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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

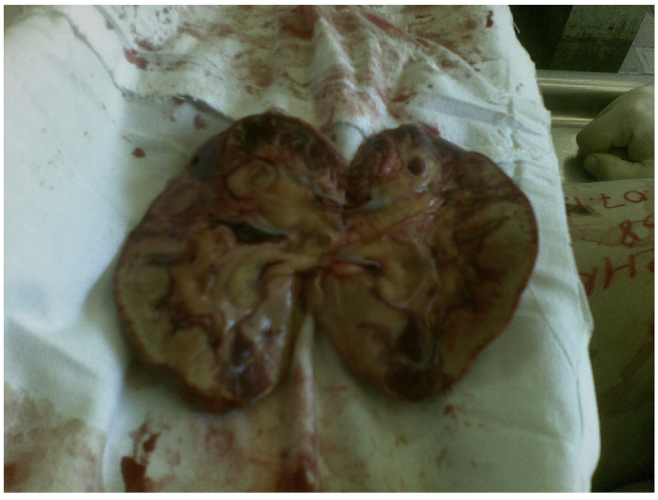

Fig. 1. Kidney thrombosis in patient with CAPS.