Successful Use of Recombinant Human C1-INH in a Patient with Acquired Angioedema due to C1 Inhibitor Deficiency and an Unusually High Titer of Anti-C1-Inhibitor Autoantibodies

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Recurrent angioedema, in particular bradykinin-mediated types, constitutes a genuine diagnostic and therapeutic challenge. The 2 forms of recurrent angioedema are hereditary angioedema (HAE) and acquired angioedema (AAE). The more common of the two is AAE, which is associated with angiotensin-converting enzyme inhibitors (ACEi). Acquired deficiency of C1-INH is another, albeit rarer cause of AAE (C1-INH-AAE). Various mechanisms in acquired C1-INH deficiency have been described and are linked mainly to underlying diseases, such as lymphoproliferative disorder and autoimmune disease [1]. In certain patients, both mechanisms (eg, increased consumption of C1-INH in the background of lymphoproliferative disease and the presence of anti–C1-INH autoantibodies) simultaneously participate in the pathophysiology of C1-INH-AAE and the development of clinical symptoms [2].

We present the case of a 67-year-old man with an acquired form of angioedema due to C1-INH deficiency characterized by an unusually high titer of specific autoantibodies against C1-INH. The patient was referred to our center with recurrent nonpruritic angioedema of the face, lips, and tongue and submucosal edema in the larynx associated with dyspnea, which required intubation. No family history for recurrent angioedema or allergies was evident. The patient had been treated in the past for arterial hypertension with ACEi (5 mg of ramipril per day). Discrete symptoms of angioedema were present before the treatment with ACEi, which increased the frequency and, slightly, the severity of angioedema. Owing to recurrent angioedema and cough, the ACEi was switched to amlodipine. However, the angioedema persisted, and its intensity and frequency gradually increased even after cessation of ACEi treatment. Angioedema was treated with antihistamines (single and 4-fold increase in dose) and systemic corticosteroids, with no clinical impact. Given that the patient had second-degree atrioventricular blockage and paroxysmal supraventricular tachycardia, he underwent cardiac pacemaker implantation. After this intervention, he experienced his first severe attack of laryngeal angioedema requiring intubation and was referred to our center. The initial laboratory examination revealed a significantly decreased concentration and function of C1-INH and decreased concentration of C4 and C1q complement components. The diagnosis of AAE with C1-INH deficiency was established through 2 separate measurements in 3 months (Table). Hematological examination excluded any hematologic-oncologic diseases. Indirect fluorescence revealed a strong presence of antinuclear antibodies (coarse speckled pattern), and ELISA revealed anti-dsDNA (62 U/mL, normal range <20 U/mL). The patient did not show any signs of clinical rheumatic diseases. An examination for autoantibodies against C1-INH was conducted in the Complement Laboratory at Semmelweis University, Budapest, Hungary. A high anti–C1-INH IgG titer (35 U/mL; normal range, 0-2 U/mL) was detected, and a diagnosis of C1-INH-AAE type 2 was established (Table). Given the patient's history of venous thrombosis (contraindication for antifibrinolytics), successful prophylaxis was initiated with attenuated androgens (200 mg of danazol once daily). The breakthrough angioedema attacks were treated with recombinant human C1-INH (rhC1-INH). To date, 6 attacks of facial angioedema and 4 attacks of laryngeal angioedema have been treated with 2100 U (body weight 92 kg), resulting in a significant improvement 0.5-2 hours after treatment and complete resolution of angioedema symptoms in 12-24 hours.

AAE with C1-INH deficiency shares the same clinical presentation as other types of bradykinin-mediated angioedema, although its etiology is completely different. Moreover, the clinical symptoms of C1-INH-AAE could precede the diagnosis of the underlying disease. While detection of autoantibodies against C1-INH is useful, only a few laboratories can provide this examination, since commercial kits are not available [3].

Table. Selected Laboratory Parameters[a]

Parameter	Result 1	Result 2	Normal Range	Unit of Measure	Evaluation
C3	2.03	1.5	0.90-1.80	g/L	H/N
C4	0	0.14	0.15-0.55	g/L	L
C1 inhibitor concentration	0.08	0.13	0.15-0.30	g/L	L
C1 inhibitor functional activity	0	89	70-110	%	L/N
C1q	3	115	60-180	mg/L	L/N
Anti-C1-INH IgG	35	39	0-2	U/mL	H
Anti-C1-INH IgA	0.07	0.07	0-0.6	U/mL	N
Anti-C1-INH IgM	0	0.02	0-12	U/mL	N
Anti-C1q IgG	5	6	0-52	U/mL	N

Abbreviations: H, higher than normal; L, lower than normal; N, normal.
aThe interval between the 2 samples was 3 months. Treatment with androgens commenced during this period and improved the selected parameters in the second sample.

Moreover, it appears that anti–C1-INH autoantibodies may have the capacity to predict the response to therapy with C1-INH concentrate [2].

Therapies regulating kallikrein and bradykinin activity are recommended. Treating the underlying condition is also recommended. Tranexamic acid, attenuated androgens, and plasma derived C1-INH can be used for long-term prophylaxis. Antifibrinolytic agents seem to be more effective than in HAE [4]. Androgens are effective only in a small proportion of C1-INH-AAE patients. For the most severely affected patients, regular administration of plasma-derived C1-INH can be selected. The presence of anti–C1-INH autoantibodies necessitated higher doses of pdC1-INH in some patients [2]. Icatibant and ecallantide have also been used successfully [5].

AAE can result from the use of ACEi, and in some patients, the clinical symptoms of angioedema can persist even after cessation of the ACEi [6]. Only 2 cases of AAE treated with recombinant C1-INH concentrate have been reported to date. In 2014, Manson et al [7] reported the case of a patient with AAE treated with 4200 U of rhC1-INH for an abdominal and facial angioedema attack. Previous treatment with pdC1-INH (even at 1000-1500 U) was not effective. The symptoms improved within 1 hour of treatment with rhC1-INH, although after 12 hours, new abdominal pain and facial swelling developed. The authors did not provide information about anti–C1-INH autoantibodies [7]. Another case report showed the excellent efficacy of rhC1-INH in treating laryngeal attacks with negative anti–C1-INH-autoantibodies in a patient with type 1 C1-INH-AAE [8]. We initially used a lower dose for treatment of the angioedema attack (2100 IU). Since this was successful and fully effective, we used the same dose for the following attacks, with no decline in clinical efficacy. It seems that rhC1-INH could carry a lower risk for the formation of neutralizing antibodies than pdC1-INH. In a study of 155 HAE patients treated with repeated application of rhC1-INH, the authors detected anti–rhC1-INH in 6 (in 1 patient these were already present before the first treatment). No neutralizing antibodies against rhC1-INH were found [9]. Moreover, the glycosylation profile of rhC1-INH differs from that of pdC1-INH, and the drug does not contain neuraminic acid [10].

We report a successful, repeated application of recombinant human C1-INH concentrate in a patient with type 2 C1-INH-AAE due to unusually high anti–C1-INH IgG. It can be concluded that rhC1-INH is an effective alternative for treatment of angioedema attacks in affected patients, even in the presence of anti–C1-INH antibodies.

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Conflicts of Interest

MJ received grants from CSL Behring, Shire/Takeda, and Pharming, served as an advisor for these companies, and participated in clinical trials/registries for BioCryst, CSL Behring, Pharming, and Shire/Takeda.

PB participated in clinical trials/registries for BioCryst, CSL Behring, Pharming, and Shire/Takeda.

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The remaining authors declare that they have no conflicts of interest.

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