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REVIEW ARTICLE

Eculizumab in refractory catastrophic antiphospholipid syndrome: a case report and systematic review of the literature

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Abstract
Catastrophic antiphospholipid syndrome (CAPS) is a rare disorder, characterized by the development of multiple vascular thrombosis over a short period of time, in patients with persistently detectable antiphospholipid antibodies (aPLs). The vascular occlusions predominantly affect small vessels. The overall mortality is 36.9%, despite the recent progress in the therapeutic approach. It has been shown that aPLs are able to induce a hypercoagulability state through different mechanisms of action, including complement activation, which in turn plays a key role in the pathogenesis of some thrombotic microangiopathies. Consequently, complement inhibition may be proposed as a targeted intervention to effectively prevent the progression of the microthrombotic storm. The employment of the complement inhibitor eculizumab has been proposed in CAPS on the basis of occasional reports and expert opinion. We report the case of a 54-year-old woman with a CAPS refractory to conventional therapies, who was successfully treated with eculizumab. The administration of this anti-C5 monoclonal antibody aborted the acute progressive thrombotic events and prevented further clinical episodes of thrombosis in the following year. We also faced our case to a systematic literature review, by analyzing all reported cases of CAPS in which eculizumab was added to conventional therapy. Even if further investigation is needed, our results suggest that the inhibition of one mechanism of aPL-induced organ damage may be an add-on treatment for this condition.

Keywords Eculizumab · Catastrophic antiphospholipid syndrome · Complement · Thrombotic microangiopathy

Introduction

Catastrophic antiphospholipid syndrome (CAPS) is a rare and life-threatening disorder, defined as an intravascular thrombosis affecting three or more organs, systems and/or tissues either simultaneously or within 1 week, in patients with persistently detectable antiphospholipid antibodies (aPLs) [1, 2]. The development of vascular occlusion predominantly affects small vessels [1]. The term "catastrophic," initially introduced by Asherson et al. in 1992, was referred to the high mortality rate (50%) of CAPS patients [3, 4]. The pathogenesis is still a matter of debate, and the European Forum on Antiphospholipid Antibodies set up the "International CAPS Registry" in 2000 to improve the knowledge of this syndrome [5]. It is now clear that CAPS is not only associated with primary antiphospholipid syndrome (APS), which accounts for about 60% of cases, but also with other autoimmune conditions, such as systemic lupus erythematosus (SLE) (30%), lupus-like disease (4%), and others (< 6%) [6]. Approximately, less than 1% of APS patients develop CAPS [7].

Some laboratory features are very characteristics: Severe thrombocytopenia and schistocytes are frequently found (in 67% and 22% of CAPS patients, respectively), whereas features consistent with microangiopathic hemolytic anemia (MAHA) and disseminated intravascular coagulation (DIC) have been seen in 16% and 11% of cases [6].

Clinical manifestations may vary according to the extent of the thrombosis and the involved organs, predominately

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affecting kidneys (73%), lungs (60%), brain (56%), heart (50%), and skin (47%) [6].

Definite CAPS diagnosis requires the histopathologic confirmation of thrombosis in at least one organ or tissue (see Table 1 for diagnostic criteria), although in many cases, patients' clinical severity, the coexisting thrombocytopenia, and/or coagulation factors consumption do not allow to perform biopsy [8, 9]. When only two organs are affected, or small vessel occlusion cannot be pathologically confirmed, and the third event develops in more than a week but less than a month despite anticoagulation, the diagnosis is considered to be probable (see Table 1 for diagnostic criteria) [9].

The best treatment strategy, the so-called triple therapy, is based on the combination of anticoagulation, steroids, plasma exchange (PE), and/or intravenous immunoglobulins (IVIG) beside the treatment of "precipitating" factors, when present [6, 10, 11]. Intravenous cyclophosphamide is recommended in CAPS associated to SLE [12]. To date, the overall mortality averages 36.9% of cases, although patients receiving the triple therapy have shown a better prognosis, with a mortality rate of 28.6% [10].

Patients who did not respond to therapy and died in the acute phase or those with recurrent episodes of catastrophic APS are identified as patients with refractory CAPS [13]. Among the several prognostic factors related to the refractory forms, the evidence of MAHA, normally found in the 16% of patients at first CAPS episode [6], has been strongly associated with recurrent episodes of CAPS, being found in 72% of patients [14, 15].

