

Acquired Angioedema Associated with Primary Antiphospholipid Syndrome in a Patient with Antithrombin III Deficiency

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Established facts

- Acquired C1 inhibitor deficiency is a very rare clinical entity, associated with lymphoproliferative diseases (type I) or autoantibodies against C1 inhibitor (type II).
- Acquired angioedema is characterized by recurrent bouts of edema (subcutaneous tissues, larynx, gastrointestinal tract).
- Conventional therapy (antihistamines, steroids, epinephrine) is ineffective.

Novel insights

- This is the first report on the coincidence of acquired angioedema and primary antiphospholipid syndrome (overlap of type I and type II).
- Thrombophilia might be considered as a provoking factor of acquired angioedema.
- Complement testing is suggested in thrombosis and angioedema resistant of conventional therapy.

Key Words

Acquired angioedema • Thrombosis • Primary antiphospholipid syndrome • C1 inhibitor deficiency • Antithrombin III deficiency

Abstract

Acquired angioedema (AAE) due to the functional deficiency of the C1 inhibitor (C1-INH) is a rare disease characterized by recurrent bouts of edema that involve subcutaneous tissues, the larynx or the gastrointestinal tract. In the present paper, we report the case of a male patient with symptoms of AAE and recurrent deep venous and arterial thrombosis.

As a trigger of AAE in the present patient, we revealed primary antiphospholipid syndrome accompanied by antithrombin III deficiency, along with malignancy in the history, and angiotensin-converting enzyme inhibitor therapy. Although anti-C1-INH titers (type I AAE) were normal initially, we observed a sharp increase in anti-C1-INH titers (suggestive of type II AAE) during follow-up. It seems that thrombosis might worsen angioedematous attacks in functional C1-INH deficiency. Thrombophilia should be considered a provoking factor of AAE and should be carefully sought for in these patients, as the key to successful management of AAE is the effective treatment of the underlying disease.

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Table 1. Laboratory parameters of the patient during follow-up

	30/05/2005	13/07/2005	11/11/2005	16/03/2006	16/08/2006	Normal range
CH ₅₀ /ml	0	17	0	0	0	48–103
C1q, mg/l	19	10	13	16	10	60–180
C3, g/l	1.24	0.85	1.16	1.14	0.85	0.70–1.80
C4, g/l	0.05	0.013	0.03	0.02	0.00	0.15–0.55
C1-INH concentration, %	0	0	7	0	0	64–166
C1-INH activity, %	0	0	0	1	0	70–100
Anti-C1-INH (IgG), AU/ml	0.92	0.58	1.00	1.60	0.20	0–2.0
Anti-C1-INH (IgA), AU/ml	0.68	5.02	2.7	19.30	2.70	0–0.6
Anti-C1-INH (IgM), AU/ml	3.53	7.33	7.00	1.00	3.00	0–12.0
Anti-C1q (IgG), U/ml	7.0	32.5	25.0	23.0	27.0	0–52
Thrombin time versus control, s	17 vs. 21				22 vs. 21	15–22
Activated partial thromboplastin time versus control, s	23 vs. 34				22 vs. 35	28–45
International normalized ratio	0.90				0.90	0.90–1.20
Prothrombin time, %	108				108	70–120
Thrombocyte count, × 10 ⁹ /l	285				241	180–400
Fibrinogen, g/l	3.40				3.70	2.00–4.00
Protein C activity, %	96.0				123.8	70–149
Protein S activity, %	63.0				70.5	59–130
AT-III activity, %	56.0				59	70–120
Cardiolipin screening	positive	positive			positive	
Anti-cardiolipin (IgG), U/ml	8	7			9	0–10
Anti-cardiolipin (IgM), U/ml	4	7			5	0–7
Anti-cardiolipin (IgA), U/ml	NA	NA			117	0–10
Anti-β ₂ -glycoprotein I (GAM), U/ml	50	62			47	0–10
Anti-β ₂ -glycoprotein I (IgG), U/ml	NA	NA			16.2	0–10
Anti-β ₂ -glycoprotein I (IgM), U/ml	NA	NA			8.3	0–10
Anti-β ₂ -glycoprotein I (IgA), U/ml	NA	NA			105	0–10
Anti-prothrombin, U/ml	24	9				0–20
Anti-phosphatidyl serine (IgG), U/ml	16	3				0–9
Anti-phosphatidyl serine (IgM), U/ml	8	8				0–9

