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The diagnosis and clinical management of the catastrophic antiphospholipid syndrome: A comprehensive review

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ABSTRACT

The catastrophic antiphospholipid syndrome (CAPS) is a life-threating variant of the antiphospholipid syndrome characterized by the development of multiple thrombosis in a short period of time, usually ending up in the failure of function of several vital organs. Most CAPS episodes are related to a prothrombotic situation or precipitating factor such as infections, surgical procedures or malignant diseases. In patients with CAPS, the development of multiple thrombosis leads to an important cytokine release that worsens the already critical patient's situation. The disease usually involves the kidneys, the lungs and the heart, although any organ system can be affected. Although occasionally the disease affects large vessels, in the majority of cases it affects small vessels, leading to a disseminated microangiopathic syndrome resembling thrombotic thrombocytopenic purpura. Treatment is based on the administration of anticoagulants, corticosteroids, plasma exchange and/or intravenous immunoglobulins. Cyclophosphamide is recommended in those CAPS cases associated to systemic lupus erythematosus. Additionally, rituximab and eculizumab have been used in refractory cases. Mortality is still around 30% despite current treatment.

1. Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by an increased risk of thrombosis and pregnancy loss associated with antiphospholipid antibodies (aPL) [1]. Persistently positive lupus anticoagulant (LAC), moderate to high titers of anticardiolipin (aCL) or anti-β2-glycoprotein I (aβ2GPI) antibodies, in isolation or in any combination, are the aPL included in the updated revised classification criteria for APS [2].

This syndrome is currently considered the most frequent cause of acquired thrombophilia. In a recent systematic review, the frequency of aPL in young patients with cerebrovascular events was estimated at 17%, increasing to 22% for aCL in patients with stroke [3]. Regarding pregnancy morbidity, myocardial infarction, and deep venous thrombosis, the overall frequency of aPL was estimated as 6%, 11%, and 9.5%, respectively [4]. These figures are of paramount importance considering that APS is not only a frequent disorder but also an effectively treatable disease. In general, current consensus is to treat APS patients with thrombotic manifestations with long-term oral anticoagulation therapy and those with obstetric features with aspirin or the combination of aspirin and heparin [5].

Approximately 1% of APS patients develop a severe clinical picture characterized by multiple thromboses involving mainly small vessels [6]. In the first descriptions of this devastating type of APS, mortality raised to 50% of patients [7]. Due to this poor prognosis, the term “catastrophic” was introduced to describe this life-threatening form of APS [8]. Patients with catastrophic APS (CAPS) have in common: a) clinical evidence of multiple organ involvement (commonly, three or more organs) developing over a very short period of time; b) histopathological evidence of multiple small vessel occlusions, and c) laboratory confirmation of the presence of aPL, usually in high titers [9].

Therefore, although uncommon, its potentially lethal outcome emphasizes its importance in clinical medicine today. Most patients with CAPS end up in intensive care units (ICU) with multi-organ failure. Unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed, resulting in a disastrous outcome for these patients [10].

Due to the rarity of this syndrome, an international registry of patients with CAPS was created in 2000 by the *European Forum on Antiphospholipid Antibodies,* a network of research groups devoted to the development of multicenter projects with large populations of APS patients [11]. This database is named “CAPS Registry” and currently documents the clinical, laboratory and therapeutic data of more than 500 patients with CAPS. The periodical analysis of these data has

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allowed not only the description of the clinical and laboratory characteristics of this syndrome [12–15] but also the elaboration of diagnostic algorithms [10], classification criteria and therapeutic guidelines [9].

2. Pathogenesis

Unfortunately, the pathogenesis of the APS is not well understood. It is still unclear why some patients will develop sporadic thrombosis, often confined to a single site and mainly affecting large vessels (i.e., classic APS), while others develop rapidly recurring vascular occlusions, predominantly affecting small vessels simultaneously or over a short period of time, and at multiple sites (i.e., CAPS). The explanation of the lack of studies on the pathophysiological mechanisms of the CAPS is the difficulty in collecting serum samples during an acute episode due to the low prevalence of the condition, the difficulty of differential diagnosis with other microangiopathic conditions, and the high rate of mortality.

One of the most characteristic findings in CAPS is the presence of precipitating factors. They have been identified in more than 50% of patients and include, by order or frequency, infections (present in 49% of the cases), surgical procedures (17%), malignancies (16%), anticoagulation withdrawal or low international normalized ratio (8%), pregnancy complications (8%), drugs (5%), and diseases activity of systemic lupus erythematosus (SLE) (3%) [16]. Regarding infections, the most common site was the respiratory (33%) and urinary tracts (19%), followed by the skin (13%) and the gastrointestinal tract (8%). Considering the microorganism, the most frequently isolated was *Escherichia coli* (13%), followed by *Streptoccocus pyogenes* (6%), *Staphyloccocus aureus* (4%), *Pseudomona aeruginosa* (4%) and Candida sp. (3%) [17]. However, many viruses, fungi, and protozoa have been described as precipitating factors of catastrophic episodes. Furthermore, infections are the main trigger of CAPS in the pediatric age [18].

Regarding malignancies, hematological diseases were the most frequent, including Hodgkin's and non-Hodgkin's lymphoma, acute lymphatic leukaemia, angiocentric lymphoma, and chronic myelocytic leukaemia. The more common solid neoplasms identified were lung carcinoma (17% of CAPS patients) and colon adenocarcinoma (9%) [19].

Women developing CAPS during pregnancy and puerperium were characterized by the presence of HELLP (hemolysis, elevated liver enzymes and low platelet) syndrome in 53% of them, placental infarctions in 27%, and pelvic thrombosis in 7% of cases [20].

All these precipitating factors, but mainly infections and neoplasms, share with APS the increased tendency to thrombosis and the development of systemic inflammatory response syndrome (SIRS). In fact, acute presentation of CAPS may resemble a severe sepsis and, in both entities, a proinflammatory microenvironment associated to high levels of cytokines (tumour necrosis factor-α, interferon-γ, and interleukin 1) may be the cause of this multisystem organ involvement.

The evidences of the existence of SIRS in CAPS are only indirect. Firstly, CAPS has been recently included in the "thrombotic storm" conditions together with *purpura fulminans* or HELLP syndrome. This new concept defines a group of entities characterized by an extreme prothrombotic phenotype including multiple thrombotic events occurring over a brief period of time [21]. In addition, some patients with thrombotic storm presented high levels of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, fibrinogen and/or factor VIII levels suggesting the evidence of an acute inflammatory state [22].