MAHA is also the hallmark of several thrombotic microangiopathies (TMAs) (see Table 2), and most cases of CAPS present as microangiopathic storms rather than large vessels occlusion [9]. Recent clinical evidences and studies in mouse models showed that aPLs are involved in the development of complement-mediated TMAs [16, 17], and refractory cases of CAPS have been both associated with the evidence of MAHA and uncontrolled complement activation [16, 18, 19].

As a consequence, beside the treatment of aPL-induced direct organ damage, a more targeted intervention, such as complement inhibition, may effectively prevent the

Table 2 Hereditary and acquired thrombotic microangiopathies (adapted from Erkan D. [17])

Hereditary
Thrombotic thrombocytopenic purpura (TTP) (ADAMTS13 deficiency)
Complement-mediated TMA
Acquired (primary)
Thrombotic thrombocytopenic purpura (TTP) (ADAMTS13 deficiency)
Complement-mediated TMA
Shiga toxin-mediated TMA (hemolytic uremic syndrome)
Acquired (secondary)
Infection
Cancer
Preeclampsia
Syndrome autoimmune disorders (e.g., lupus, systemic sclerosis, and antiphospholipid syndrome)
Hematopoietic stem cell or organ transplantation
HELLP
Drug-related

Table 1 Diagnostic criteria for CAPS (adapted from Cervera R [6])

(1) Evidence of involvement of three or more organs, systems, and/or tissues[a]
(2) Development of manifestations simultaneously or in less than 1 week
(3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
(4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]
Definite CAPS
All four criteria
Probable CAPS
All four criteria, except for only two organs, systems, and/or tissues involved
All four criteria, except for the absence of laboratory confirmation owing to the early death of a patient never tested for antiphospholipid antibodies before the CAPS
Criteria (1), (2), and (4)
Criteria (1), (3), and (4) and the development of a third event between 1 week and 1 month after presentation, despite anticoagulation

[a]Usually clinical evidence of vessel occlusions confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (> 180/100 mm Hg), and/or proteinuria (> 500 mg/24 h)

[b]For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally

[c]If the patient had not previously been diagnosed as having an APS, the laboratory confirmation requires that the presence of antiphospholipid antibodies must be detected on two or more occasions at least 12 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS

propagation of the microthrombotic storm in refractory CAPS [16, 18–20].

The employment of eculizumab, a humanized monoclonal antibody against complement (C) 5, in CAPS is based on occasional case reports and expert opinion, as this drug is FDA approved only for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (HUS).

Herein, we report a case of refractory CAPS, in which the evidence of MAHA was associated with complement consumption, and long-term remission was achieved following therapy with eculizumab. We also analyzed all currently reported cases of CAPS associated with MAHA, in the absence of other TMA-triggering conditions, in which standards of care have failed, and eculizumab was added. Our results suggest that a treatment strategy inhibiting one pathway of aPL-induced organ damage may be an effective approach to treat this condition.

Case report

A 54-year-old woman presented to the emergency department for the recent onset of aching pain and lack of arterial pulse at the right foot. On examination, she appeared pale and was found to be hypertensive, with a blood pressure of 200/115 mmHg. Her past medical history included a primary APS diagnosed 1 year before, after an episode of intestinal infarction in the presence of repeatedly positive anti-β_2-glycoprotein I antibodies, and lupus coagulant. At that time, she was discharged with hydroxychloroquine, prednisolone, and anticoagulation therapy with warfarin. On admission in our department, laboratory tests evidenced anemia (9.2 g/dL), thrombocytopenia (65.000/μL), increased LDH (311 U/L), and serum creatinine levels (2.5 mg/dL vs. previously documented concentration of 0.6–0.7 mg/dL). The international normalized ratio (INR) was 1.9. Doppler ultrasound evaluation showed thrombosis of the anterior right tibial artery and intravenous heparin therapy was started. An in-deep laboratory evaluation showed positive IgG and IgM anticardiolipin antibodies (209.4 and 34 U/mL, respectively, r.v. < 20), IgG and IgM anti-β2-glycoprotein I (211.6 and 28.5 U/mL, respectively, r.v. < 20), as well as positive lupus anticoagulant (dRVVT = 2.6, r.v. < 1.2, aPTT 4.4 r.v. < 1.2).

