

Letter to the Editor

Short-term prophylaxis in a patient with acquired C1-INH deficiency

To the Editor:

Acquired angioedema resulting from the deficiency of the C1-inhibitor (AAE-C1-INH) was first described by Caldwell et al¹ in 1972. In 1986, Jackson et al² discovered autoantibodies against the C1-inhibitor (C1-INH). AAE-C1-INH often accompanies lymphoproliferative—and occasionally—autoimmune disorders, neoplasms, and infections. Low C1-INH level is associated with activation of the kinin-bradykinin cascade, leading to the formation of bradykinin, increasing capillary permeability, and tissue swelling.³ AAE-C1-INH is characterized by recurrent episodes of subcutaneous or submucosal edema formation, with initial onset after the age of 40 years. The family history is negative. The diagnosis can be established from clinical symptoms and complement testing. In AAE-C1-INH, the antigenic level of C1-INH is normal or low, as well as its functional activity—along with that of C4—is low. The C1q level is reduced in 70% of the cases. In a proportion of patients, oligoclonal or monoclonal autoantibodies against C1-INH can be detected in the serum.⁴

Only case reports and smaller observational studies have been published on the treatment of AAE-C1-INH.⁵⁻⁷ Plasma-derived C1-INH concentrate (pdC1-INH—mostly Berinert; CSL Behring, Marburg, Germany), as well as icatibant, ecallantide, and fresh frozen plasma, has been used to good effect for the acute treatment of edematous attacks. The elimination of potential trigger factors and the therapy of underlying disease (when present) are essential.^{4,8} Attenuated androgens, antifibrinolytic agents, and pdC1-INH concentrate may improve the symptoms.⁴ The anti-CD20 mAb rituximab has been found beneficial in some cases.⁷⁻⁹ Relevant data on the short-term prophylaxis of AAE-C1-INH are rare. We found just a single case report in which pdC1-INH concentrate was administered as preprocedural prophylaxis.⁶

This is the first case report on short-term prophylaxis in AAE-C1-INH, with the administration of recombinant human C1-inhibitor (rhC1-INH), derived from milk of transgenic rabbits. The 66-year-old female patient had hypertension known for 15 years and treated with enalapril. During the last 10 months, abdominal symptoms (colicky abdominal pain, vomiting) recurred once a month initially and then every 10 days. During this period, she experienced edema of the shoulder, thigh, and feet on 3 occasions. Her symptoms persisted for 7 to 8 hours and then, resolved over 2 to 3 days. She required emergency medical attention several times for abdominal symptoms. Computed tomography imaging of the abdomen during the attacks depicted free peritoneal fluid on several occasions. The gastroenterology