Secondly, high levels of ferritin, an iron storage protein considered also as acute phase reactant, have been found in 71% of CAPS patients [23]. Moreover, levels of ferritin were significantly higher in these patients with CAPS when compared with those with classic APS. In fact, the new concept of the hyperferritinemic syndrome has emerged, characterized by high levels of proinflammatory cytokines. Of note, it includes, in addition to CAPS, adult-onset Still disease, macrophage activation syndrome, and severe sepsis [24].

According to all these data, it seems plausible that patients with CAPS may promote a cytokine storm leading to an inflammatory state. However, the reason why, in the presence of aPL, some patients develop simultaneously several vascular occlusions, predominantly affecting small vessels in a short period of time is unknown. Possibly, activation or disruption of endothelial cells in the microvasculature in some special circumstances (infection or neoplasm), cell-specific membrane components of infectious agents such as lipopolysaccharide or endotoxin, or genetic factors for CAPS may play a role to explain the development of a catastrophic event in a patient with aPL [25].

3. Clinical features

The detailed analysis of the 500 patients included in the "CAPS Registry" [12] showed that 69% were female, with a mean age of 38 years. Sixty percent suffered from primary APS, 30% from SLE, 4% from lupus-like disease, and 6% from other autoimmune diseases. Patients may develop CAPS *de novo*, without any previous history of a thrombosis (46%) [26].

In general, the clinical manifestations of CAPS have been related with two factors: the extent of the thrombosis and the organs directly affected by them and the manifestations of the SIRS promoted by cytokine storm. However, both factors may originate some manifestations.

3.1. Manifestations associated to thrombosis

Intra-abdominal thrombotic complications affecting the kidneys, adrenal glands, splenic, intestinal and mesenteric or pancreatic vasculature were most commonly found in the "CAPS Registry" and the patients frequently presented with abdominal pain or discomfort. Renal disease was present in 73% of patients (Figs. 1 and 2). Pulmonary complications were next in frequency (60%), with acute respiratory distress syndrome (ARDS) and pulmonary emboli accounting for most of these patients, while pulmonary hemorrhage, microthrombi, pulmonary edema and infiltrates occurred in a minority of patients. The main pathological finding was non-inflammatory thrombotic microangiopathy, present in 70% of the patients in whom a lung specimen (biopsy/necropsy) was available. Cerebral manifestations (infarcts, encephalopathy, seizures or cerebral venous occlusions) were also frequent (56%). Microthrombosis was present in 48.9% of those patients who died, and necropsy was performed. Cardiac problems occurred in 50% (Fig. 3), often with valvular defects (mitral, aortic), while

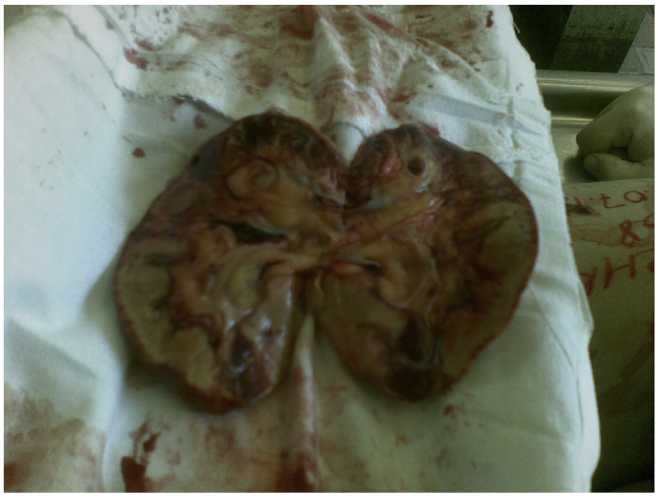

Fig. 1. Kidney thrombosis in patient with CAPS.

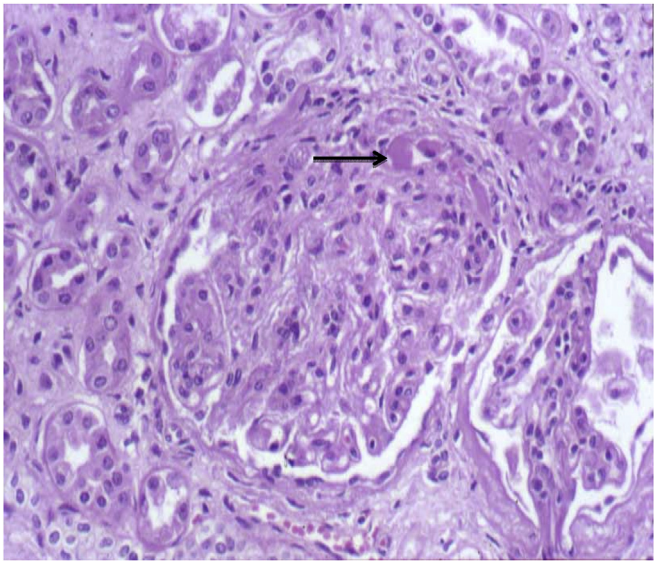

Fig. 2. Glomerular microthrombosis.

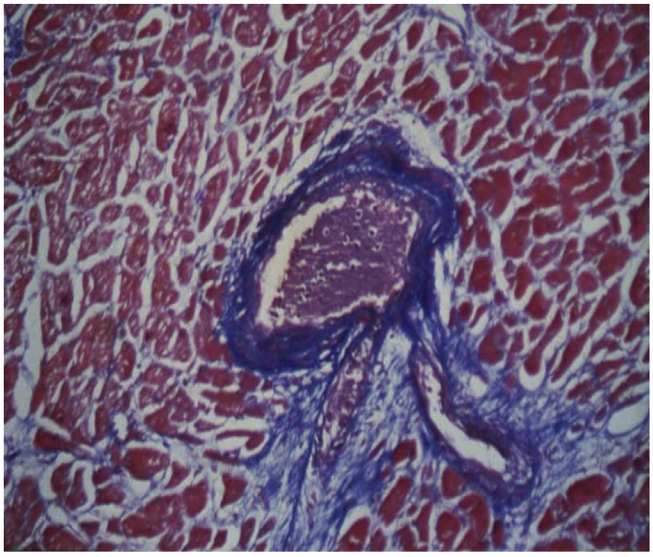

Fig. 3. Myocardial microthrombosis.

myocardial infarctions were a presenting feature in 44% of cases.

Skin complications, such as *livedo reticularis*, purpura and skin necrosis, were next, occurring in 47% (Fig. 4). Additionally, other organs may be occasionally affected, including testicular/ovarian infarction, necrosis of the prostate, acalculous cholecystitis, bone marrow infarction, esophageal rupture, giant gastric ulceration, colonic ulcerations, thrombotic pancreatitis, and adrenal infarction, among other features [26].

