

Update on the Diagnosis, Treatment, and Prognosis of the Catastrophic Antiphospholipid Syndrome

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Abstract The catastrophic antiphospholipid syndrome (APS) is a potentially life-threatening condition, the diagnosis of which requires a high degree of clinical awareness on the part of attending physicians. Patients with APS present with 1) clinical evidence of multiple organ involvement developed over a very short time; 2) histopathologic evidence of multiple small-vessel occlusions; and 3) laboratory confirmation of the presence of antiphospholipid antibodies, usually in high titer. A combination of anticoagulants, corticosteroids, intravenous immunoglobulins, and plasma exchanges is the basic treatment for all patients with this severe condition. Unfortunately, despite current therapies, the mortality rate is still high (around 30%). However, once patients with catastrophic APS have recovered, they usually follow a stable course with continued anticoagulation and few patients present with a relapse of the catastrophic episode.

Keywords Catastrophic antiphospholipid syndrome · Antiphospholipid antibodies · Anticardiolipin antibodies · Lupus anticoagulant

Introduction

In 1992, the adjective *catastrophic* was added to define an accelerated form of the antiphospholipid syndrome (APS) and to highlight a new subset of this syndrome, resulting in often fatal multiorgan failure [1]. This subset is now also referred to as Asherson's syndrome to honor Ronald A.

Asherson—who recently passed away—for his impressive work on this condition [2]. Patients with catastrophic APS present with 1) clinical evidence of multiple organ involvement developing in a very short time; 2) histopathologic evidence of multiple small-vessel occlusions; and 3) laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titer. Further, a precipitating event (mainly infections) precede about 60% of catastrophic episodes [3–5].

Although less than 1% of patients with APS develop this complication, its potentially lethal outcome emphasizes its importance in clinical medicine today [6]. Most patients with catastrophic APS present to intensive care units (ICUs) with multiorgan failure and, 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.

It is still unclear why some patients develop recurrent thromboses, mainly of large vessels (simple or classic APS), whereas others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels (catastrophic APS). General factors implicated in the causation of thromboses—including prolonged bedrest, sedentary situations (e.g., long-haul flying), dyslipidemias, diabetes mellitus, nephrotic syndrome, and obesity—do not seem to be important in the pathogenesis of the catastrophic APS and, interestingly enough, patients suffering from the hereditary coagulopathies (e.g., protein C and S or antithrombin III deficiencies and factor V Leiden or prothrombin gene mutations) also do not seem prone to this complication. It seems to be a primary autoimmune situation associated with high levels of aPL and, in most cases, also accompanied by other severe autoimmune disturbances, such as severe thrombocytopenia or microangiopathic hemolytic anemia, which can complicate the clinical picture and, hence, diagnosis and treatment.

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Diagnosis

The heterogeneity of different forms of clinical presentation led to the development of consensus criteria for the definition and classification of these patients. In September 2002, a presymposium workshop during the Tenth International Congress on aPL established preliminary criteria for the classification of catastrophic APS [7] that were then validated (Table 1) [8].

At least 53% of patients seem to have developed catastrophic APS following an identifiable trigger factor, with the most common factors being infections (22%); surgical procedures (even minor interventions [e.g., dental extractions]; 10%); anticoagulation problems (drug withdrawal or low international normalized ratio [INR]; 8%); and medications (7%) [9••]. Diagnostic difficulties may arise, as infections may result in the generation of aPL. Therefore, a previous history of thrombotic events (e.g., deep vein thrombosis, stroke, myocardial infarction, or recurrent fetal loss in women) or preexisting autoimmune disease (systemic lupus erythematosus [SLE], particularly) is of great importance for an accurate diagnosis [10].

Table 1 Preliminary criteria for the classification of catastrophic APS

1. Evidence of involvement of 3 or more organs, systems, and/or tissues. 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).
2. Development of manifestations simultaneously or in <1 wk.
3. Confirmation by histopathology of small-vessel occlusion in at least one organ or tissue. For histopathologic confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies). If the patient had not been previously diagnosed as having an antiphospholipid syndrome (APS), the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 wk apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS [9].