Four days after, dyspnea, tachycardia, and jugular venous distension suddenly ensued. Echocardiography findings were consistent with acute overload of the right heart chambers, due to the severe pulmonary involvement subsequently documented by chest contrast-enhanced computed tomography (CT) that evidenced pulmonary bilateral ground-glass opacities, interstitial infiltrates, and bilateral pleural effusion (Fig. 1). A further laboratory evaluation

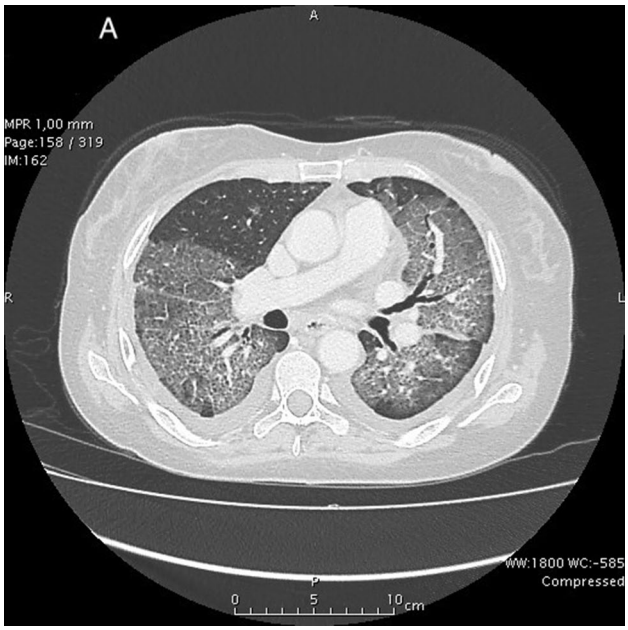

Fig. 1 Chest contrast-enhanced computed tomography (CT) evidencing pulmonary bilateral ground-glass opacities, interstitial infiltrates, and bilateral pleural effusion

showed reduced haptoglobin (< 30 mg/dL; r.v. 30–300 mg/dL), increased LDH level (588 U/L), a negative direct antiglobulin (Coombs) test, reduced C3 and C4 levels, as well as schistocytes (3–4/hpf) in the peripheral smear. Then, patient's respiratory function abruptly worsened, up to deserving invasive ventilation. According to the presence of multiorgan involvement (i.e., tibial artery thrombosis, kidneys with acute renal failure, and pulmonary damage), without identifiable infectious foci, a diagnosis of probable CAPS was made. Tissue biopsy was not performed because of thrombocytopenia and the need of continuous anticoagulation. So, an immunosuppressive therapy with high-dose methylprednisolone (1 g/day for 3 days), immunoglobulin (400 mg/kg/day for 5 days), and plasma exchange (four sessions) was administered. Despite these therapies and documented therapeutic anticoagulant activity, her condition became life-threatening. Therefore, a treatment with eculizumab, a humanized monoclonal antibody blocking the complement C5 cleavage, was started. Three days after a loading dose of 600 mg, both clinical conditions and CT features (Fig. 2) impressively improved and the patient did not require further respiratory support. Administration of eculizumab allowed also achieving a concomitant progressive improvement, with a plateau reached into the next 2 weeks, of thrombocytopenia (150.000/μL), anemia (10.1 g/dL), and serum creatinine (1.60 mg/dL), beside the normalization of C3 and C4 serum levels. Eculizumab was continued with a weekly administration for 1 month (600 mg/week), with concomitant steroids, warfarin, and hydroxychloroquine, and

