LETTER TO THE EDITOR

ACQUIRED ANGIOEDEMA WITH C1 INHIBITOR DEFICIENCY ASSOCIATED WITH ANTICARDIOLIPIN ANTIBODIES

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Acquired angioedema (AAE) with C1 inhibitor deficiency is often associated to B cell lymphoproliferative disorders or autoimmune diseases. We report a case of AAE associated with IgM anti-cardiolipin antibodies, with frequent edematous attacks, that disappeared completely after a slight immunosuppression and danazol therapy.

Angioedema not associated to urticaria is a recurrent, non-pruritic and self-limiting swelling of the skin and mucosae due to a transient increase of endothelial capillary permeability of subcutaneous or submucosal tissue. Angioedema attacks may also occur as cutaneous abdominal, genital and upper airway involvement. While cutaneous and abdominal localizations are very disabling, the laryngeal involvement can be fatal if not promptly treated. Non-allergic angioedema occurs as hereditary (HAE), acquired (AAE), Angiotensin converting enzyme (ACE) inhibitor-induced (RAE), pseudoallergic angioedema (PAE) and idiopathic angioedema (IAE) (1). HAE and AAE are due to a genetic or acquired deficit of C1 inhibitor, respectively (2), although forms of AAE with levels of C1 inhibitor quantitatively normal have been described.

The common final pathogenetic event is an increased production of bradykinin, which, in turn, binds to specific and constitutively expressed B2 receptors and triggers increase of endothelial permeability. As a consequence, plasma flows out of the intravascular to the extravascular compartment forming the interstitial oedema.

AAE is a rare disease (about 160 cases described in the literature) (3) characterized by an increased catabolism of C1 inhibitor, classically associated to: a) B cell lymphoproliferative disorders or monoclonal gammopathies of undetermined significance (type I); b) autoimmune diseases associated or not to the presence of autoantibodies against C1 inhibitor (Type II) (4-6). However, we find in literature some cases of type I AAE in presence of antibodies against C1-INH; therefore this classification must be revisited (7).

Key words: acquired angioedema, anticardiolipin antibody, immunosuppressive therapy, C1-INH deficiency

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Table I. *Laboratory findings before and after treatment with azathioprine, danazol and ticlopidine.*

	Before treatment	After treatment on the 3rd month	After treatment on the 14th month	Normal range
ERS* 1st hr	51 mm 1st hr	28 mm 1st hr	15 mm 1st hr	< 10 mm
C reactive protein,	9.3 mg/dL	5.7 mg/dL	3.7 mg/dL	0 – 5.0
Blood fibrinogen	490 mg/dL	386 mg/dL	280 mg/dL	200 - 400
γ globulins	22%	18.4%	18.3%	11.0 – 19.0 %
α2 globulins	13.7%	8.3%	9.5%	8.2 – 13.0%
Quantitative C4	1.4 mg/dL	8 mg/dL	15 mg/dL	10 - 40
Quantitative C1q	6 mg/dL	12 mg/dL	12 mg/dL	10 - 25
Quantitative C1 inhibitor	3 mg/dL	12 mg/dL	27 mg/dL	21 - 39
Functional C1 inhibitor	1.7%	Not available	Not available	> 68%
IgM anticardiolipin	>120 MPL/mL	75 MPL/mL	14 MPL/mL	< 10

*erythrocyte sedimentation rate

Herein, we describe a case of AAE associated to anticardiolipin antibodies and its favourable outcome.

A 68-year-old female patient arrived at the Unit of Allergology and Clinical Immunology, University of Bari, complaining of recurrent angioedema attacks during the previous 5 years (2-3 episodes per month) localized on the eyelids, lips and tongue. Clinical manifestations arose generally after lunch and were preceded by a sense of tension and paresthesia in the sites of angioedema.

Due to the fear for her survival caused by the angioedema attacks, the patient had previously attended the emergency room of our Hospital on several occasions, where she was treated with i.v. anti-histamines and corticosteroids with a minimal or absent beneficial effect, since the episodes persisted for an average of 6-10 hours. The patient's clinical history showed no other diseases, or previous surgical or dental interventions, and she was not receiving ACE inhibitors or other drugs able to induce AAE. In addition, no other family members reported angioedema attacks. Physical examination was not relevant for any specific morbid condition.

To exclude an allergic angioedema, *in vivo* and *in vitro* allergic tests were carried out: skin prick tests for common inhalants and for foods gave negative response, and specific IgE for foods were negative with a value <0.35 KUA/l (UniCAP, Phadia S.r.l, Milan, Italy).

