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Evidence of complement activation in the thrombotic small vessels of a patient with catastrophic antiphospholipid syndrome treated with eculizumab

Dear Editor,

Currently the therapeutic approach to life threatening catastrophic antiphospholipid syndrome (CAPS), a severe subset of antiphospholipid syndrome, is a combination of anticoagulants, steroids, plasma exchange and/or intravenous immunoglobulins (IVIG) aiming to suppress the thrombotic storm and cytokine cascade [1,2]. Mortality continues to be high (37%) despite these interventions [1]. Complement consumption and release of complement activation products have recently been described in the blood of a CAPS patient treated successfully with eculizumab [3], a humanized monoclonal antibody that binds to the C5 component and inhibits terminal complement activation. The present study provides, for the first time, evidence of complement activation in the heart thrombotic small vessels of a patient presenting a dramatic CAPS episode refractory to conventional therapy treated with eculizumab.

A 32-year-old female patient at the 7th week of pregnancy presenting a relapsing deep vein thrombosis was admitted in March 2016 to the University Hospital of Padua. An echocardiogram revealed a floating thrombus in the right atrium (size 22 × 10 mm). Screening analysis for antiphospholipid antibodies uncovered positivity for lupus anticoagulants and medium IgG anticardiolipin and IgG anti-β2Glycoprotein I (aβ2GPI) antibody levels. Given the high risk of maternal/fetal complications, a second-line treatment protocol consisting of weekly plasma exchange sessions and fortnightly IVIG infusions (1 g/kg) was prescribed in addition to conventional heparin/low-dose aspirin therapy [4,5], resulting in a clinical improvement, a reduction in the atrial thrombus and a normal progression of the pregnancy. A Quinton catheter was placed in the right femoral vein at the 28th week. At the 29th week (August 19) the patient had fever with chills, and abnormalities in the fetal cardiotocography were noted. Cesarean delivery of a healthy female infant weighing 1230 g was performed. On August 21, fever reappeared, reaching 40.7 °C; a high white cell count with neutrophilia, and a progressive increase in C-reactive protein and procalcitonin were noted. A chest CT scan revealed bilateral pulmonary infiltrates (ground glass opacities) and pleural effusions suggesting pulmonary alveolitis. Broad-spectrum antibiotic therapy was intensified; three days later the fever, neutrophilia, C-reactive protein and procalcitonin levels began to decline steadily and progressively. Increasing troponin I values reaching 915 ng/L, decreasing platelet count falling to 42 x 10^3ml, and increasing D-dimer levels reaching 10,930 μg/L along with ischemic lesions on the fingers were observed at that time. According to CAPS classification criteria a “probable CAPS” was diagnosed [6] and on August 24, daily plasma exchange sessions, each followed by administration of a 500 mg bolus of methylprednisolone, were prescribed in addition to heparin therapy for five days. Despite these aggressive measures, the patient's clinical condition worsened. The left ventricle ejection fraction dropped to 35% (Fig. 1A) and hypotension, renal failure with massive fluid retention, severe respiratory failure and lactic acidosis occurred. Emergency implantation of bedside arteriovenous Extra-Corporeal Membrane Oxygenation became necessary on August 28, due to the occurrence of cardiogenic shock. At the same time boluses of IVIG (400 mg/kg/day for five consecutive days) in combination with therapeutic heparin doses and 60 mg methylprednisolone per day were prescribed. Given severe biventricular dysfunction and worsening of the respiratory exchanges, an extra-body biventricular assist device was successfully implanted on August 30. Some fragments of the left ventricle apex that were harvested during device implantation were examined. Histology showed thrombosis of the subendocardial capillaries and arterioles (Fig. 2A). In the light of these findings, “definite CAPS” was diagnosed [6]. Immunofluorescence studies revealed C5b-9, C3d, C4d and IgG deposits in the capillaries and/or arterioles (Figs. 2B–E) affected with thrombosis, as demonstrated by fibrinogen deposition (Fig. 2F), all confirming complement involvement in the pathogenesis of the small vessels thrombosis. On September 1, the first infusion of 1200 mg of eculizumab was administered. At that time, the pulsatile curve of the heart was absent and the aortic valve was constantly closing. Nine weekly infusions were administered, three of 1200 mg and six of 900 mg. The last infusion (the 11th one), which was of 900 mg, was administered (December 1), 27 days after the precedent one. A remarkable recovery of cardiac function was noted already after the second infusion (Fig. 1A). The patient was discharged on October 7 without any noteworthy consequences. Currently the patient is well and taking warfarin with low-dose aspirin. Serial serum and plasma samples were collected before, during, and after the eculizumab infusions and stored at −80 °C for complement studies and antiphospholipid antibody detection according to the methods described elsewhere [7–9]. The results are illustrated in Figs. 1B–D.

