| C3 N.R. 82-180 mg/dl | 106 | 107 | 115 | 125 |
| C1q N.R. 10-25 mg/dl | 14.3 | 22 | 16.1 | 21.5 |
| D-Dimer N.R. 0-500 ng/ml | < 150 | 230 | 420 | 390 |
| Plasma Prekallikrein (activity) N.R. 70-120% | 99 | 95 | 128 | 132 |
| High-molecular-weight kininogen (activity) N.R. 70-120% | 73 | 91 | 120 | 120 |

N.R. Normal ranges





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