According to previously described diagnostic procedures, we proceeded to exclude other diseases (1). Routine blood tests revealed normal cell blood count, but altered markers of inflammation: erythrocyte sedimentation rate (ERS, 1st hr) 51 mm (ref. value < 10 mm), blood fibrinogen 490 mg/dL (ref. values 200-400 mg/dL), C reactive protein 9.3 mg/dL (ref. values 0-5.00 mg/dL), α2 globulins 13.7% (ref. values 8.2-13.0%), γ globulins 22% (ref. values 11.0-19.0%) with no monoclonal peak. Assay for complement factors gave a decrease of quantitative C4: 1.4 mg/dL (ref. values: 10-40 mg/dL), C1q: 6 mg/dL (10-25 mg/dL); antigenic C1 inhibitor levels: 3 mg/dL (ref. values: 21-39 mg/dL); functional C1 inhibitor levels: 1.7% (ref. values: >68%) with a normal value of C3. Immunofluorescence assays for antinuclear antibody (ANA), antibody to double-stranded DNA (anti-dsDNA), p-ANCA and c-ANCA produced negative results, and the ENA-screening was negative as well. Interestingly, the patient manifested a high positive result for IgM anticardiolipin (> 120 MPL/mL; normal values: <10 MPL/mL), while IgG anticardiolipin was negative. A test for anti-cardiolipin antibody

carried out four months before our evaluation had shown IgM anticardiolipin antibody at a titre > 80 MPL/mL. Chest x-ray, abdominal ultrasonography, color doppler ultrasonography of lower limbs, total body computerized tomography were negative. The patient refused bone marrow biopsy.

Based on these findings a diagnosis of acquired angioedema (AAE) with positive serology for antiphospholipid antibodies without signs and symptoms of Hughes syndrome (8) was made. On the therapeutic side, a low dosage immunosuppressive regimen with azathioprine at a dose of 50 mg qd, associated to ticlopidine 250 mg qd and danazol 100 mg qd was started. After three months of this treatment, the patient claimed that angioedema attacks had completely disappeared, and after 14 months (last clinical control) this condition persists. In addition, a follow-up immunologic investigation showed: a decrease of ERS (15 mm 1st hr), C reactive protein (3.7 mg/dL), blood fibrinogen, γ globulins and α2 globulins, an increase of C4, C1q and antigenic C1 inhibitor levels. Also, a strong reduction of IgM anticardiolipin antibodies was observed (Table I).

A PubMed search with Mesh terms 'anticardiolipin antibody and angioedema' generated only one report in which one of four cases of AAE presented an IgG anticardiolipin antibody in a context of a lymphoproliferative disorders with an associated monoclonal gammopathy (9). Therefore, this is the first report of an AAE associated to IgM antiphospholipid antibodies, a unique finding, in absence of an overt clinical antiphospholipid syndrome. In this case, we suppose that the pathogenetic mechanism of angioedematous lesions is linked to the presence of IgM anticardiolipin antibodies that may cause complement activation through the classical pathway, as plausibly demonstrated by the low C1q and C4 levels, and quantitative consumption of C1 inhibitor. Formation of idiotype-anti-idiotype immune complexes involving IgM anticardiolipin antibodies capable of complement fixation could be an alternative explanation. Although the assay for anti-C1 inhibitor autoantibody was not carried out, we can rule out its presence, given the strict dependence of C1 inhibitor levels on the presence of anticardiolipin antibody, and the reduced levels of C1q (2). Accordingly, the

immunosuppressive treatment with azathioprine was started in association with danazol and ticlopidine. The action of these drugs is synergic. Danazol is an attenuated androgen that stimulates the synthesis of C1 inhibitor and C4 (3, 10). In addition, in women, it induces deprivation of oestrogen, a well-known trigger of angioedema. Azathioprine at a low dosage was used to induce a reduction of autoantibody production due to its action in blocking the proliferation of various lymphocyte cell types (11). Ticlopidine was chosen to prevent thrombotic events since the patient referred a previous ASA intolerance consisting of asthma and wheezing.

After the control visit at Week 14, the therapy was reduced (azathioprine at a dose of 200 mg/week, danazol 400 mg/week and ticlopidine 250 mg qd). During the follow-up, the patient was monitored by liver function parameters and abdominal ultrasound which revealed no alteration excluding any adverse reactions to danazol.

The assigned treatment allowed the remission of angioedema, confirmed by absence of further angioedema attacks and by the changes in laboratory findings with a strong reduction of IgM anticardiolipin antibodies and of values of inflammatory parameters in association to normalization of C4, C1q and antigenic levels of C1 inhibitor. This observation suggests that acquired C1 inhibitor deficiency may occur in association with IgM antiphospholipid antibody and, most notably, it may favourably respond to a low-dose immunosuppressive treatment and danazol.

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