Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Review Article

Catastrophic antiphospholipid syndrome

Ignasi Rodriguez-Pintó[a], *Brenda López-Benjume*[b], *Gerard Espinosa*[b], *Ricard Cervera*[b,*]

[a] *Autoimmune Diseases Unit, Mutua de Terrassa Hospital, Terrassa, Catalonia, Spain*
[b] *Department of Autoimmune Diseases, Clínic Hospital, Barcelona, Catalonia, Spain*

ARTICLE INFO

Article history:
Received 30 November 2020
Accepted 18 February 2021
Available online 10 May 2021

Keywords:
Antiphospholipid syndrome
Catastrophic antiphospholipid syndrome
Antiphospholipid antibodies

ABSTRACT

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the development of thrombotic events and/or obstetric morbidity in the presence of antiphospholipid antibodies (aPL), such as the lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-β 2-glycoprotein I antibodies (aβ2 GPI). In 1992, Ronald A. Asherson described a very aggressive clinical variant of this syndrome characterized by the development of multiple thrombotic manifestations, simultaneously or in a short period of time. The term catastrophic APS was proposed and since then it is known by this name.

Síndrome antifosfolípido catastrófico

Palabras clave:
Síndrome antifosfolípido
Síndrome antifosfolípido catastrófico
Anticuerpos antifosfolípidos

RESUMEN

El síndrome antifosfolípido (SAF) es una enfermedad sistémica autoinmune, caracterizada por el desarrollo de eventos trombóticos y/o morbilidad obstétrica en presencia de anticuerpos antifosfolípidos (aPL), tales como el anticoagulante lúpico (AL), los anticuerpos anticardiolipina (aCL) o anticuerpos anti-ß2-glicoproteína I (aß2GPI). En 1992, Ronald A. Asherson describió una variante clínica muy agresiva de este síndrome, caracterizada por el desarrollo de múltiples manifestaciones trombóticas, de manera simultánea o dentro de un corto periodo de tiempo. Se propuso entonces el término SAF catastrófico y desde entonces se le ha conocido por ese nombre.

Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the development of thrombotic events and/or obstetric morbidity in the presence of antiphospholipid antibodies (aPL), such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-β_2-glycoprotein I antibodies (aβ_2GPI). In 1992, Ronald A. Asherson described a very aggressive clinical variant of this syndrome characterized by the development of multiple thrombotic manifestations, simultaneously or over a short period of time. The term

* *Corresponding author.*
E-mail address: rcervera@clinic.cat (R. Cervera).
https://doi.org/10.1016/j.rcreu.2021.02.004

catastrophic APS was proposed and since then it is known by this name.[1]

Catastrophic APS presents in less than 1% of all patients with APS; however, its high mortality – between 30% and 50% – and its complex clinical presentation justify a differential approach from the rest of patients with the classic APS variants.

The rare occurrence of this form of APS presentation has hindered its knowledge and research since it was initially described. This prompted the creation in 2000 of an international registry, known as "CAPS Registry". It gathers all cases published in the medical literature or reported to the registry coordinators and currently comprises almost 600 cases of catastrophic APS (available on-line at: https://ontocrf.grupocostaisa.com/en/web/caps/home).[1] Much of our current knowledge about this condition is derived from the data extracted from the cases included in this registry. This has allowed for improved definitions of its clinical manifestations and suggestions of therapeutic approaches.

Pathogenesis

The pathophysiological mechanisms of catastrophic APS are unknown. The reason why some patients with aPL do not develop thrombosis while others develop a single thrombotic event, and yet others develop multiple vascular occlusions that predominantly affect the small vessels over a short period of time and in multiple sites is still a matter of research.[2]

To explain these findings, the two-hit hypothesis was suggested according to which a patient with an increased susceptibility risk (first hit) might develop a thrombotic event when exposed to a trigger (second hit). Therefore, a precipitating factor is needed to develop the clinical event. This "second hit" would be another thrombophilic condition that increases the risk for clot formation. One of the most prominent features of the catastrophic APS is the association with a precipitating factor in more than 50% of cases.[1] Infections, surgeries and malignancies, among others, have been linked to the development of catastrophic APS.[3]