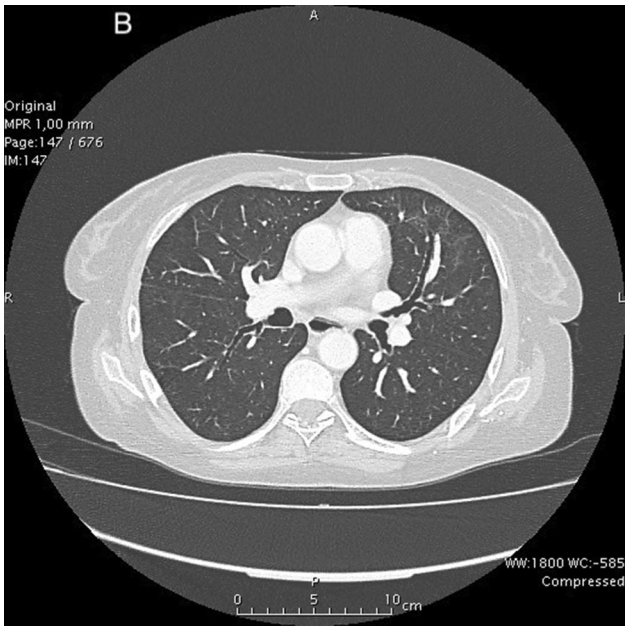

Fig. 2 Chest contrast-enhanced computed tomography (CT) showing marked improvement in the pulmonary lesions, following eculizumab therapy

was associated with no further clinical episodes of thrombosis during 1 year of therapy.

Methods

A systematic review of the literature concerning patients who received eculizumab in addition to standard therapies in CAPS was carried out up to December 2018 by searching on PubMed MEDLINE and EMBASE the following terms: "catastrophic antiphospholipid syndrome," "CAPS," "eculizumab," "thrombotic microangiopathy," and "TMA." In addition, references were also revised to identify any further cases. Out of 639 initially screened articles, 403 were relevant to the research items. Finally, ten reported cases of CAPS treated with eculizumab were reviewed [16, 18, 19, 21–26] (see Fig. 3, for study selection process). Only cases of active CAPS and reported evidence of MAHA were included. Therefore, five cases were eliminated: Three because eculizumab treatment was aimed to prevent CAPS flare before renal transplant [21, 22]; one because the patient had no laboratory evidence of MAHA [24], and one because the authors did not report patients' laboratoristic profile [25]. According to the proposal to revise the diagnostic criteria of CAPS by substituting the "histopathology criteria" with the "exclusion of other diagnoses" [6], we included in the current survey patients with both "definitive" and "probable" CAPS. Patients were also assessed for other causes of thrombotic microangiopathy (TMA), such as TTP (thrombotic thrombocytopenic purpura), hemolytic uremic syndrome (HUS), atypical HUS (aHUS), hypertension-related, and drug-related microangiopathic syndromes.

Results

We analyzed the history, clinical, and laboratory features of six patients (including our case), with a CAPS refractory to conventional treatments, in which eculizumab was successfully added. Demographic data including sex, age, and patients' primary autoimmune disease are summarized in Table 3. Patients' clinical features, previous treatments, eculizumab doses and duration, and the relative clinical outcomes are reported in Table 4. The analyzed case reports included five women and one man with a median age of 44 years (range 28–78). Two patients had a prior diagnosis of APS [18, our case], whereas CAPS was the first manifestation of APS in two patients [23, 26], one patient had primary SLE [16], and in one, a history of APS was associated with SLE [19].

One patient had a history of recurrent CAPS [16], and another experienced a severe relapse during the hospitalization due to the premature discontinuation of eculizumab [18]. This small but well-characterized sample mirrors the reported prevalence in the whole population of CAPS patients in terms of age, gender, and primary disorders [6].

According to data from the CAPS Registry, in which the presence of a "trigger" event has been associated with the development of the catastrophic scenario in 50% of patients [6], one patient had a history of recent surgery [19], one had an underlying infection [18], and in our case, the INR value was outside the therapeutic range. In the other patients, no factors precipitating CAPS were found, and it can be hypothesized that a flare-up of the underlying autoimmune disease triggered this condition. Indeed, infections, malignancies, surgery, flare-up of the autoimmune condition, and suboptimal INR values have been strongly associated with the development of the catastrophic scenario [6, 9].