3.2. Manifestations associated to SIRS

Some manifestations of SIRS, particularly ARDS, encephalopathy, seizures, and myocardiopathy are frequently reported in these patients [26,27]. Although measurements of cytokine levels in very ill patients with CAPS have not been undertaken, it is assumed that SIRS manifestations are due to cytokine activation which occurs in the acute phase of the illness. This may be superimposed on an underlying infective process, which itself may have been instrumental in "triggering" CAPS.

Fig. 4. Skin necrosis in a patient with CAPS.

4. Laboratory features

Thrombocytopenia was detected in 67% of cases from the "CAPS Registry" [12]. One third of all the patients had evidence of hemolysis and 11% had some of the features of disseminated intravascular coagulation (DIC) [12]. Laboratory features consisting with thrombotic microangiopathic hemolytic anemia (TMHA) was present in 16% of the patients analysed in this registry. Furthermore, CAPS has been found to be the most common clinical presentation in patients with TMHA associated to aPL [28]. Schistocytes, if present, are usually scanty in CAPS, unlike the abundant numbers seen in patients with TTP.

5. Classification and diagnosis

When CAPS is suspected, an aggressive treatment is required. Therefore, early diagnosis is very important to start adequate therapy and decrease the high mortality rate of these patients.

In order to facilitate the diagnosis of this severe complication, a preliminary classification criteria for CAPS were proposed during the 10th International Congress on aPL in 2002 [9] (Table 1) and later validated [29]. However, in the real-world setting, the diagnosis of CAPS may be very difficult. It is important be aware with and found actively some clinical and laboratory features that may be clues for the diagnosis of CAPS. From the clinical point of view, the first important point is to suspect this condition in front of a patient with multisystem microangiopathic involvement, that is occlusive vascular disease affecting predominantly small vessels of different organs, particularly the lungs, kidneys, liver, brain and heart. It is evident that the diagnosis will be easier if the patient has a known history of APS or persistent aPL-positivity. Therefore, obtain an accurate clinical history looking for previous thrombosis or pregnancy morbidity is essential. Given that 40% of CAPS patients have an associated autoimmune disease, in front of a patient with multiorgan involvement and a history of another autoimmune disease (particularly SLE), the clinical suspicion of CAPS is mandatory.

Searching of the potential precipitating factor, mainly infection, is the second important point to improve the diagnosis of CAPS. Small vessel involvement is the hallmarks of this syndrome and one of the requirements for diagnosis of definite CAPS is the histopathologic confirmation of significant thrombosis in at least one organ or tissue. Therefore, the easiest approach is to perform a biopsy of the most accessible organ involved, such as skin or kidney. However, the reason for most diagnosis of probable or possible CAPS in the "CAPS Registry" - instead of definitive CAPS - is the lack of biopsy. Low platelet count, coagulation factors consumption as sign of coexisting coagulopathy,

Table 1
Preliminary criteria for the classification of catastrophic antiphospholipid syndrome (CAPS).

(1) Evidence of involvement of three or more organs, systems, and/or tissues[a]
(2) Development of manifestations simultaneously or in less than one 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 one week and one month after presentation, despite anticoagulation

Given that many times biopsy and histological confirmation of small vessel occlusion cannot be obtained due to the critical condition of the patients, a proposal has been made to substitute the "histopathology criteria" by the exclusion of other diagnoses.

[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.

and the clinical severity with necessity of ICU admission are the main causes of the impossibility to carry out the histopathologic study in this setting.

From the laboratory point of view, some findings are very characteristic of CAPS and should be sought in the appropriate clinical setting. In the last review of the "CAPS Registry", thrombocytopenia was detected in 67% of patients and schistocytes in 22%, respectively. Features of thrombotic microangiopathy defined as low platelet count, hemolysis features and schistocytes were detected in 14% of patients. Finally, DIC, defined as low platelet count, D-dimer increase, and low prothrombin time, was found in 11% of cases [12].

Up to this point and as a rule, high suspicion of CAPS should be based on clinical features of multiorgan involvement and findings suggestive of microangiopathic vasculopathy, such as low platelet count, high levels of lactate dehydrogenase, low levels of haptoglobin, and the presence of schistocytes on peripheral blood smear. From the practical point of view, step-by-step approach diagnostic algorithms were proposed in the 13th International Congress on Antiphospholipid Antibodies in 2010 [10]. These algorithms represent an attempt to bring the CAPS diagnostic criteria closer to the different clinical scenarios.

However, there are a series of factors that can impede the diagnosis and must be considered. Not all aPL found in some circumstances are pathogenic; that is, in critically ill patients, aPL positive may be related with endothelial damage instead with primary autoimmune disease. The presence of aPL may be related with infections or neoplasms that, as discussed above, are the main precipitating factors for CAPS episodes. In other words, in the context of infections, mainly severe sepsis, aPL may appear but in most cases, they do not persist over time, are not pathogenic and, therefore, are not related with thrombotic events. In a recent study, Vassalo et al. [30] prospectively evaluated the prevalence and the impact of aPL in 95 critically ill patients with cancer. Overall, 70% of all patients were positive for at least one aPL. Thrombotic manifestations occurred in 18% of all patients and they did not find differences between aPL positive and aPL negative patients. In fact, after adjusting for other covariates, aPL status was not associated with mortality.

Another situation that may make the diagnosis of CAPS difficult is the false positive result of LAC due to the use of anticoagulation, usually prescribed in this type of patients. Finally, it is well known the disappearance of aPL (false negative aPL) at the time of thrombosis in APS patients attributed to its consumption. In the same sense, widespread thrombosis in patients with CAPS leading to aPL consumption, may difficult its detection in the laboratory at the time of catastrophic episode [31].

6. Differential diagnosis

Thrombotic microangiopathy is a syndrome that includes several disorders characterized by localized or diffuse microvascular thrombosis [32]. As discussed above, CAPS is characterized by multiple microvascular and macrovascular occlusions in a short time and, therefore, it should be included in the differential diagnosis of thrombotic microangiopathies [33]. Therefore, diagnosis of CAPS requires excluding other entities such as TTP, hemolytic uremic syndrome (HUS), DIC in the context of systemic infections or malignancies, hypertension-related, pregnancy-related and drug-related microangiopathic syndromes, and heparin-induced thrombocytopenia (Table 2) [34]. Some of these clinical scenarios such as severe preeclampsia and HELLP syndrome may be suspected given the appropriate clinical context such as pregnancy. In other cases, the most important point is to perform a systematic and complete clinical history and physical examination looking for previous thrombosis or pregnancy morbidity, uncontrolled hypertension, bloody diarrhea, and exposure to heparin or some concrete drugs such as ticlopidine, clopidogrel, chemotherapy agents, and alendronate that have been identified as probable cause of thrombotic microangiopathy. In addition, unexplained weight loss, gradual onset of symptoms, hepato or splenomegaly or palpable lymphadenopathies may be the clue to suspect the existence of malignancy triggering the thrombotic microangiopathy. High-grade fever accompanying chills may be the signs of systemic infection in form of severe sepsis. A previous history of acute gastroenteritis with bloody diarrhea caused by verocytotoxin (Shiga-like toxin)-producing *Escherichia coli* but also *Shigella dysenteriae type I* and *Citrobacter freundii* might help to suspect HUS. In case of severe hypertension, funduscopic exam is mandatory to rule out the evidence of exudates and papilla edema pointing to a malignant hypertension.