The clinical presentation of a catastrophic APS seems to be driven by two pathophysiologic processes that take place simultaneously. First, the multiorgan thrombosis that leads to multiorgan dysfunction and, second, the subsequent inflammation caused by the absence of blood supply. In fact, the presentation of catastrophic APS is similar to severe sepsis in which a systemic inflammatory response with multiorgan involvement occurs. Moreover, virtually all patients with sepsis have coagulation abnormalities.[4,5] These abnormalities range from subtle activation of coagulation only detectable by sensitive techniques, through somewhat subclinical stronger coagulation activation evident by a small decrease in platelet count and prolongation of global clotting times, to fulminant disseminated intravascular coagulation, characterized by widespread microthrombosis and profuse bleeding.[4] It has been suggested that the multiorgan thrombotic involvement that occurs in catastrophic APS, promotes a cytokine storm leading to an inflammatory state similar to the systemic inflammatory response in septic shock. Additionally, proinflammatory cytokines play a key role in the development of a procoagulant effect by prompting tissue factor expression on the mononuclear cells and endothelial cells, probably resulting in an increased risk for new thrombosis.

In 1998, Kitchens et al.[6] submitted the concept of thrombotic storm: patients develop a new thrombosis after a first thrombotic event. Continuous activation of coagulation by fresh thrombosis was hypothesized as the cause of the syndrome.[7] According to this theory, the blood clot would promote thrombin formation and impairment of fibrinolysis by an increase of type I plasminogen activator inhibitor (PAI). This would determine the consumption of natural anticoagulant proteins, such as protein C and anti-thrombin.

More recently, a more prominent role of platelets has been proposed. Platelet counts have been tested before and after a catastrophic event with a sharp decrease just before the event.[8] According to this hypothesis, a massive platelet consumption/deposition in the microcirculation leads to microthrombosis and subsequent organ failure. Therefore, the observed decrease in the β_2GPI concentration during the catastrophic phase indicates that platelets, β_2GPI, and aβ_2GPI antibodies would play a major role in catastrophic APS.[9]

Clinical features

The clinical manifestations of catastrophic APS have been classified into those associated with the ischemic organ and those that might be the consequence of the systemic inflammatory response triggered by cytokine release. The development of multiple thrombotic occlusions with microangiopathic anemia and thrombocytopenia are typical findings of patients with catastrophic APS. However, the clinical presentation is often difficult to differentiate from other causes of thrombotic microangiopathy.

Clinically, catastrophic APS affects mostly women (70%) in the fourth decade of life with an average age of 39 years, although cases have been described at all ages from birth to senescence.[1] Half of patients with this syndrome have not shown any other clinical manifestations of the disease in the past. One third of the patients meet the classification criteria for systemic lupus erythematosus (SLE) or have at least some clinical or immunological manifestations typical of this condition (lupus-like disease). This association is more frequent in middle-aged patients while it is less frequent in pediatric or elderly patients.[1] However, cases have been described in association with other autoimmune diseases.

The development of catastrophic APS is often associated with a precipitating factor. A trigger has been identified in more than 50% of patients. In order of frequency, infections account for 50% of cases, surgical procedures for 17%, malignancies for 16%, withdrawal of anticoagulation or low INR levels for 8%, obstetric complications for 8%, drugs for 5% and SLE flares for 3%.

Infections are the most frequent precipitating factors in pediatric age while hematological diseases and malignancies are more frequent in adulthood.[10] Most of the infections reported in patients with catastrophic APS are caused by gram-negative bacteria. These infectious agents might act co-signaling with aPL the toll-like receptors signal that sets-off the prothrombotic state that finally leads to catastrophic APS.

Not surprisingly, neoplasms known to be related to a thrombophilic state are the second most frequent precipitating factor in catastrophic APS. Several reasons have been submitted to explain the increased risk of thrombosis in cancer patients. For instance, blood flow stasis due to vascular invasion, immobilization, up-regulation of thrombophilic substances by both, tumor and endothelial cells, chemotherapy and central venous devices have been suggested as conditions that could account for the increased frequency of thrombosis in these patients.[11,12]

Clinically, catastrophic APS usually affects the kidneys (74% of cases), followed by the brain (56%), the lungs (55%), the heart (53%) and the skin (45%).[2]

Renal involvement is characterized by renal insufficiency, almost always with proteinuria that can be in the nephrotic range and with hematuria and hypertension. Often patients with renal involvement show signs of hemolysis, some meet thrombocytopenic thrombotic purpura criteria and, when a renal biopsy is performed, it often shows signs of thrombotic microangiopathy and in some cases, proliferative lupus nephritis features.