C1 inhibitor (C1-INH) deficiency can be inherited – hereditary angioedema (HAE) [1] – or acquired – acquired angioedema (AAE) [2, 3]. Clinically, the 2 forms are indistinguishable [4, 5]; both are characterized by recurrent bouts of edema that involve subcutaneous tissues, the larynx or the gastrointestinal tract and do not respond to conventional therapy with calcium, antihistamines, corticosteroids or epinephrine [4, 5].

AAE usually develops after the fourth decade of life, and patients do not have a family history of angioedema [4, 5]. The diagnosis is based on complement laboratory analysis; decreased C1q, C2, C4 and C1-INH concentrations, low C1-INH activity along with normal C3 levels are characteristic for the syndrome. The absence or presence of anti-C1-INH autoantibodies differentiates type I from type II AAE.

Recently, we reported on an AAE type II patient heterozygous for factor V (Leiden), whose symptoms were trig-

gered by deep venous thrombosis episodes [6]. In the present paper, we report the case of a male patient with symptoms of AAE and recurrent deep venous and arterial thrombosis. We also report the overlap of and discuss the relevance of distinguishing between type I and II AAE.

Case Report

From the long history of the 67-year-old male patient, we highlight hypertrophic cardiomyopathy, ischemic heart disease, alcoholic hepatopathy, insufficiency of the aortic and tricuspid valves (grade I) and hypertension. The patient also had laryngeal neoplasm and he underwent total extirpation of the larynx in 1994.

The first episode of deep venous thrombosis, which occurred in his right lower limb in March 1998, was complicated by pulmonary embolism, which was followed by severe tongue edema in April 1998. Acenocoumarol therapy was initiated, but the patient developed hemorrhagic skin necrosis (confirmed by tissue biopsy) in the right gluteal and sacral regions. Low-molecular-weight