However, differential diagnosis is not so easy in the real-world setting. On the one hand, clinical picture may be very similar between different diseases. Kidney and neurologic involvement may be present in CAPS but also in malignant hypertension, severe sepsis, and TTP/HUS. On the other hand, physicians should remember that in most causes of thrombotic microangiopathy others than CAPS, aPL may also be present. At times, it may not be clear whether aPL are an

Table 2
Common disorders associated to microangiopathic hemolytic anemia that should be included in the differential diagnosis of patients with catastrophic antiphospholipid syndrome.

- Systemic infection
- Malignancy
- Preeclampsia, eclampsia, HELLP syndrome
- Malignant hypertension
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Drug-related microangiopathic syndromes (i.e. clopidogrel, ticlopidine, chemotherapy, alendronate…)
- Heparin-induced thrombocytopenia

Table 3
Diagnostic work-up in front of a patient with suspicion of thrombotic microangiopathy (TMA).

1)
To establish the suspicion of TMA
- Thrombocytopenia (< 150 × 10^9/l or > 25% of decrease)
- Signs of microangiopathic hemolysis
- Anemia (± increase in mean corpuscular volume)
- Reticulocyte count raised
- Lactate dehydrogenase (LDH) increased with haptoglobin decreased
- Direct Coomb's test negative
- Blood smear searching schistocytes

2) To look for organ involvement
- Neurological: Confusion, headache, seizures, encephalopathy, focal deficits
- Renal: ARF, arterial hypertension, proteinuria, hematuria
- Cardiac: Cardiac failure, hypotension, ischemic cardiopathy
- Pulmonary: ARDS, respiratory insufficiency
- Gastrointestinal: Abdominal pain, intestinal angina, diarrhea, vomiting
- Hematological (thrombocytopenia): epistaxis, hemoptysis, menorrhagia, retinal haemorrhage, gastrointestinal bleeding, petechiae

3) To confirm organ involvement
- Blood analysis including renal function, cellular blood count, LDH, liver and pancreatic enzymes, creatinkinase, and troponin I
- Renal biopsy: to confirm glomerular microthrombosis
- CT/MRI brain: to determine neurological involvement
- Electrocardiogram/Echocardiogram: to document or monitor cardiac damage
- Chest radiograph/CT: to document lung involvement
- Echography/CT: to document hepatic/pancreatic/intestinal involvement
- Fundoscopic examination: to document retinal vessel involvement

4) To investigate the etiology
- ADAMTS 13 activity: < 5–10% (TTP)
- If gastroenteritis (bloody diarrhea): Shiga toxin/STEC: positive (HUS)
- If ADAMTS13 > 10%: secondary or associated TMA
- Fundoscopic examination (malignant hypertension)
- Immunologic profile: ANA, ANCA, and aPL (autoimmune diseases)
- Pregnancy test (pregnancy-related)
- CT toracoabdominal or PET: (cancer-associated)
- Clinical history looking for drugs/heparin and anti-PF4 antibodies (HIT)
- Complement study FH, FB, FI, anti-FH antibodies, genetic study (aHUS)

Abbreviations: aHUS: atypical HUS, ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, aPL: antiphospholipid antibodies, CT: computed tomography, HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome, PET: positron emission tomography, STEC: Shiga toxin *Escherichia coli*, TTP: thrombotic thrombocytopenic purpura.

epiphenomenon due to the endothelial damage rather than pathogenic antibodies. In general, double or triple aPL positivity or aPL at high titers make the diagnosis of CAPS more probable. The aPL have been reported in some patients with TTP/HUS, but usually at low titers [35,36]. In this context, decrease in ADAMTS13 activity fewer than 5% points to TTP as the most probable diagnosis. Infections are capable of inducing aPL but normally at low titer and they are not persistent over time [17]. Low titers of aPL are found in high frequency in cancer patients but they do not seem to play a role in the development of thrombotic complications [37]. With all these data, in front of a patient with thrombotic microangiopathy, a specific diagnostic workup should be carried out (Table 3).

7. Management approach

The optimal management of CAPS has been a challenge since its description. Today, CAPS mortality continues to be extremely high despite therapy [34,38–40]. Due to this high mortality rate, early diagnosis and aggressive treatment are essential clues in its successful management.

The evaluation of CAPS treatment in formal prospective randomized studies is very difficult due to its low incidence. This is why, in order to improve our knowledge on this condition, the analysis of hundreds of patients with this condition included in the “CAPS Registry” has allowed the evaluation of several therapeutic combinations and to propose the current therapeutic approach [41] (Fig. 5). These guidelines state that specific therapy together with precipitating factor treatment and supportive management should be administered to patients with clinical suspicion of CAPS. Current knowledge supports the treatment with the combination of anticoagulation (AC) with heparin and high doses of glucocorticoids (GC), as first-line treatment. Additionally, adding plasma exchange (PE) and/or intravenous immunoglobulins (IVIG) should be considered in cases with associated life-threatening situation [10,40] (Fig. 5). Intravenous cyclophosphamide is recommended in patients in which CAPS is associated to SLE [42].

Additionally, rituximab, as an add-on therapy for the treatment of CAPS patients refractory to conventional treatment or recurrent cases, has shown a benefit [43]. More recently, some authors have reported success in the treatment of CAPS with eculizumab [44,45].

Current treatment guidelines for specific CAPS therapy were established more than 15 years ago based on the analysis of CAPS patients treated according their physicians criteria [9,46]. Noteworthy, when each treatment was analysed individually, only AC had a significant effect in improving the vital prognosis; however, the combination AC + GC + PE and/or IVIG archived the highest survival rate (70%) [40,47].

Data from the patients included in the “CAPS Registry” permitted the evaluation of the treatments used up to date in a large cohort [26,40,48]. In the most recent analysis including 500 CAPS patients, AC showed to be the treatment associated to a higher recovery rate (63% in episodes treated with AC versus 22% in episodes not treated with AC; $p < 0.0001$). However, the combination of AC + GC + PE and/or IVIG achieved the highest survival rate (28.6%), while those that received treatment with other combinations had a higher mortality rates (41.1%) [40]. The use of triple therapy allowed a 47% reduction in the mortality rate of CAPS [40].

