

Diagnosing catastrophic antiphospholipid syndrome: the necessity for clinical awareness

“A high index of suspicion in order to make an early diagnosis, as well as aggressive therapy, are vital for the survival of catastrophic antiphospholipid syndrome patients. However, in a ‘real-world’ setting, even if catastrophic antiphospholipid syndrome is considered in the differential diagnosis, there are multiple factors that can impede the timely diagnosis.”

KEYWORDS: anticardiolipin antibodies ■ antiphospholipid antibodies ■ antiphospholipid syndrome ■ lupus anticoagulant ■ microangiopathy ■ systemic lupus erythematosus

The catastrophic variant of antiphospholipid syndrome (APS) is the most severe form of the syndrome. Patients with this variant present with the following characteristics: clinical evidence of multiple organ involvement that develops over a very short period of time (usually less than a week); histopathological features of small vessel occlusions; and laboratory confirmation of the presence of antiphospholipid antibodies (aPL) [1]. Described by Ronald A Asherson in 1992, this subset is now also referred to as Asherson's syndrome, thus honoring the author who passed away in 2008 [2].

Although less than 1% of patients with APS develop this catastrophic variant [3], its high mortality (currently higher than 30% in the acute event [4]) emphasizes its importance in clinical medicine today. The majority of patients with this condition end up in intensive care units with multiorgan failure. Unless considered in the differential diagnosis by the attending physicians, the condition may be completely missed, resulting in a potentially lethal outcome.

From a histopathological point of view, catastrophic APS is a thrombotic microangiopathic condition. However, at present, there are no studies on its pathophysiologic mechanisms. Two possible explanations include: extensive thromboses being responsible for the ongoing thrombosis by generating thrombin, depressing fibrinolysis and consuming the natural anticoagulant proteins; and the manifestations of the systemic inflammatory response syndrome, which are presumed to be due to excessive cytokine release from ischemic and necrotic tissues [5].

Although it is still unclear what the pathophysiologic reason for why some patients develop recurrent thromboses of medium/large vessels

(the so-called simple or classic APS), and others develop rapidly recurrent vascular occlusions of small vessels (catastrophic APS) is, our clinical knowledge on this severe variant has increased substantially during the last 20 years of intensive research [6]. The majority of the current knowledge regarding catastrophic APS comes from the analysis of patients included in the ‘CAPS Registry’ – an international web-based registry of catastrophic APS patients [7] created in 2000 by the European Forum on aPL, a study group devoted to the development of multicenter projects with large populations of APS patients [8]. The CAPS Registry contains clinical, laboratory and therapeutic data on the published cases of catastrophic APS. Additionally, many patients have been included in the registry based on self-reporting by physicians. The registry can be accessed online [10].

Necessity for clinical awareness in diagnosing catastrophic APS

A high index of suspicion in order to make an early diagnosis, as well as aggressive therapy, are vital for the survival of catastrophic APS patients. However, in a ‘real-world’ setting, even if catastrophic APS is considered in the differential diagnosis, there are multiple factors that can impede the timely diagnosis. The following settings are clear examples of the necessity for clinical awareness in diagnosing catastrophic APS.

First, false-negative aPL results may occur during acute APS events. There are reports of patients with classic APS manifestations in whom the aPL became negative at the time of thrombosis but reappeared shortly after the thrombotic events [9]. Similarly, the aPL may not be detected during widespread thromboses



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in catastrophic APS patients and this might be possibly due to their consumption.

Second, the use of anticoagulants (heparin or oral anticoagulants) can result in false-positive lupus anticoagulant (LA) test results. Interestingly, a study of 51 patients without a previous known coagulopathy hospitalized at an intensive care unit demonstrated that 69% developed prolongation of the activated partial thromboplastin time and 53% had a positive LA test. All patients had negative LA tests after discharge [10].

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Third, a positive aPL test can be associated with infections (usually low titer aPL ELISA). Although many catastrophic APS events preceded by infections have been reported [11], transient aPL positivity can occur during infections [12]. At times, it can be difficult to exclude the possibility that positive aPL tests occurred as bystanders, not necessarily as contributors for thrombosis. Infections themselves might result in the generation of aPL and, therefore, a previous history of thrombotic events (e.g., deep vein thromboses, strokes, myocardial infarctions or recurrent fetal losses in females) or the pre-existence of an autoimmune disease, particularly systemic lupus erythematosus, is of great importance for an accurate diagnosis.

Forth, heparin-induced thrombocytopenia may mimic catastrophic APS. Patients suffering from heparin-induced thrombocytopenia have paradoxical thromboembolic events while receiving this anticoagulant (usually after 4–10 days of heparin treatment). The severe type II form is an immune-mediated disorder characterized by the formation of antibodies against the heparin–PF4 complex and its diagnosis is based on detection of these antibodies. However, antiheparin–PF4 antibodies could also be found in heparin-naïve systemic lupus erythematosus and/or aPL-positive patients [13]. Therefore, the presence of these antibodies can result in diagnostic difficulties in heparin receiving aPL-positive patients with thrombocytopenia and multiple organ thromboses.

Fifth, sepsis and catastrophic APS share many similarities and may coexist. Sepsis is defined

by the presence of definite evidence of infection together with systemic inflammatory response syndrome. It is termed severe sepsis when it is associated with multiple organ dysfunction. When severe sepsis is associated with disseminated intravascular coagulation, common complications that can appear include bleeding, thrombocytopenia and microthrombosis, all these features also being frequently found in patients with catastrophic APS. Thus, both the pathophysiological mechanisms and the clinical manifestations of catastrophic APS resemble sepsis with systemic inflammatory response syndrome with the ultimate development of a multiple organ dysfunction syndrome [14].

Sixth, the presence of an acute thrombotic microangiopathy, with or without schistocytic hemolytic anemia, has a broad differential diagnosis: a continuum of thrombotic microangiopathic conditions exists, including; thrombotic thrombocytopenic purpura; hemolysis, elevated liver enzymes and low platelets syndrome; hemolytic uremic syndrome; and catastrophic APS. Owing to the significant overlapping features it may, at times, be difficult to differentiate between these conditions. Since catastrophic APS patients have higher incidence of disseminated intravascular coagulation, schistocytes, hemolysis and fibrin degradation products, the term ‘microangiopathic APS’ has been proposed [15]. Thus, in some aPL-positive patients with multiple organ thromboses, the aPL positivity might not imply that they are in fact pathogenic. Unfortunately, the true prevalence of aPL in different microangiopathic conditions is not known and comparison studies between catastrophic APS and other thrombotic microangiopathies are not in existence at present.

Conclusion & future perspective

Catastrophic APS is an uncommon, but potentially life-threatening, condition and is in need of high clinical awareness. It is evident that the majority of patients with this condition manifest microangiopathy – that is occlusive vascular disease affecting predominantly small vessels of different organs, particularly the lungs, kidney, liver, brain and heart. A basic and sudden disturbance of the coagulation or fibrinolytic systems induced by the aPL is highly probable in this group of patients; however, precipitating factors remain unknown in most of them. Therapeutically, the implication is that this may be corrected with the combination of anticoagulants plus glucocorticoids plus attempts at achieving a prompt reduction of aPL titer (i.e., plasma exchange and/or

intravenous immunoglobulins). Therefore, it is of paramount importance that the future sees the development of mechanistic studies.

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Website

- European Forum On Antiphospholipid Antibodies Multicentre Studies CAPS Registry. www.med.ub.es/MIMMUN/FORUM/CAPS.HTM