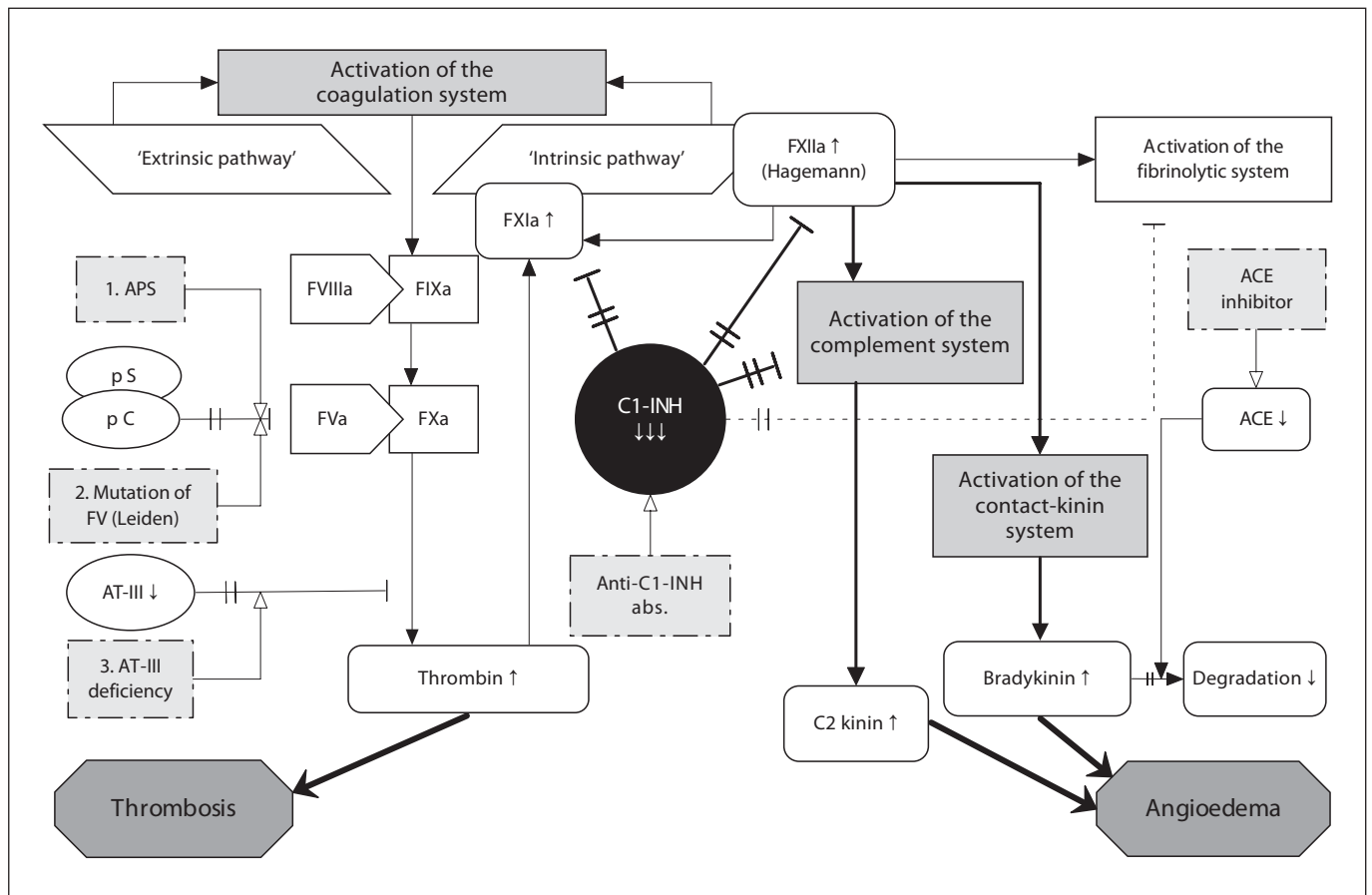


Fig. 1. Hypercoagulation and angioedema in the absence of C1-INH function. Activation of the coagulation system – either by the extrinsic or the intrinsic pathway – leads to increased thrombin production. Acting through a positive feedback mechanism, thrombin can increase the formation of activated factor XI, resulting in a positive feedback loop. On the other hand, activated factor XII (Hagemann) can activate the classical complement pathway resulting in enhanced C2 kinin production and in the activation of the contact-kinin system that leads to enhanced bradykinin formation. Bradykinin is cleaved by ACE, which is blocked by ACE inhibitors. These processes may prove clinically relevant in C1-INH deficiencies, as the inhibitory function of C1-INH on co-

agulation factors XIa, XIIa and complement C1 is lost. Thus, insufficient regulatory function of C1-INH might lead to thrombin production – and thrombosis – while it also contributes to the development angioedema symptoms. Specifically, hypercoagulation resulting from the APS (1) and the deficiency of AT-III (2) has led to thrombophilia and thrombosis, while the dynamic balance between coagulation, fibrinolysis, complement and contact-kinin systems was deranged by the loss of C1-INH function eliminated by the hyperactivation of the complement or by the specific blocking autoantibodies. F = Coagulation factor; C = complement component; p C = protein C; p S = protein S; abs. = antibodies.

heparin therapy was initiated, but was arbitrarily stopped by the patient. In November 1998, deep venous thrombosis recurred in both lower limbs and was again followed by tongue edema. Between 1998 and 2005, edematous swellings of the lips and tongue, as well as of the lower limb recurred 5–6 times per year and the patient was hospitalized on 2 occasions, with severe abdominal complaints.