To the best of our knowledge, deposition of C5b-9 terminal complement complex in the walls of the thrombotic capillaries and arterioles of affected organs has never been demonstrated in CAPS patients justifying the use of a C5 inhibitor. C5b-9 deposits in the subendocardial capillaries and arterioles together with high plasma C5b-9 complex levels were detected in our patient before therapy was begun. In addition to blocking 50% of serum complement hemolytic activity, eculizumab treatment lowered the C5b-9 levels and was associated with a rapid, stable clinical improvement. Overall, these findings suggest that complement activation, which took place in the small vessels of the heart, induced severe damage that was restored by the C5 blockade linked to eculizumab. The fall in the serum IgG aβ2GPI antibody levels and the presence of IgG and C5b-9 complex deposits at the anatomical site of the thrombosis during the acute CAPS phase seem to indicate that aβ2GPI antibodies play a key role in thrombus formation. In fact, some studies have shown that activation of the complement system by antibody-β2GPI complexes plays a critical role in thrombus formation

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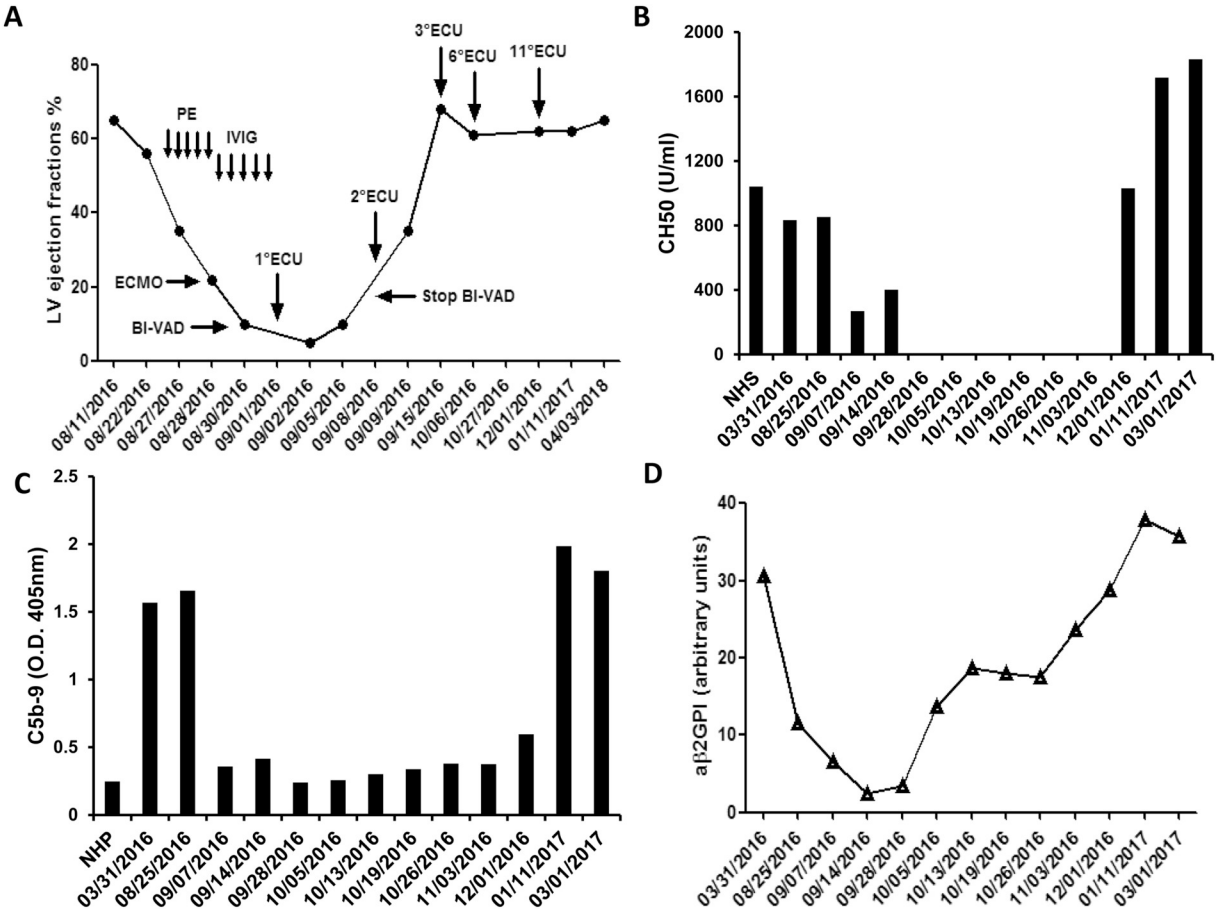