Definite catastrophic APS

All four criteria

Probable catastrophic APS

All 4 criteria, except for only 2 organs, systems, and/or tissues involvement.

All 4 criteria, except for the absence of laboratory confirmation at least 6 wk apart caused by early death of a patient never previously tested for aPL before the catastrophic APS event.

Criteria 1, 2, and 4.

Criteria 1, 3, and 4, and the development of a third event in >1 wk but <1 mo, despite anticoagulation.

International Registry

Because of the rarity of this syndrome, an international registry of patients with catastrophic APS (CAPS Registry) was created in 2000 by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients [11]. This registry documents the entire clinical, laboratory, and therapeutic data of all published cases with catastrophic APS, as well as of many additional patients whose data have been fully registered. This registry can be freely consulted online (<http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM>) and it is expected that the periodical analysis of these data will increase the knowledge of this condition.

Clinical Features

Detailed analysis of the first 280 patients included in the CAPS Registry shows that 72% are women, with a mean age of 37 years (range, 11–60 y). Forty-six percent suffered from primary APS, 40% from SLE, 5% from lupus-like disease, and 9% from other autoimmune diseases. Patients may develop catastrophic APS *de novo*, without any previous history of thrombosis (46%). However, it can be seen that previous deep vein thrombosis, fetal loss, or thrombocytopenia are the most frequently encountered aPL-associated previous manifestations [9••].

The clinical manifestations of catastrophic APS mainly depend on two factors: 1) organs affected by the thrombotic event and the extent of the thrombosis; and 2) manifestations of the systemic inflammatory response syndrome (SIRS), presumably caused by excessive cytokine release from affected and necrotic tissues. Thus, there are two separate and distinct sets of manifestations, each of which requires effective therapy. Therefore, distinct differences exist between patients with simple/classic APS and those with catastrophic APS (Table 2) [12–16].

Thrombotic Manifestations

Intraabdominal thrombotic complications affecting the kidneys, adrenal glands, splenic, intestinal, and mesenteric or pancreatic vasculature are most commonly encountered, with patients frequently presenting with abdominal pain or discomfort. Renal disease is present in 71% of patients, but patients do not succumb from uremia. Pulmonary complications are next in frequency (64%), with acute respiratory distress syndrome (ARDS) and pulmonary emboli accounting for the majority, whereas pulmonary hemorrhage, microthrombi, pulmonary edema, and infiltrates occur in a minority of patients. Cerebral manifestations (infarcts,

Table 2 Distinct differences between catastrophic and simple antiphospholipid syndrome

1. Rapid development of predominant small vessel occlusions following an identifiable trigger factor in 50% of cases
2. Unusual organs affected (e.g., ovaries, uterus, testes, bone marrow)
3. High frequency of pulmonary complications such as acute respiratory distress syndrome or diffuse alveolar hemorrhage (uncommon)
4. Patients often present with abdominal pain because of intraabdominal vascular complications affecting bowel, gall bladder, pancreas, adrenal glands, or spleen
5. Early loss of consciousness complicating systemic inflammatory response syndrome
6. Serologic evidence of disseminated intravascular coagulation without hemorrhagic manifestations in one fifth of patients. This may cause problems in differential diagnosis.
7. Severe thrombocytopenias, which may result in hemorrhage (particularly cerebral)
8. High frequency of hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome in pregnancy-associated cases
9. Poor prognosis

encephalopathy, seizures, or cerebral venous occlusions) also occur frequently (62%). Small-vessel cerebrovascular occlusive disease is probably more common than has been reported and may cause the encephalopathic features of the syndrome. Cardiac problems occur in 51%, with valve defects (mitral, aortic) often present. Myocardial infarctions are a presenting feature in 25% of cases. Skin complications, such as livedo reticularis, purpura, and skin necrosis are next, occurring in 50% of patients.

Additionally, other organs may occasionally be 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 [9••].