The patient was referred to the Hungarian HAE Center [7] for differential diagnosis in May 2005. The presence of an infective focus and allergic etiology were ruled out; viral serology tests were also negative. Complement testing revealed extremely low CH₅₀, C1q, C4 levels, normal C3 levels and undetectable C1-INH con-

centration and activity (table 1). As we could not detect markedly elevated titers of anti-C1-INH autoantibodies (measured by an in-house assay) [for complete description, see ref. 8], the patient was diagnosed with AAE type I. During the follow-up, increasing titers of anti-C1-INH immunoglobulin A (IgA) were detected (table 1), which was suggestive of AAE type II. No lymphoproliferative disease could be identified.

The diagnostic process involved in-depth investigation of the cause of thrombosis. Elevated anti-β₂-glycoprotein I titers were found along with normal lupus anticoagulant activity at the time of diagnosis and 6 weeks later. During the follow-up, we performed an isotype-specific anti-β₂-glycoprotein I testing and

found elevated titers against IgA- and IgG-specific anti- β_2 -glycoprotein I and high titers of IgA anticardiolipin antibodies (table 1). Although high IgA type anti-C1-INH, anti- β_2 -glycoprotein I and anticardiolipin antibodies were found, the total levels of the different Ig isotypes were normal, and no monoclonal band was identified. As antinuclear, anti-dsDNA and anti-Sm antibodies were negative, primary antiphospholipid syndrome (APS) was diagnosed. The results of coagulation studies are shown in table 1. Markedly decreased antithrombin III (AT-III) levels were found, although the patient was not a carrier of the variant allele of factor V (Leiden R506O) or the mutation of prothrombin (G20210A), as revealed by molecular genetic analyses.

Long-term prophylaxis of AAE could not be introduced, since antifibrinolytics and attenuated androgens were both contraindicated owing to the recurrence of thrombosis and the presence of hepatopathy. Furthermore, as angiotensin-converting enzyme (ACE) inhibitors can increase the frequency of attacks in AAE [5, 9], antihypertensive medication of ramipril was immediately changed to 2 mg/day doxazosin. The patient rejected anticoagulation with low-molecular-weight heparin. During the 15-month-long follow-up period, arterial thrombosis developed in the right popliteal artery followed by angioedema of the lips, and the patient experienced severe angioedema of the lips and tongue on further 2 occasions. During acute angioedematous attacks, administration of C1-INH concentrate was effective in both instances and the patient did not experience any side effects.

Discussion

The presence of autoantibodies against C1-INH [10] distinguishes type I AAE – associated with lymphoproliferative disorders – from type II AAE [3], characterized by anti-C1-INH antibodies and the lack of underlying diseases. However, associations of AAE and a variety of diseases – including systemic autoimmune syndromes [11, 12] – have been reported [13]. As a trigger of AAE in the present patient, we revealed primary APS accompanied by AT-III deficiency, along with malignancy in the history, and ACE inhibitor therapy. Although anti-C1-INH titers

(type I AAE) were normal initially, we observed a sharp increase in anti-C1-INH titers (suggestive of type II AAE) during follow-up. Such an overlap between AAE types is not uncommon [11, 13, 14], and this prompts us to support the assumption of D'Incan et al. [14] and Cicardi et al. [13] that the distinction between the 2 AAE types might be artificial, inappropriate and clinically not relevant.

To our knowledge, this is the first report on the coincidence of AAE and primary APS. Previously, Nagy et al. [12] reported the association of secondary APS with asymptomatic acquired C1-INH deficiency. The case presented here, considered together with previous reports from the literature [6, 15, 16], supports the assumption that thrombosis might worsen angioedematous attacks in functional C1-INH deficiency, probably by the loss of control on factor XI and XII activation (fig. 1). Effective control of hypercoagulation and elimination of other risk factors were shown to abolish angioedema symptoms in our previously reported case [6].

In conclusion, thrombophilia might be considered as a provoking factor of AAE and should be carefully sought for in these patients, as the key to successful management of AAE is the effective treatment of the underlying disease. It seems that multiple provoking factors are not rare in AAE, and thus, the presence of anti-C1-INH antibodies does not rule out another underlying disease. On the other hand, complement testing should be performed in coincident cases of thrombosis and angioedema resistant of conventional therapy.

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