In all the examined cases, eculizumab was added on standard therapy because of the refractoriness of the disorders. All patients had laboratory evidence of MAHA, and in our case and in the revised ones, the presence of TTP, HUS, aHUS, hypertension-related, and drug-related microangiopathic syndromes, other common triggering factors of MAHA, was excluded (see Table 1 for differential diagnosis). No one had clinical and laboratory characteristics, childhood onset, or familial history of TMA, and when authors suspected a TTP, the normal activity of ADAMTS13 ruled out this hypothesis [23, 26].

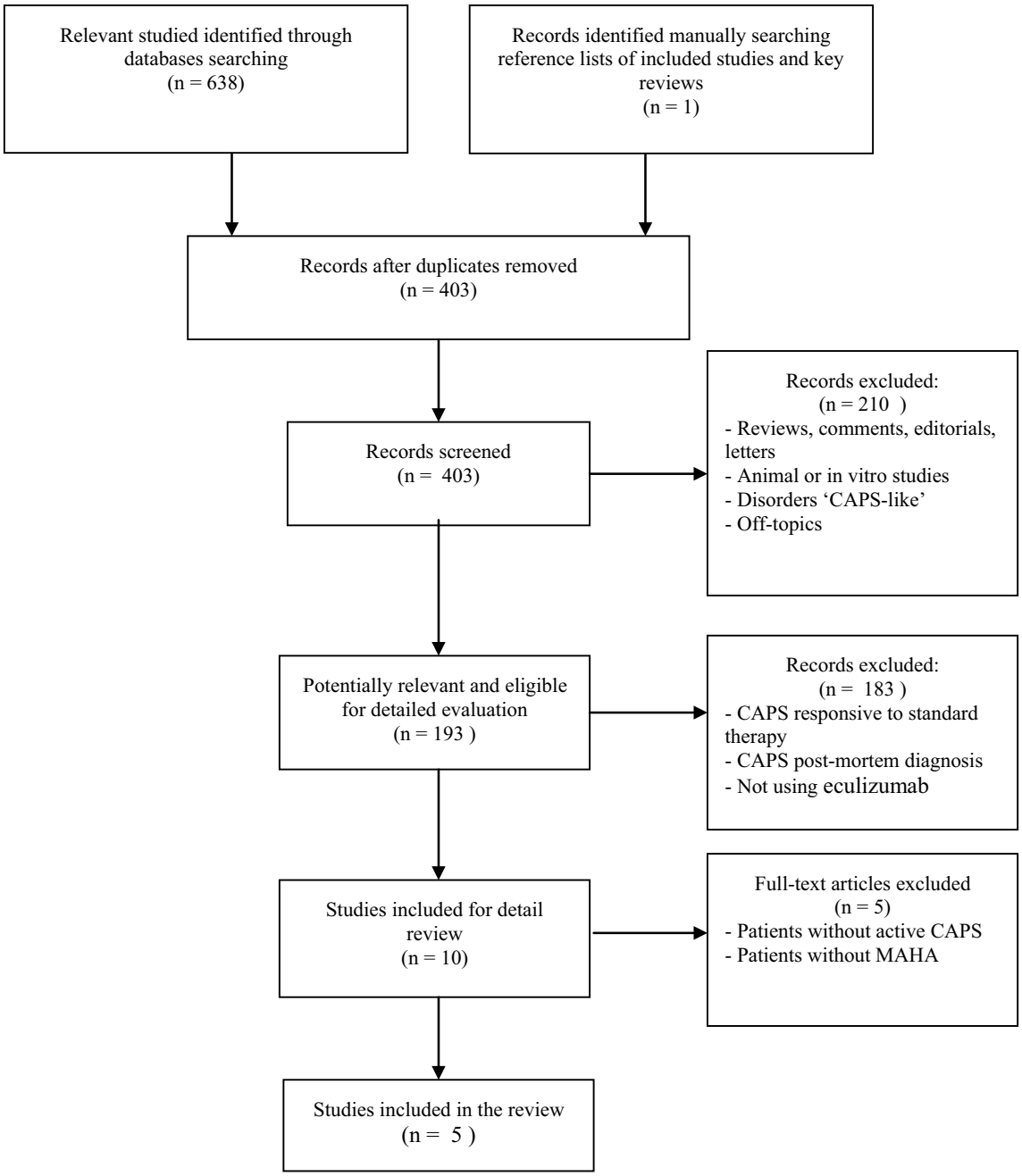

Fig. 3 Study selection process

Discussion

Antiphospholipid antibodies (aPLs) are able to induce a hypercoagulability through different mechanisms of actions, and one is represented by complement activation through the classical, lectin, and alternative pathways [17, 27, 28]. Products of complement activation, complement (C) 3, C5a, and membrane attack complex (MAC) are potent mediators of platelet and endothelial cell activation and amplify aPL-induced thrombosis [17]. Mice deficient in complement components C3, C5, C6, or C5a receptors is resistant to aPL-induced enhanced thrombophilia and endothelial cell activation [17, 28]. Moreover, complement deposition was found in human placenta of patients with APS [29].

Uncontrolled complement activation is per se, responsible of the development of some TMAs (see Table 2), whose hallmark is MAHA. In our analyzed refractory cases, other causes that may trigger TMAs, such as TTP, aHUS, hypertension-related, and drug-related microangiopathic syndromes were excluded.

Table 3 General characteristics of the seven patients

Median age (years)	44 (range 28–78)
Sex	
Female	5
Male	1
Primary autoimmune disease	
APS	3
Unrecognized APS	1
SLE 1	1
APS + SLE	1

In four patients [16, 18, 19], including our case, complement activity was analyzed in detail, and the presence of high titers of aPLs was associated with reduced level of complement factors, as per consumption. Shapira et al. [16] demonstrated the inverse relationship between platelet count and complement activity after eculizumab administration. Barrat-Due et al. [18] found a marked increase in the classical and lectin pathway activation based on the high C4bc/C4-ratio, as well as an excessively activated sC5b-9 terminal pathway associated with a severe thrombocytopenia, and an inverted trend after the administration of eculizumab. Kronbichler et al. [19] found also low