Manifestations of SIRS

This multisystem inflammatory syndrome is caused by cytokine activation and, although actual measurements of cytokine levels in very ill patients with catastrophic APS have not been undertaken, it is assumed that this process is ongoing in the acute phase of the illness. Certainly, some non-thrombotic manifestations, particularly ARDS [17], are frequently encountered in SIRS. Cytokines involved include tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, and macrophage-migration inhibitory factor. These cytokines are responsible not only for ARDS but also for the cerebral edema, which may be a factor in the initial confusion and deterioration of consciousness in these patients, as well as myocardial dysfunction encountered. IL-18 is also implicated in acute lung inflammation via increasing neutrophil migration and lung vascular permeability; this cytokine may also be implicated in the pathogenesis of ARDS. This process

may be superimposed on an underlying infective process, which itself may have been instrumental in triggering catastrophic APS. Therefore, strong consideration should be given to the early administration of antibiotic therapy.

ARDS associated with septic shock and severe trauma is often complicated by disseminated intravascular coagulation (DIC), a not infrequent finding in patients with catastrophic APS [18].

Laboratory Features

Thrombocytopenia was detected in 46% of cases from the CAPS Registry. One third have evidence of hemolysis and 15% have some features of disseminated intravascular coagulation (DIC) [9••]. Schistocytes, if present, are usually scanty, unlike the abundant numbers seen in patients with thrombotic thrombocytopenic purpura (TTP) [19]. IgG anticardiolipin antibodies are usually positive, with IgM being less frequent. Patients with SLE demonstrate positive antinuclear antibodies, antibodies to double-stranded DNA, and antibodies to extractable nuclear antigens.

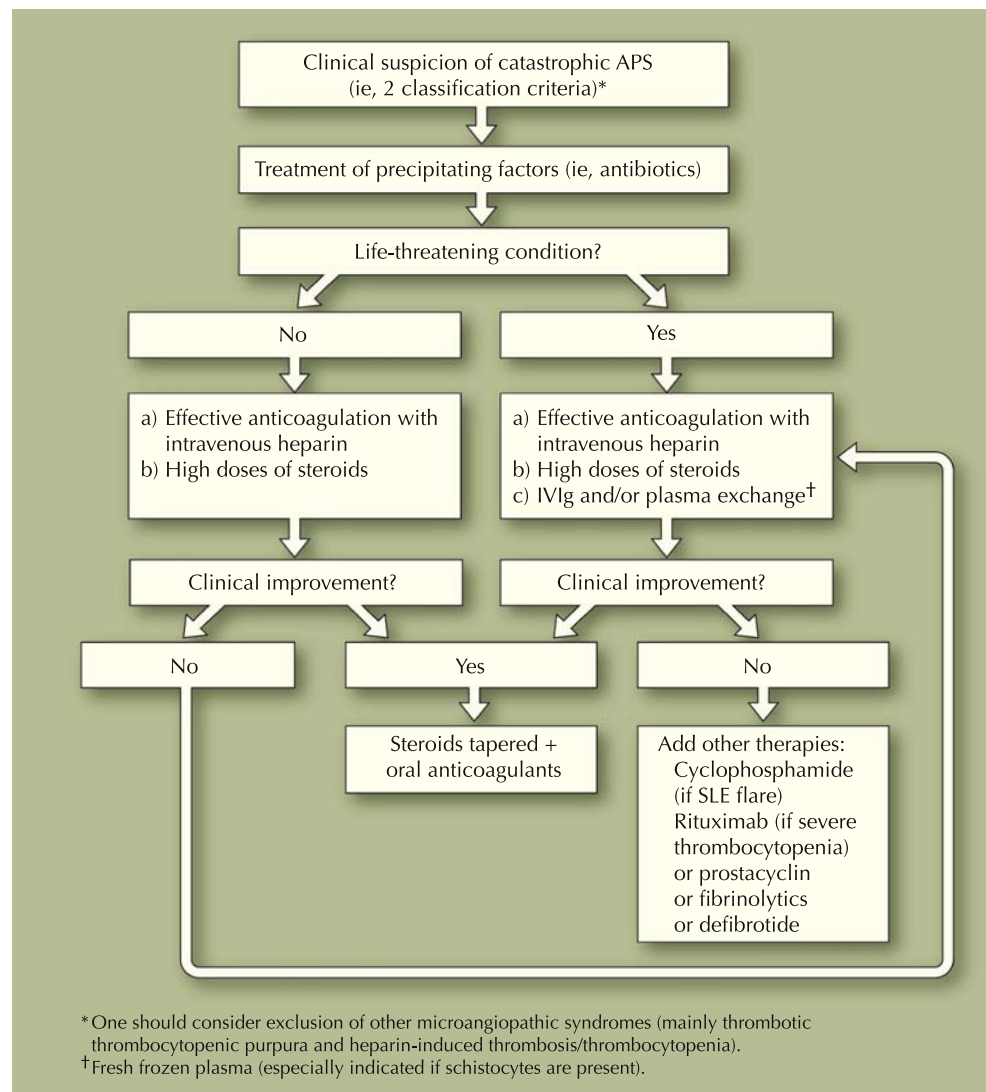
Relationship with Other Microangiopathic Syndromes