evaluation (gastroduodenoscopy, colonoscopy, stool test for parasites, protozoa, and bacteria, antigliadin antibodies) performed during a symptom-free period was negative. Ten months after the onset of the initial symptoms, the possibility of C1-INH deficiency occurred to the practitioner during an abdominal attack and therefore, he referred the patient to the National Angioedema Center. The angiotensin-converting enzyme inhibitor (ACEI) was not discontinued at this time because the patient had mostly abdominal symptoms, which are rather uncharacteristic of ACEI-mediated angioedema. The primary care provider's unfamiliarity with this condition may have led to inappropriate management of this patient. AAE-C1-INH was diagnosed from the clinical symptoms, the complement screen (Table 1), and the negative family history. Because the known trigger factors of bradykinin-mediated angioedema attacks include ACEIs, we replaced enalapril with bisoprolol on the initial presentation of the patient. Just a single, mild abdominal attack occurred during the next 6 months. Pancytopenia, which had evolved during the follow-up period, warranted iliac crest biopsy, which confirmed non-Hodgkin lymphoma of the splenic marginal zone type. Splenectomy was performed (the spleen weighed 1.49 kg and measured 19 × 16 × 12 cm) after pretreatment with erythropoietin, as the patient rejected blood transfusions for religious reasons. Plasma-derived pdC1-INH concentrate was at hand, but surgery and the postoperative course were uneventful. Edematous attacks have not recurred during the last 2 years and therefore, neither acute nor maintenance therapy was necessary. The patient's hematological and complement parameters have been checked regularly since then (Fig 1). A monoclonal protein of the IgG λ type—which had not been detectable at the onset of the edematous episodes—appeared in the serum (3.34 g/L), possibly in relation to the lymphoma. Although Hauptmann et al⁵ described the normalization of complement components after splenectomy, we could not confirm such a change (Fig 1). During the past 2.5 years, the patient had surgery on 3 occasions. Although she was symptom-free, short-term prophylaxis was administered before these interventions because her complement status remained unchanged and C1-INH deficiency persisted. On 2 occasions, she received 1000 U of pdC1-INH concentrate (Berinert) before oral surgery (multiple dental extractions and suture). On 1 occasion, before cataract surgery, we introduced short-term prophylaxis with 2100 U of rhC1-INH concentrate Ruconest (Pharming, Leiden, The Netherlands). Testing for specific IgE against rabbit dander before rhC1-INH treatment was negative. Both drugs were administered intravenously, 1 hour before the procedure. We switched from the plasma-derived to the recombinant preparation because the rhC1-INH concentrate had become available in the meantime. Moreover, the patient also preferred

TABLE 1. The patient's complement parameters at diagnosis

	Classical total complement (CH50/mL)	C1q (mg/L)	C3 (g/L)	C4 (g/L)	C1-INH concentration (%) [*]	C1-INH activity (%) [†]	Anti-C1INH (IgG) (U/mL)	Anti-C1INH (IgA) (U/mL)	Anti-C1INH (IgM) (U/mL)	Anti-C1q (IgG) U/mL
Value	0	13	1.3	0.02	21	1	0	0	0	0
Reference range	48-103	60-180	0.90-1.80	0.15-0.55	64-166	70-100	0-2.0	0-0.6	0-12	0-52

^{*}To quantify antigenic C1-INH levels, radial immunodiffusion was performed using antibodies from DiaSorin (Stillwater, Minn), and an in-house calibrator for C1-INH.

[†]The functional activity of C1-INH was measured with an enzyme immunoassay kit (Quidel, San Diego, Calif).