Pulmonary involvement affects almost 60% of cases, mainly as acute respiratory distress syndrome and lung embolism. Few patients develop pulmonary hemorrhage. A similar percentage of patients develop central nervous system involvement with encephalopathy, stroke or seizures sometimes leading to coma. A smaller number of patients develop cardiac complications that manifest as heart failure and myocardial infarction. Valvular heart disease has been shown in one third of the patients with catastrophic APS. Skin microangiopathy presents clinically as livedo reticularis but some evolve to skin necrosis, ulcers or digital ischemia. One third of patients with catastrophic APS develop peripheral vascular disease, often venous, but a half of them have arterial vessel thrombosis. Other organ systems less commonly involved are the gastrointestinal tract, the spleen, the adrenal glands, the pancreas, the retina and the bone marrow.

Laboratory manifestations

Laboratory tests show thrombocytopenia and sometimes the presence of schistocytes and signs of microangiopathic hemolytic anemia can be observed. In terms of aPL, LA was present in 83% of the episodes, IgG isotype of the aCL in 81%, IgM aCL in 51%, aβ-GPI in 75% and IgM aβ-GPI in 44%.

Diagnosis and differential diagnosis

The differential diagnosis of patients with multiple thrombosis is not easy. Most cases of catastrophic APS present as microangiopathic storm rather than large vessel occlusion, although cases with large vessel involvement have been reported. However, the presence of multiple occlusions should always be suspicious of a thrombophilic state. Indeed, very often there could be an interplay of several thrombophilic events, leading to thrombosis in multiple body sites.

The diagnosis of catastrophic APS is challenging since it is a rare disease and most physicians fail to include this condition in their initial differential diagnosis; however, when they do, several other mimickers must be ruled out, which makes the final diagnosis even more difficult. A major diagnostic drawback is the lack of specific tests to better subgroup catastrophic APS patients, as well as to differentiate them from those with other thrombotic microangiopathic conditions.

Based on the catastrophic APS classification criteria, a definite diagnosis of catastrophic APS is made when three or more organs develop thrombotic episodes over less than one week and microvascular thrombosis is shown in at least one organ in patients with persistent aPL. However, some APS patients develop microvascular complications due to the presence of aPL such as diffuse pulmonary hemorrhage or renal thrombotic microangiopathy, but these are beyond the scope of our current understanding of catastrophic APS.

The differential diagnosis in a patient with thrombotic microangiopathy is broad. Thrombotic microangiopathy describes a microvascular disease with ischemia due to fibrin formation and platelet aggregation resulting in small vessel occlusions. This state might be associated with several other conditions such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), atypical HUS, disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), Haemolysis Elevated Liver Enzymes Low Platelet (HELLP) syndrome, sepsis, and scleroderma renal crisis.[13]

For the differential diagnosis of catastrophic APS, the physician should perform several blood tests to rule out other mimickers, such as aPL, platelet count, schistocytes count, anti-platelet factor-4 antibodies, ADAMTS13, fibrinogen levels, anti-complement factor H antibody or tissue biopsies under immunofluorescence for complement identification. Even when all of these tests are available, it is still challenging to determine which of the thrombotic microangiopathic conditions is the major driver behind the clinical presentation.

Treatment

Therapeutic management of patients with catastrophic APS may be complicated by the concomitant presence of thrombosis, hemorrhagic risk factors (e.g., thrombocytopenia, DIC) or the need for surgical procedures.

Currently, the treatment suggested is based on an interdisciplinary approach that includes the support therapy usually provided in the ICU. External ventilation support and hemodialysis may be necessary, but in general, just close hemodynamic and respiratory control is required. Classical thrombotic risk factors should be controlled and avoided whenever possible. It is better to adjourn any surgical procedures if appropriate, although sometimes removal of necrotic tissue may be required.