The Task Force on CAPS that met in 2014 on occasion of 14th International Congress on aPL reviewed the evidence on CAPS treatment at that time. Taking together the evidence so far, it recommended the triple therapy (AC + GC + PE and/or IVIG) with a grade of recommendation B. Furthermore, the addition of cyclophosphamide to the triple therapy was suggested for patients with SLE with a grade of recommendation D [49].

7.1. Supportive general measures

General measures should be the backbone in the treatment of these patients since their bad clinical condition frequently warrants vital support to preserve their clinical stability. According to the patient medical condition, appropriate supportive care should be established. Often it includes ICU admission [50]. External ventilation support, inotropic drugs, and hemodialysis might be necessary, but mostly only tight control is necessary. Classical thrombotic risk factors should be controlled and avoided whenever possible. It might include the use of external pneumatic compression devices when immobility is a concern. Any surgery should be postponed when its aim is not to remove necrotic tissue to control the cytokine storm. Additionally, CAPS patients may benefit from glycemic control, stress ulcer prophylaxis and blood pressure control [51].

7.2. Trigger guided therapy

Aggressive treatment of any identifiable trigger factor should be attached to the specific treatment. When an infection is suspected, the infection site pharmacokinetics and microorganisms pharmacodynamics should be considered to select the antibiotic. However, any effort should be undertaken to recover responsible microorganism. At the same time, removing necrotic tissue or limb amputation is advised with the aim of controlling systemic inflammatory response [51–53].

The perioperative management of patients with APS or aPL carriers should be very cautious with the purpose of decreasing thrombotic recurrence risk or the development of a catastrophic episode. Thus,

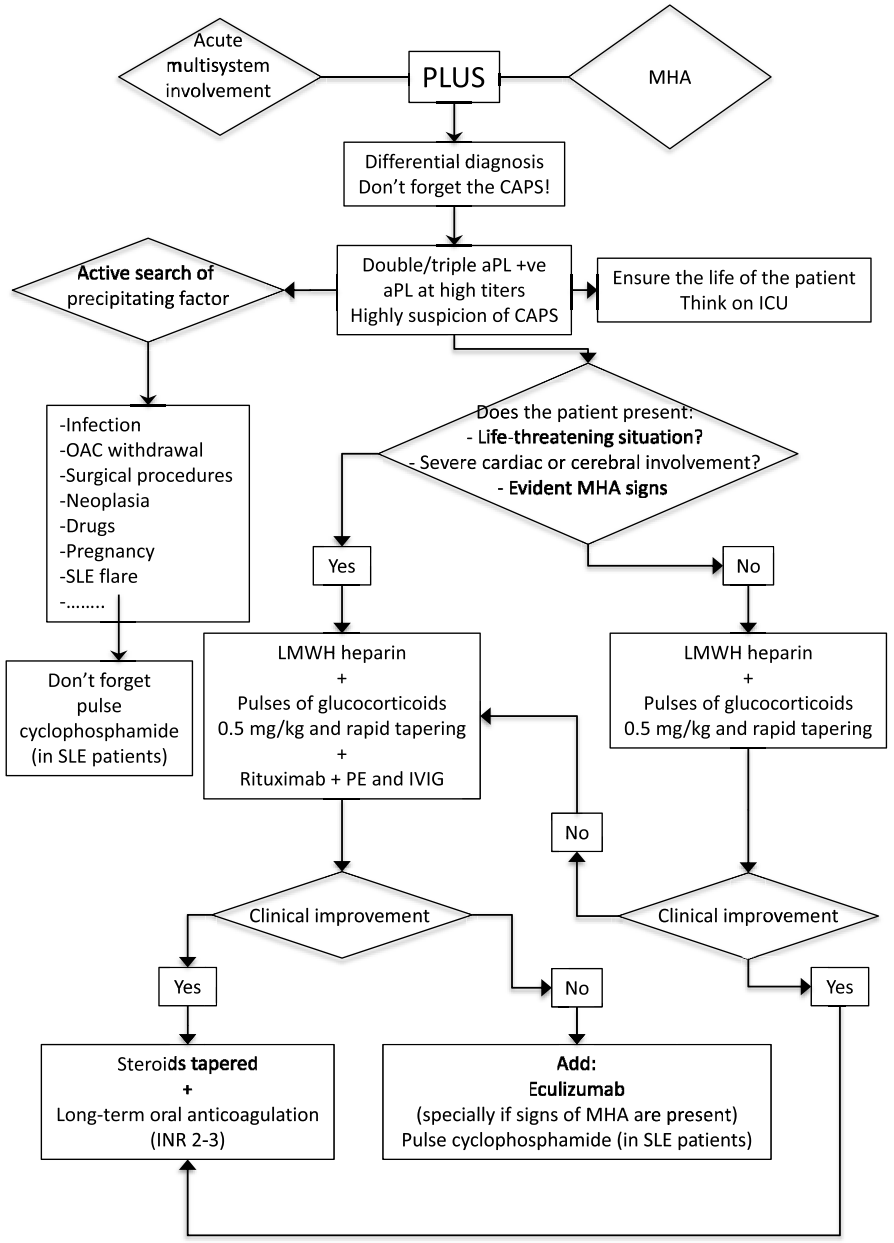

Fig. 5. Proposed treatment algorithm of catastrophic antiphospholipid syndrome. Abbreviations: aPL: antiphospholipid antibodies; CAPS: catastrophic antiphospholipid syndrome; ICU: intensive care unit; IVIG: intravenous immunoglobulin; LMWH: low molecular weight heparin; MHA: microangiopathic haemolytic anemia; OAC: oral anticoagulation; PE: plasma exchange; SLE: systemic lupus erythematosus.

careful bridging between oral anticoagulant to heparin is required. Probably, a multidisciplinary approach with an hemostasis specialist to each case might be necessary [54]. Additionally, puerperium should be adequately covered for a minimum of 6 weeks with prophylactic dose of low molecular weight heparin (LMWH).

7.3. Anticoagulation

AC with heparin is the mainstay CAPS treatment. The main reason for its use is the inhibition of ongoing clotting and its ability to break up existing clots that may contribute to the ongoing thrombosis [21,27,55–59]. Moreover, although its pharmacodynamic mechanisms are not completely understood, anti-inflammatory activity of heparin seems to account for its extraordinary usefulness in CAPS [60] and, additionally, heparin seems to inhibit aPL binding to their target on the cell surface [61]. Most CAPS patients are initially treated with unfractionated heparin because non-fractionated heparin enables throwing back its effect in case of requirement. This is often a need during ICU period either because electively to perform invasive procedures or because of bleeding. Later, non-fractionated heparin can be switched to LMWH and finally to oral AC. However, physicians should not rush to change heparin to other AC because a long time under heparin treatment favors clot fibrinolysis. A seven to ten days course under heparin treatment is recommended. Still, heparin should not be withdrawn before achieving a correct international normalized ratio (INR) between 2 and 3 with oral AC treatment.