C1q level along with persistently reduced C3 and C4 serum levels behind the features of MAHA, completely resolved after the administration of eculizumab. In our case, complement activation was confirmed by the finding that serum levels of C3 and C4 were significantly lowered, while disease was active, returning in the normal range after the administration of eculizumab. Strakhan et al. [23] and Guillot et al. [26], although not analyzing complement activity, ruled out all other causes of TMA, except massive complement activation triggered by aPLs; they found that the administration of eculizumab was

Table 4 CAPS clinical features, patient's previous treatments, eculizumab doses and duration, and efficacy

References	CAPS features	Eculizumab doses and duration	Associated treatment	Efficacy
Shapira et al. [16]	Hematoma of the right abdominal wall Infarction of the left liver lobe with thromboses of the hepatic artery and a branch of the portal vein Left hemiparesis and right fronto-parietal peripheral infarcts MAHA	Pulse methylprednisolone PE	First induction dose: 600 mg/week for 6 weeks; second induction dose: 900 mg/week for 3 weeks; maintenance dose: 1200 mg every 2 weeks for 1 year, and then 600 mg/month for the subsequent 2 years	CAPS remission
Strakhan et al. [23]	AKI NSTEMI Intraretinal hemorrhage Multiple cerebral ischemia MAHA	PE Pulse prednisolone	Induction dose: 900 mg/week for 4 weeks; maintenance dose: 1200 mg every 2 weeks	CAPS remission
Kronbichler et al. [19]	AKI Myocardial ischemia with heart failure Diffuse alveolar hemorrhage and respiratory distress MAHA	Pulse methylprednisolone Rituximab PE Immunoadsorption therapy	Induction dose: 900 mg/week for 4 weeks; maintenance dose: 1200 mg every 2 weeks	CAPS stabilization
Barrat-due et al. [19]	Acute respiratory distress Circulatory collapse and cardiac arrest AKI MAHA	N/A	N/A	CAPS remission
Guillot et al. [26]	AKI Parietal and occipital ischemic lesions MAHA	Pulse methylprednisolone Heparin PE	Induction and maintenance dose: 900 mg every 2 weeks, for 2 months	CAPS
Our case	Acute respiratory distress Lower limb arterial thrombosis AKI MAHA	Heparin Pulse methylprednisolone PE IVIG	Induction and maintenance dose: 600 mg/week for 5 weeks	CAPS remission

MAHA, microangiopathic hemolytic anemia; AKI, acute kidney injury; NSTEMI, non-ST elevation myocardial infarction; PE, plasma exchange; and IVIG, intravenous immunoglobulin

followed by the resolution of patient's clinical symptoms when laboratory evidence of MAHA was present.

