Acquired Angioedema due to C1-Esterase Inhibitor Deficiency: A Diagnostic and Therapeutic Challenge

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Acquired angioedema due to C1-esterase inhibitor deficiency (AAE-C1-INH) is a rare disease sharing clinical and laboratory findings with hereditary angioedema (HAE). Angioedema is caused by increased permeability in blood vessels in response to elevated levels of bradykinin as a result of low levels of C1-inhibitor antigen (C1-INH-a) and function (C1-INH-f). Clinically, it mimics HAE type I or II. Onset is generally in adulthood in persons with a negative family history [1].

AAE-C1-INH can be associated with underlying conditions such as monoclonal gammopathy of undetermined significance, non-Hodgkin lymphoma, and autoimmune disease (mostly autoimmune thyroiditis and systemic lupus erythematosus) [2,3]. Two main mechanisms have been proposed to explain this link between hematological or autoimmune disease and AAE-C1-INH: adsorption of C1-INH on the surface of malignant clones and cleavage of C1-INH by anti–C1-INH antibodies [4]. In some patients, no associated disorder can be found [2,3]. There are no specific treatments licensed by regulatory authorities for AAE-C1-IHN, and all current approaches are based on treatments validated for HAE [5-9].

We present our experience in the management of an idiopathic case of AAE-C1-INH. The patient gave his written informed consent for publication. A 65-year-old man with no relevant medical or familial history was referred to our unit in January 2018 with episodes of recurrent angioedema. At the time of his first evaluation, these episodes had been peripheral and mild, with a frequency of 1-2 per year. At that time, levels of C1-INHa, C1-INHf, C4, and C1q were low, while free anti–C1-INH antibodies and C1-INH–anti–C1-INH complexes were not detected (Table). He was diagnosed with AAE-C1-INH and extensively studied to rule out hematologic and other malignancies, autoimmunity, and infectious diseases. However, no underlying cause was detected. Since his clinical symptoms were mild and sporadic, only icatibant was prescribed for acute attacks.

By the end of 2018, the number of angioedema attacks had increased to 1-2 per month, including laryngeal episodes

Table. Biological Characteristics and Patient-Reported Outcome Measures According to Long-term Prophylaxis

	2018	2019	2020	2021		2022		2023	2024
Long-term prophylaxis	**None**	**AA**	**AA**	**Berinert**	**Lanade-lumab**	**Lanade-lumab**	**Rituximab**	**Rituximab**	**Lanade-lumab**
C4 (15-53 mg/dL)	< 1.7	1.8	5.5	< 1.7	< 1.7	<1.7	< 1.7	0.4	0.8
C1-INH antigen (21-38 mg/dL)	11	24	39	16	14	13	14	12	11
C1-INH functional (70%-130%)	18	75	65	< 10	12	14	13	14	15
C1q (>12 mg/dL)	6	23	32	7	< 2	ND	< 2	< 2	8
Free anti–C1-INH antibodies	-	ND	ND	ND	ND	+	ND	ND	ND
C1INH–anti–C1-INH antibody complex detection	-	ND	ND	ND	ND	+	ND	ND	ND
AAS	ND	5	12	6	0	0	0	14	0
AE-QoL	ND	8	18	10	0	0	0	21	0

Abbreviations: AA, attenuated androgens; AAS, Angioedema Activity Score; AE-QoL, Angioedema Quality of Life; ND, no data.

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with respiratory distress. Long-term prophylaxis (LTP) with attenuated androgens (danazol 100 mg/d) was initiated, leading to a good clinical and laboratory response that was maintained for the following 2 years (Table). Tolerance was initially excellent, and no variations in liver function were detected.

In 2021, the patient developed a peripheral thrombosis requiring antiplatelet and anticoagulant treatment, and danazol was stopped. A new line of LTP with purified C1 inhibitor (Berinert, CSL Behring) in subcutaneous doses of 60 IU/kg 3 times weekly was started. The clinical course was satisfactory, except for hematoma and eczema around the injection sites; increasing the dosing interval to minimize this adverse effect resulted in recurrence of angioedema.

Based on the increased frequency and severity of the symptoms, a third line of LTP was started with lanadelumab (Takhzyro, Takeda Pharmaceuticals) (300 mg every 2 weeks) [7]. The patient tolerated treatment well, with total control of angioedema. The favorable progression enabled us to move to a monthly schedule, without incidents. At this time, repeat determination of free anti–C1-IHN antibodies and anti–C1-INH complexes yielded a positive result (Supplementary Material). Exhaustive examinations were again conducted to identify underlying diseases, although they yielded no specific results. In other cases of AAE-C1-INH with positive antibodies without hematologic disorders, rituximab has proven successful [6,10]. Therefore, the patient signed the informed consent document, lanadelumab was stopped, and intravenous rituximab 375 mg/m^2 was administered weekly for 4 weeks with good tolerance.

The patient remained asymptomatic for approximately 9 months; however, a new cycle of rituximab was needed at this time because of recurrence. Six months after this second cycle of rituximab, the angioedema episodes reappeared, leading us to represcribe lanadelumab. The patient remains asymptomatic with monthly subcutaneous lanadelumab (300 mg).

Differential diagnosis can prove difficult in AAE–C1-INH, and treatment may be even more problematic. In the present case, therapies licensed for HAE-C1-INH were effective. The attenuated androgen danazol was helpful but had to be stopped because of adverse events. Long-term prophylaxis with a purified C1 inhibitor or lanadelumab was also effective initially. However, the C1-inhibitor could not achieve full control of angioedema at licensed doses and was associated with local adverse effects induced by antiplatelet and anticoagulant treatment, whereas lanadelumab effectively improved the patient's symptoms and quality of life (Table).

The late finding of anti–C1-INH antibodies led us to expect a good response to rituximab. However, the patient's response was only partial and nonsustained.

To our knowledge, this is the first report of patients with AAE-C1-INH treated successfully with lanadelumab in Spain, and one of the scarce reports worldwide [7,10].

Larger case series are required to reach solid conclusions regarding the use of these treatments in routine clinical practice.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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