7.4. Glucocorticoids

GC are the most commonly used anti-inflammatory drugs in the treatment of autoimmune diseases. GC are used to overcome the excessive inflammatory response triggered by multiple blood flow

occlusions and resultant ischemic necrotic tissue. Additionally, beneficial effects of GC treatment have been invocated because steroids inhibit nuclear translocation and function of proinflamatory transcription factors such as activator protein 1 and nuclear factor-κB that are in the core of intracellular signal elicited by aPL binding to endothelial cells. Moreover, due to their anti-inflammatory effects, GC decrease antibody production and, therefore, aPL production.

Although, no direct evidence supports GC use in patients with severe infections unless patients develop adrenal insufficiency [62,63], strong rational arguments and observational evidence drove investigators to think that GC should be administered to patients with CAPS [25,40]. However, the best initial dose, the route of administration, and the tapering strategies are still an investigation field. Data from the "CAPS Registry" showed that GC are given as intravenous pulses of 500–1000 mg/day for 1–3 days in a third of episodes and as oral or intravenous dosages of 1–2 mg/kg/day in another third. Nevertheless, most physicians continue GC treatment until the patient is discharged in a daily oral dose and then taper the dose until it is being administered in low doses.

Given the current knowledge on the mechanisms of action of GC, a more beneficial approach would be to administer pulses of methylprednisolone (250–750 mg/day for 3 days) and then continue with 0.5 mg/kg/day of prednisone trying a rapid dose tapering. With this therapeutic guideline, adverse events produced by genomic effects may be minimized. In severe situations, such as CAPS, pulse methylprednisolone, avoiding high doses of oral prednisone and taking, as rule, maintenance doses not higher than 5 mg/day would be desirable.

7.5. Plasma exchange

PE is a technique designed to remove large molecular weight molecules from plasma. It consists in removing large quantities of plasma (usually 2–5 L) and replacement by either fresh-frozen or stored plasma. The term "plasmapheresis" should be kept to refer to the extraction of a smaller quantity of plasma (around 600 ml) without reposition [64]. Thus, the use of PE in CAPS rely on the rational that it removes aPL and cytokines from the patient while volume replacement with fresh frozen plasma would restore natural anticoagulants such as antitrombin-III. Its use comes by analogy to the management of classical microangiopathic conditions where this treatment has shown its beneficial effects in randomized controlled trials [65]. Therefore, PE is specially suitable in those patients with CAPS who present serological features of microangiopathy (i.e., schistocytes) [66]. The use of therapeutic PE in CAPS is recommended with a grade of evidence of 2C by the American Society for Apheresis (ASA) [67]. It is indicated when a patient with CAPS evolves to a life-threating situation as an add-on therapy to effective AC with intravenous heparin and high dose steroids [68].

There is no consensus on the replacement fluid of choice for therapeutic PE in CAPS, and fresh frozen plasma, human albumin and solvent/detergent plasma have been used. Following ASA recommendations, a combination of plasma and albumin would provide the necessary benefit of therapeutic PE and minimize potentially serious and undesirable side effects from excessive exposure to plasma.

There is not recommendation about the duration of this procedure. It is generally continued for a minimum of 3–5 days; however, clinical response is the main parameter that should dictate discontinuation of the therapy.

7.6. Intravenous immunoglobulins

IVIG are used in a wide variety of autoimmune and inflammatory conditions although the mechanisms of action by which IVIG exert their immunomodulatory and anti-inflammatory effects remain unclear. Probably, high intravenous antibodies concentration leads to Fc receptor overload, thus inhibiting pathologic autoantibody to develop their detrimental effects, and increasing their clearance. At the same time, it might increase regulatory T cells (Tregs) downregulating cytokine storm [68]. Only recently, the beneficial effects of IVIG in primary APS have been proved by decreasing aPL titers and, therefore, reducing the thrombotic risk of these patients [69,70]. Thus, IVIG may be effective to achieve a prompt reduction of aPL titers and downregulate proinflamatory levels proving to be beneficial in patients with CAPS [40].

There is no established recommendation on the dose that might be beneficial in patients with CAPS. Although, by analogy to other autoimmune diseases, they have been used following two different schemes: 400 mg/kg daily for 5 days and a total dose of 2 gr/kg of body weight infused over a period of 2–5 days. However, when PE is performed, IVIG are administered after PE session and, additionally, often an extra IVIG dose is administered after PE in order to replace IVIG removed by it.

IVIG are usually well tolerated, but there are some reports of thromboembolic events and acute renal failure after IVIG, especially in those cases of CAPS to whom AC has to be stopped because of bleeding. Thus, IVIG should be administered slowly, especially in elderly patients with high blood pressure, diabetes or hypercholesterolemia.

7.7. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-alkylating agent that binds to deoxyribonucleic acid in immune cells leading to their death. At the same time, cyclophosphamide enhances T effector cells proliferation while suppressing Th1 helper activity and upregulating Th2 response and abrogates the function of Tregs [71]. In CAPS, lymphoid tissue suppression leads to aPL and cytokines levels reduction, thus, downregulating the elicited storm.

According to the "CAPS Registry", cyclophosphamide was prescribed in a third of episodes of CAPS, mostly as an intravenous pulse but also as an oral dose. However, different dosages and routes of administration did not lead to statistically relevant difference between patients who died and those who survived nor did the addition of cyclophosphamide to combined therapy [26].

Bayraktar et al. [42] performed a multivariate analysis of the data included in the "CAPS Registry" that showed cyclophosphamide to be associated to a decrease in mortality rate in those patients with CAPS associated to SLE. Thus, cyclophosphamide is recommended in cases of severe CAPS in patients with SLE.

Regarding doses, although no specific data is available in CAPS, similarity to other autoimmune conditions, a recommended regimen of 750 mg/m^2 monthly or 500 mg fortnightly during 6 or 3 months has been proposed [72].

7.8. Defibrotide

Defibrotide, a polydisperse mixture of 90% single-stranded and 10% double-stranded phosphodiester oligonucleotides derived from the controlled depolymerisation of porcine intestinal mucosal DNA, has demonstrated several hemostatic properties (i.e., upregulates the release of prostacyclin and prostaglandin E2 and reduces concentrations of leukotriene B4 and modulates platelet activity) [56].