Fig. 1. (A) Left ventricle ejection fraction values, (B) CH 50% hemolytic activity, (C) levels of soluble C5b-9 complex and (D) serum anti-β2Glycoprotein I (aβ2GPI) antibody levels before, during and after eculizumab infusions. The graph also shows the dates of plasma exchange (PE), intravenous immunoglobulins (IVIG) and eculizumab (ECU) administration and those of bedside arteriovenous Extra-Corporeal Membrane Oxygenation (ECMO) and extra-body biventricular assist device (BI-VAD) implantations.

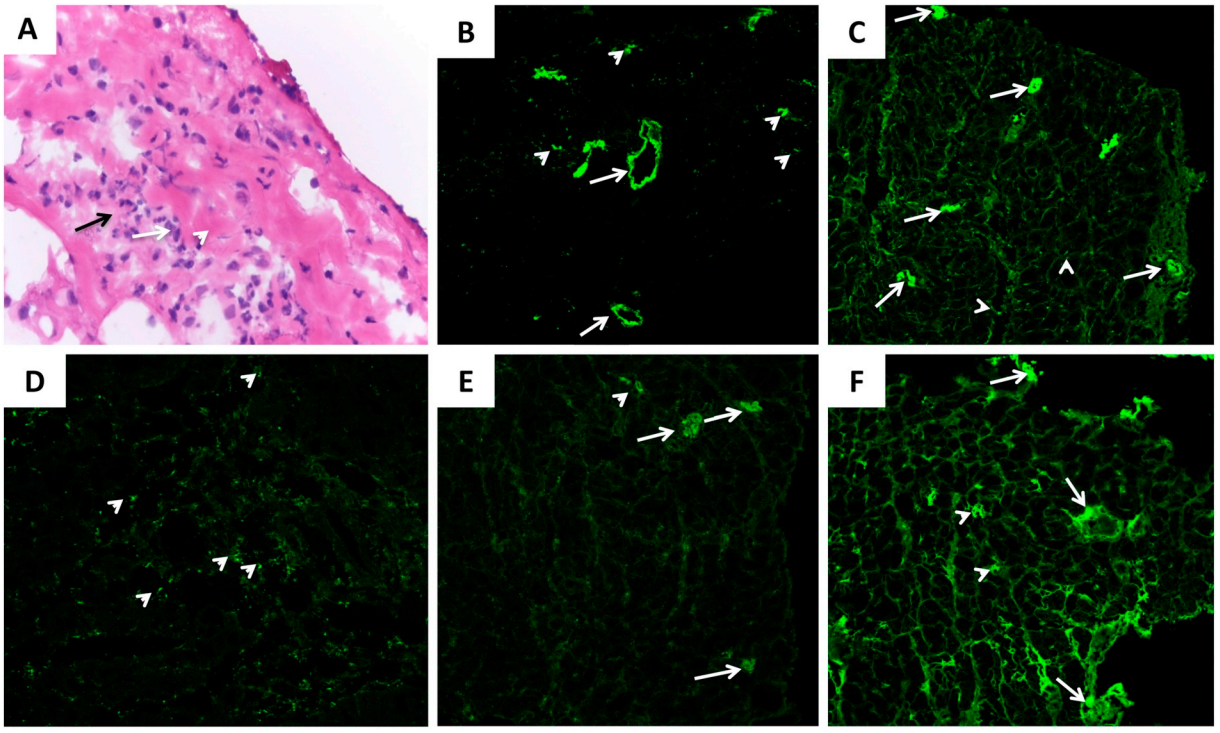

Fig. 2. Histological and immunofluorescence studies on endomyocardial fragments. (A) Hematoxylin and eosin staining shows microthrombosis of a small vessel (black arrow) with inflammatory infiltrate (white arrow) and myocardial damage (head of the white arrow) (×400). Direct immunofluorescence method reveals deposits of (B) C5b-9 complex, (C) C3d, (D) C4d, (E) IgG and (F) fibrinogen in the arterioles (white arrows) and/or in the capillaries (head of the white arrows) (×200 for all).

[10,11] as C5 inhibitors prevented blood clots in animals receiving intravascular anti-β2GPI antibody infusions [12]. The stable recovery of IgG aβ2GPI antibody levels to pre-CAPS values occurring during the clinical improvement associated with eculizumab treatment appears to confirm this hypothesis.

The data outlined here shed light on the dynamics of complement activation associating it to the clinical course of CAPS and provide a rationale for therapeutic complement inhibition in these patients.

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