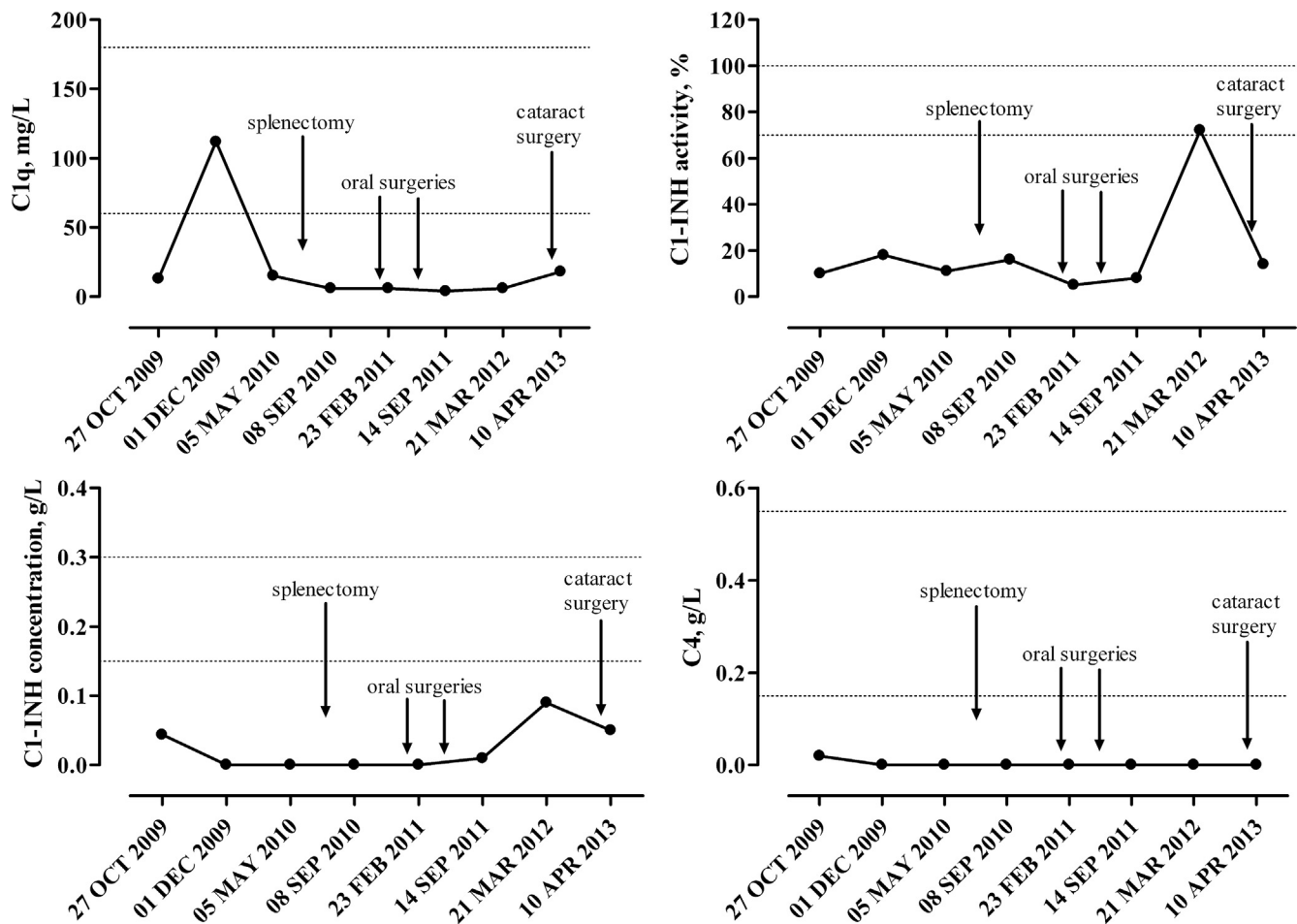


FIG 1. Follow-up of the complement parameters over years. Although the levels of the complement components did not return to normal after splenectomy, the patient is symptom-free. The transient elevation of functional and antigenic C1-INH levels might have been related to an upper respiratory tract infection accompanied by fever, for which the patient received an antibiotic (amoxicillin). The dates of the interventions are indicated by arrows.

the latter to the plasma-derived product on religious grounds. All procedures were uneventful; drug adverse reactions were not observed.

In addition to eliminating the trigger factors, treatment of the underlying disease, management of acute symptoms, and drug prophylaxis are similarly important in AAE-C1-INH. As shown by this case, short-term prophylaxis would be justified in acquired C1-INH deficiency, just as it is in the hereditary form, because invasive procedures may also cause edema formation in the former. It is impossible to predict whether an edematous episode will or will not occur after an intervention. Therefore, the decision on the introduction of short-term prophylaxis is an individualized one, made after the evaluation of benefits and risks. In this case, both pdC1-INH and rhC1-INH proved effective: the invasive procedures and postoperative wound healing were uneventful, angioedema attacks did not occur, and antibodies to C1-INH did not develop. Multicenter, placebo-controlled clinical studies would be necessary, as the medicinal products licensed currently for use in hereditary angioedema due to C1-inhibitor deficiency are not authorized for the treatment of AAE-C1-INH. Reporting a series of cases would be necessary to

change this. However, gathering the number of patients required for a case series study would be difficult because of the small number of patients (the estimated prevalence of AAE-C1-INH ranges between 1:100,000 and 1:500,000).⁴

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