The use of off-label defibrotide has been published in two patients with CAPS [14,57]. The first was a 55-year-old man who had shown intractable progression of multiorgan thrombosis during 1 week despite the treatment with full-dose intravenous heparin, aspirin and dipyridamole. In the context of an investigational new drug protocol, a therapeutic trial with defibrotide was attempted while all antithrombotic and antiplatelet were stopped. Defibrotide was continued as a sole therapy at a dose of 80 mg/kg/day administered as a 24 h continuous infusion. The outcome of the patient was satisfactory. The second patient was a 53 year-old female who presented with renal, intestinal and cutaneous thrombotic involvement. She was treated with anticoagulation and defibrotide but the patient was unresponsive and

died.

7.9. Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, a surface protein expressed on B cells membrane. Although rituximab seems not to have any effect on memory B and plasma cells, because they discontinue CD20 expressing when they mature, some regulatory effects of B cells independent of antibody production have been claimed to explain rituximab effect in acute disease.

Rituximab is approved by the regulatory agencies for the treatment of chronic lymphocytic leukemia, diffuse large B-cell, advanced follicular lymphoma, refractory rheumatoid arthritis and severe vasculitis remission induction [73]. However, rituximab is often used off-label for the treatment of several autoimmune diseases [74–76]. Indeed, an open-label trial showed rituximab to be safe and useful controlling non-criteria manifestations of APS such as thrombocytopenia, skin ulcers, nephropathy and cognitive dysfunction [77]. Furthermore, rituximab was able to decrease recurrence rate in patients with recurrent thrombosis or refractory thrombocytopenia [78]. In this regard, rituximab has been used as an alternative second line therapy when facing refractory or recurrent cases of CAPS.

The main evidence for the use of rituximab in patients with CAPS comes from the recent review performed by our group [43]. In this review, we identified 20 out of 441 (4.6%) patients included in the "CAPS Registry" as of May 2013 who were treated with rituximab. Regarding treatment, AC was the most frequent treatment, being used in all patients followed by GC in 17 (85%) patients, IVIG in 16 (80%), PE in 13 (65%), and cyclophosphamide in 4 (20%). Overall, 16 (80%) patients were initially treated with the complete combination of AC plus GC plus PE and/or IVIG. Rituximab was the first-line treatment associated with combined therapy of CAPS in 8 (40%) patients. In six of them, the reason was the initial severity of clinical picture and in the remaining two, rituximab was administered as a treatment of lymphoma. In 12 (60%) patients with poor response to initial treatment or recurrent episodes of CAPS, worsening of thrombocytopenia, or development of new thrombosis, rituximab was the second line-therapy. Rituximab was used in different regimens; the most frequent was two fortnightly doses of 1000 mg (8 patients), followed by four weekly doses of 375 mg/m^2 (6 patients). Considering the outcome, 16 (80%) patients recovered from the acute CAPS episode and 4 (20%) died at the time of the event. Two of the patients who died had received rituximab as a first line therapy. The median follow-up time was 9.5 months (range, 1–36 months). A recurrent episode of thrombocytopenia 24 months after the episode of CAPS developed in a patient requiring the increase of prednisone dosing and a second course of rituximab. Other patient presented with cutaneous necrosis 9 months after CAPS event and he required high-dose of intravenous methylprednisolone and a second 4-week course of rituximab (375 mg/m^2/week) with complete resolution. Interestingly, no further episodes of thrombosis developed in the remaining patients.

Regarding the effect of rituximab in aPL profile, this data was available in only 8 patients. Overall, half of patients remained with persistent aPL in the follow-up with positive LAC at 11 weeks and LAC plus aCL at 2, 3, and 5 months of follow-up, respectively. In the remaining 4 patients (50%), aPL became negative. Briefly, in one patient, LAC became negative 7 months after the infusion without information on the aCL and aβ2GPI antibodies status after and before rituximab administration. In the second patient, LAC became negative several weeks later after the discharge from the hospital. Unfortunately, no information about aCL and aβ2GPI antibodies status after rituximab was done. In the third patient, triple aPL negativity was described after one month of follow-up. Finally, the fourth patient became negative for aβ2GPI antibody. Information on LAC and aCL antibody was not done. Despite the scientific value of this review, it has several limitations such as the low number of patients with CAPS treated with rituximab and the difficulty of analyzing the isolated effect of rituximab given the fact that all these patients received a combined therapy including AC, GC, PE and/or IVIG.

7.10. Eculizumab

Eculizumab is a monoclonal antibody that binds with high affinity to complement protein C5, inhibiting its cleavage and, thus, preventing C5a formation and its chemoattractant function so as the membrane attack complex assembly. It is approved by the US Food and Drug Administration for the treatment of paroxysmal nocturnal hemoglobinuria and for atypical hemolytic uremic syndrome [79]. Furthermore, basic research has shown that sublytic concentration of membrane attack complex stimulates endothelial cells adhesion molecules expression, tissue-factor synthesis and induce apoptosis leading to endothelial cells detachment, basement membrane collagen exposure and subsequent indirect clotting pathway activation. Since CAPS is often triggered by a concurrent infection, a targeted therapy against C5 offers an attractive therapeutic approach to CAPS because its capacity to inhibit complement cascade at the level of C5 preserves C3b-mediated infectious agents and immune complexes opsonisation and thus, immune mediated mechanisms to control infections.

Moreover, although renal transplant is commonly contraindicated in CAPS patients with end-stage renal disease based on the risk of CAPS recurrence, Lonze et al. [80] reported a successful renal transplant in a patient with a previous history of CAPS prophylactically treated with eculizumab together with anticoagulation and standard immunosuppression. In this regard, a phase 2 open label clinical trial (NCT01029587) was launched in order to prove the efficacy and safety of eculizumab to prevent recurrence in patients with previous history of CAPS who undergo a renal transplant. However, the low incidence of this condition precluded enrolment of enough patients to conduct any trial and this study had to be finished prematurely.

Recently, some authors reported success with eculizumab use in patients with refractory episodes of CAPS [44,45,80,81]. Dosage has been taken over from the experience on other thrombotic microangiopathies. Weekly doses of 900–1200 mg of eculizumab have been used in the acute phase decreasing its frequency after effervescence to 900 mg administered every 2 weeks. However, there is no known clue to decide the duration of the treatment and, then, often, not only effectivity has to be taken into consideration but also its efficiency.

Eculizumab seems to be an attractive promising treatment for patients with CAPS or at least to prevent its recurrence in high-risk situations, although a larger experience is needed to define eculizumab place in CAPS treatment. However, its high cost throws back many initiatives to use it. Probably, expected future economic cost drop will increase its use in CAPS providing the required experience.