Given the above reports, complement inhibition may have a role as an adjuvant on main therapy for patients with refractory CAPS; however, both publication bias and the lack of systematic clinical studies are as many concerns. Thus, more mechanistic and clinical studies are needed before eculizumab can be recommended.

Our observations support the hypothesis that the involvement of the microvascular beds may be due to the double damaging effects on the endothelium exerted by the antiphospholipid antibodies (aPLs) and the activated complement.

Historically, the management of CAPS has focused on treating the underlying autoimmune disorder and the developed thrombotic phenotype [1, 6, 30]. The currently, widely accepted management for the catastrophic scenario has been established on the analysis of CAPS patients and is based on the combination of anticoagulation, immunosuppression, PE, and IVIG. Analyzed individually, only anticoagulation has shown a significant effect in improving survival [6] maybe because at least one mechanism of action by which heparin may contribute to the treatment of CAPS is complement inhibition [2]. PE did not show to add a value when patients presented MAHA features [10], also after adjusting for possible confounders [10]. However, complement activation may only amplify aPL-induced organ damage, and overall, the combination of anticoagulation, immunosuppression, PE, and IVIG achieved the highest survival rate (70%) [6]. Our analyzed patients, before starting treatment with eculizumab, received a combination of: anticoagulation (two patients), glucocorticoids (five patients), PE (five patients), and IVIG (one patient) (Table 4). The treatment approach was selected according to each specific clinical scenario. FDA approved eculizumab use for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and aHUS, respectively, since 2007 and 2011. Prospective clinical trials on CAPS are significantly challenged by the rare and abrupt nature of this condition. The add-on use of eculizumab in CAPS is currently supported by case reports (Table 4). The only registered ongoing phase II trial investigates the use of eculizumab in patients who develop end-stage renal disease (ESRD) after an episode of CAPS (clinicaltrials.gov #: NCT01029587). Noteworthy, all the patients of our case series with refractory CAPS and MAHA responded favorably to eculizumab treatment. Although there is not a univocal interpretation of refractory disease, it should be stressed that the treatment with the monoclonal antibody was started in all cases after the failure of the conventional therapy. As a fact, in these patients, we observed assorted choices of conventional therapies used before initiation of eculizumab, as well as an extreme variability in the time-elapsing from the diagnosis of CAPS to the first dose of eculizumab, which in turn was largely physician-dependent. However, all patients survived and showed improvement in platelet counts and hematologic values, as well as functional improvement in damaged organs after the administration of eculizumab. Obviously, the information obtained from the current review is limited, because it only relies on case reports. The latter do not allow to draw firm conclusions about the timing of clinical and laboratory responses to eculizumab, which were not always reported. In our case, we noted an improvement in clinical and laboratory parameters in the first 2 week after the initiation of eculizumab. We recorded also a variety of data concerning the duration of therapy with eculizumab, ranging from 2 months to ongoing treatment. The discontinuation of the drug was considered in each individual case based on findings of MAHA remission and significant improvement in clinical parameters.

In aHUS, the use of eculizumab was initially thought to be lifelong, due to the genetic basis of the disease in up to 50% of cases [20, 31]. However, successful withdrawal of eculizumab in selected cases of aHUS after 3–6 months of treatment has also been reported [32, 33]. Despite the admitted limitations of our analysis, the findings from our case series strongly support the hypothesis that the efficacy of eculizumab in refractory CAPS may depend on the uncontrolled complement activation taking place when CAPS associates with MAHA.

Conclusion

Although the clinical experience with eculizumab in CAPS is limited, favorable results with this anti-C5 monoclonal antibody have been observed in some case reports, namely in those with massive aPL-induced complement activation. The clinical efficacy of eculizumab in refractory CAPS demonstrates both the role of complement in CAPS and the therapeutic benefit of complement inactivation. However, current conclusions are exclusively based on case reports, and further investigations are needed to better elucidate the role and optimal timing of eculizumab treatment in CAPS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from our patient.

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