Additionally, effective treatment of any precipitating factors is important to break the vicious circle. Antibiotic treatment should be administered if infection is suspected since it may be the triggering factor.

With regards to specific treatment, it is currently accepted that the best first-line treatment is triple therapy that includes treatment with anticoagulants, corticosteroids, and plasma exchange and/or intravenous immunoglobulins. This

approach has been reported to improve patient survival by 45%.[14]

Heparin anticoagulation is the backbone of catastrophic APS treatment. Inhibition of ongoing clot formation and the ability to break up existing clots are critical to stop the evolving disease. Furthermore, its anti-inflammatory activity and its ability to inhibit aPL binding to target cells and inhibit complement deposition could explain its effectiveness in patients with catastrophic APS. Most catastrophic APS patients are initially treated with unfractionated heparin because anticoagulation can be reversed in case any invasive procedures have to be conducted during ICU admission. Subsequently, the switch is usually made to low molecular weight heparin (LMWH) and finally to vitamin K antagonist.

Steroids are used as anti-inflammatory drugs based on their beneficial effects to overcome the systemic inflammatory response elicited by the necrotic tissue found in ischemic tissue. Additionally, they are thought to inhibit nuclear translocation of proinflammatory molecules elicited by aPL when they bind to endothelial cells and have been shown to decrease aPL titters. Steroids are usually administered as intravenous pulses of 500–1000 mg/day for 1–3 days. Then, most physicians continue steroid treatment in a daily oral dose until the patient is discharged and then taper the dose until it can be safely withdrawn.

Plasma exchange is a technique that removes large quantities of plasma and replaces it with fresh frozen plasma or albumin solution. In catastrophic APS, this is used based on the rationale that plasma exchange removes aPL and cytokines from the plasma stream restoring the natural anticoagulants with fresh frozen plasma. This treatment is especially recommended for patients with catastrophic APS that present clinical features of microangiopathic thrombosis. The American Society for Apheresis recommends plasma exchange with a grade of evidence 2C. However, there is no consensus on the replacement fluid of choice in these patients but, probably a combination of plasma and albumin may deliver the optimal risk-benefit balance to minimize potentially serious and undesirable side effects and the necessary balance in terms of coagulation factors.

The mechanism of action of intravenous immunoglobulins is unknown. However, they have been proven to be beneficial in a variety of inflammatory conditions. A high intravenous concentration of antibodies may probably result in lymphocyte Fc receptor overload, inhibiting the pathologic autoantibodies that trigger the inflammatory cascade and increasing their clearance.

Intravenous immunoglobulins are usually well tolerated; however, thromboembolic events and acute renal failure have been reported following their administration. Close monitoring is advisable for early detection of complications, particularly in cases in which anticoagulation therapy has to be withhold, and in elderly patients with high blood pressure, diabetes or hypercholesterolemia for whom a 5-day infusion regimen may be more appropriate.

Cyclophosphamide is recommended in cases of severe catastrophic APS in patients with SLE. Cyclophosphamide is a nitrogen mustard-alkylating agent that binds to deoxyribonucleic acid in the immune cells and causes cell death. In catastrophic APS, lymphoid tissue suppression may decrease aPL titers and cytokine levels, thus leading to a downregulation of the storm.

The use of new therapeutic agents such as rituximab or eculizumab has been suggested in refractory cases, although these should currently be considered as second line therapies.[15,16]

Prognosis

The mortality rate of catastrophic APS is high. The first studies observed a mortality rate of around 50%, although more recent studies have reported a reduction in mortality down to 36%.[2,17,18]

Moreover, at the time of diagnosis of catastrophic APS, patients with SLE-associated characteristics have a higher mortality risk after adjusting for age, sex, organ involvement, and treatment.[17]

The main causes of mortality are infections (20%), followed by stroke (19%), cardiac failure (17%) and multiorgan failure (17%). Almost half of the patients die due to thrombotic events, such as stroke, or as a result of systemic inflammatory response syndrome manifestations, such as acute respiratory distress syndrome or encephalopathy.[19]

Catastrophic APS usually occurs as a monophasic disease and most patients surviving a catastrophic episode do not relapse and remain symptom-free with anticoagulation. However, some patients develop subsequent APS-related events.[20] A few patients experience recurrent catastrophic APS events. Interestingly, these patients frequently exhibit microangiopathic hemolytic anemia laboratory features.[21]

Conflict of interest

Authors declare to have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.02.004.