7.11. New oral anticoagulants

Vitamin K antagonists have a slow onset of action, a narrow therapeutic window, numerous interactions and, thus, regular INR monitoring is required. These limitations have driven a search for new alternative AC drugs. Recently, new oral AC have appeared to the hemostasis therapy armamentarium. They are administered in a fixed dose with predictable effect and do not require regular AC monitoring because their effect is not influenced by diet and drug interaction. Pivotal phase III randomized controlled trials have established their comparable efficacy and safety to vitamin K antagonists in patients with deep vein thrombosis. Moreover, recently some phase II/III randomized controlled clinical trial have been started in order to prove their efficacy in patients with classical APS. However, they have never been used during the acute phase of CAPS. Before they can be used in this clinical scenario, some problems might need to be overcome since, nowadays, throwing back their effect is not possible what is frequently required in patients admitted in the ICU where invasive procedures often need to

be undertaken. Additionally, in contrast to the treatment with heparin, no effects are known from the new AC on complement system. Thus, until a larger experience with the use of new AC is available, heparin continues to be the recommended AC drug for CAPS. However, new AC may have a role in the future at least as a prophylaxis for those cases that develop CAPS while under treatment with vitamin K antagonists.

7.12. Intracellular signal modulation

Recently, the mammalian target of rapamycin (mTOR) pathway has been proposed to be a key step in the vascular stenosis that results from mechanical endothelial injury of patients with CAPS [82]. The mTOR is a large protein kinase ubiquitously and constitutively expressed [83]. It associates with various proteins to generate two structurally and functionally distinct complexes termed mTOR complex 1 (mTORC1) and mTORC2 [84]. Under high nutrient supply, mTORC1 promotes protein synthesis, lipogenesis and energy metabolism [85]. Endothelial intimal hyperplasia in kidney biopsies from patients with APS nephropathy was associated to mTORC pathway activation despite adequate anticoagulation [86]. Further, mTORC pathway activation and endothelial cell proliferation was proved in both carotid and left anterior descending arteries of patients with CAPS [86]. Hence, mTORC pathway activation by aPL seem to drive part of the vascular injury noted in patients with CAPS although the mechanism through what aPL lead to cell activations remains unknown.

Sirolimus is a macrolide antibiotic produced by *Streptomyces hygroscopicus*. Initially, it was evaluated as an antifungal, but later; it proved to be a potent immune-suppressant. In 1999, sirolimus was approved for the regulatory agencies as a treatment to prevent acute renal transplants rejection. Later, sirolimus has shown to be able to avoid restenosis in patients undergoing percutaneous coronary intervention when eluted from stent. Indeed, sirolimus-eluting stents are currently in use as a potent antiproliferative drug in patients to avoid arterial restenosis. However, some evidences point to a prothrombotic effect of mTORC inhibitors and thus its potential benefit in patients with CAPS remain as a matter of debate [87].

Simultaneously, some new pathways are being traced which point to possible new therapeutic targets. Bacterial infection and lipopolysaccharides released are known to induce intracellular signaling through toll-like receptor 4. It leads to tissue factor and adhesion molecules up regulation, which probably accounts for some of the clinical manifestations seen in disseminated intravascular coagulation and probably in CAPS triggered by infections. GC are known to block nuclear translocation of NF-kB and although they seem to be of small benefit in sepsis [88], they proved to improve patients outcome when they are used in patients with CAPS. In this sense, an specific proteasome inhibitor MG-132 has been shown to inhibit the thrombogenic properties of aPL in mice [89]. However, its usefulness in patients with APS has not yet been proved.

8. Refractory catastrophic antiphospholipid syndrome

The term refractory CAPS refers to both patients who died despite the use of first-line therapies as well as to patients suffering recurrent episodes of CAPS [90].

Considering patients with recurrent episodes of CAPS ("relapsing" catastrophic APS), our group documented in 2008 three patients with seven episodes [91]. The median time between the episodes of CAPS was 12.5 months (range, 2.5–48). From the clinical point of view, the most significant manifestations were renal involvement (present in 5 episodes), followed by central nervous system and cardiac involvement (4 episodes each), and pulmonary and hepatic involvement (3 episodes each). Interestingly, thrombocytopenia (platelet count less than 50×10^9/L) and red cell fragmentation (schistocytes) were reported in all 7 episodes. Laboratory features of definite TMHA (hemolytic anemia, schistocytes on peripheral-blood smears, and negative Coombs test associated to thrombocytopenia) were present in 5 of 7 episodes of relapsing CAPS. The remaining episodes presented with thrombocytopenia, schistocytes, and anemia but data concerning hemolysis and Combs test were not reported.

More recently, 9 additional cases have also been collected out of 282 (3%) patients from the "CAPS Registry" with a total of 35 episodes of CAPS [92] (6 patients presented 2 recurrences, 2 patients suffered 3 relapses, and one patient developed 17 relapses). The last patient was not included in the descriptive analysis because their clinical and immunological characteristics were not fully reported. The frequencies of the major demographic, clinical, and immunological features of relapsing CAPS were also comparable to the most recent review of CAPS derived from the "CAPS Registry" [12]. There were no differences in the organ involvement at time of CAPS episode. Of note, laboratory features of TMHA were present in 72% of the episodes that were analysed. The prevalence of TMHA features in patients with CAPS from the "CAPS Registry" who relapsed was significantly higher than in those who did not relapse (72% vs. 7%; $p < 0.0001$; 95% CI 0.459–0.841). These data open the door to establish an association between TMHA and relapsing CAPS [91].

9. Mortality and prognosis factors

Among the 500 patients analysed from the "CAPS Registry", 37% died at the time of the CAPS event [40]. The presence of SLE was associated with a higher mortality (47%) [40]. Moreover, at the time of CAPS diagnosis, those with SLE associated had a higher risk for mortality alter adjusting for age, sex, organ involvement, and treatment [26].

The main cause of mortality was infection (20%), produced by bacterial sepsis (12%), fungal sepsis (4%), *Pneumocystis jiroveci* pneumonia (3%), and suppurative peritonitis (1%). In terms of frequency, stroke was the second cause of death (19%), followed by cardiac failure (17%) and multiorgan failure (17%). In the whole series, almost half of the patients died due to thrombotic events, such as stroke, or to SIRS, such as ARDS or encephalopathy [58].

The only study about prognosis of patients who survive the initial catastrophic event demonstrated that 66% of them remained symptom-free with anticoagulation during an average follow-up of 67.2 months [93]. Conversely, 26% of patients developed further APS-related thrombosis after the initial CAPS event. In addition, 8 (15%) patients were functionally impaired because of CAPS. Specifically, three had end-stage cardiac failure, two had end-stage renal disease requiring hemodialysis, one suffered symptomatic arrhythmia, one had chronic renal insufficiency, and one had gait abnormalities and visual symptoms.

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