REFERENCES

1. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15:1120–4.
2. Ortega-Hernandez O-D, Agmon-Levin N, Blank M, Asherson RA, Shoenfeld Y. The physiopathology of the catastrophic antiphospholipid (Asherson's) syndrome: compelling evidence. J Autoimmun. 2009;32:1–6.
3. Rodríguez-Pintó I, Soriano A, Espinosa G, Shoenfeld Y, Cervera R. Catastrophic antiphospholipid syndrome: an orchestra with several musicians. Israel Med Assoc J: IMAJ. 2014;16:585–6.
4. Levi M. The coagulant response in sepsis. Clin Chest Med. 2008;29:627–42, viii.
5. Levi M, Schultz M, van der Poll T. Sepsis and thrombosis. Semin Thromb Hemost. 2013;39:559–66.

6. Kitchens CS. Thrombotic storm: when thrombosis begets thrombosis. Am J Med. 1998;104:381–5.
7. Ortel TL, Kitchens CS, Erkan D, Brandão LR, Hahn S, James AH, et al. Clinical causes and treatment of the thrombotic storm. Exp Rev Hematol. 2012;5:653–9.
8. Joseph JE, Harrison P, Mackie IJ, Isenberg DA, Machin SJ. Increased circulating platelet-leucocyte complexes and platelet activation in patients with antiphospholipid syndrome, systemic lupus erythematosus and rheumatoid arthritis. Br J Haematol. 2001;115:451–9.
9. Banzato A, Pengo V. Clinical relevance of β2-glycoprotein-I plasma levels in Antiphospholipid Syndrome (APS). Curr Rheumatol Rep. 2014;16.
10. Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, Puerta JG, Espinosa G, et al. The role of malignancies in patients with catastrophic anti-phospholipid (Asherson's) syndrome. Clin Rheumatol. 2007;26:2109–14.
11. Font C, Vidal L, Espinosa G, Tàssies D, Monteagudo J, Farrús B, et al. Solid cancer, antiphospholipid antibodies, and venous thromboembolism. Autoimmun Rev. 2011;10:222–7.
12. Vassalo J, Spector N, de Meis E, Rabello LS, Rosolem MM, do Brasil PE, et al. Antiphospholipid antibodies in critically ill patients with cancer: a prospective cohort study. J Crit Care. 2014;29:533–8.
13. Cervera R, Rodríguez-Pintó I, Espinosa G. The diagnosis and clinical management of the catastrophic antiphospholipid syndrome: a comprehensive review. J Autoimmun. 2018;92:1–11.
14. Rodríguez-Pintó I, Espinosa G, Erkan D, Shoenfeld Y, Cervera R, CAPS Registry Project Group. The effect of triple therapy on the mortality of catastrophic anti-phospholipid syndrome patients. Rheumatology. 2018;57:1264–70.
15. Berman H, Rodríguez-Pintó I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev. 2013;12:1085–90.
16. Espinosa G, Berman H, Cervera R. Management of refractory cases of catastrophic antiphospholipid syndrome. Autoimmun Rev. 2011;10:664–8.
17. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. 2006;54:2568–76.
18. Espinosa G, Bucciarelli S, Asherson RA, Cervera R. Morbidity and mortality in the catastrophic antiphospholipid syndrome: pathophysiology, causes of death, and prognostic factors. Semin Thromb Hemost. 2008;34:290–4.
19. Cervera R, Tektonidou MG, Espinosa G, Cabral AR, González EB, Erkan D, et al. Task force on catastrophic antiphospholipid syndrome (APS) and non-criteria aps manifestations (I): Catastrophic APS, APS nephropathy and heart valve lesions. Lupus. 2011;20:165–73.
20. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis. 2003;62: 530–3.
21. Espinosa G, Rodríguez-Pintó I, Gomez-Puerta JA, Pons-Estel G, Cervera R. Relapsing catastrophic antiphospholipid syndrome potential role of microangiopathic hemolytic anemia in disease relapses. Semin Arthritis Rheum. 2013;42:417–23.