It has recently been suggested that a continuum of conditions, all demonstrating aPL, may exist, comprising some patients with TTP; hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; or catastrophic APS. A new term, *microangiopathic APS*, has been proposed to embrace this group of patients [20–23]. Certainly, patients with TTP and catastrophic APS may share similar, but not identical, triggering factors (e.g., infections, drugs, carcinomas, occurrence during pregnancy and the puerperium), similar clinical manifestations with small-vessel occlusions predominating, the presence of hemolytic anemia and thrombocytopenias (often severe), and the same therapies have been advised (e.g., plasma exchanges). As we now know, both conditions may be relapsing. In patients with HELLP syndrome, the liver appears to be the main target organ affected and hepatic infarctions are not uncommon. Peripheral vascular occlusions are, however, uncommon.

Treatment

Management of the catastrophic APS is challenging for attending physicians. Early diagnosis and aggressive therapies are essential to “rescue” such patients from succumbing to this potentially fatal condition. Unfortunately, despite all therapies advised, the current mortality rate is extremely high (around 30%) [5]. A treatment guideline algorithm for the catastrophic APS has been

Fig. 1 Treatment algorithm of catastrophic antiphospholipid syndrome (APS). IVIg intravenous immunoglobulins, SLE systemic lupus erythematosus



proposed (Fig. 1) [7]. Treatment may be divided into three major categories: 1) prophylactic therapy; 2) specific therapies; and 3) nonspecific therapies.

Prophylactic Therapy

As it is unclear why some patients with APS develop recurrent episodes and others (a minority) suffer multiorgan failure, in any APS patient, therefore, particular attention should be given to the following guidelines: 1) any infection, however trivial, should be energetically treated with the appropriate antibiotics; 2) APS patients undergoing surgical procedures, however minor, should all receive parenteral anticoagulation during the procedure instead of remaining on warfarin; 3) the puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants (e.g., subcutaneous heparin); and 4) severe SLE flares, although uncommonly associated with catastrophic APS, should also be treated with parenteral anticoagulation.

Specific Therapies

First-line Therapies

Anticoagulants are usually provided in the form of heparin, the mainstay of treatment in patients with catastrophic APS. The CAPS Registry analysis also confirms the lower rate of mortality in anticoagulated patients compared with those not receiving anticoagulants (36.9% vs 77.8%, respectively; $P < 0.0001$) [4]. It is important to note that the beneficial effect of heparin in APS patients is likely beyond the inhibition of thrombin generation and, based on APS murine models, heparin also inhibits complement activation [24]. It is usually administered for 7 to 10 days followed by oral anticoagulants to an INR of about 3.

Corticosteroids should be administered for a minimum of 3 days (1,000 mg/d of methylprednisolone) but may require longer continuation depending on patient response. It should be noted that corticosteroids alone do not improve

outcomes upon analysis of the CAPS Registry. However, corticosteroids inhibit nuclear factor (NF)- κ B, which is an important mediator in both SIRS and aPL-mediated thrombosis [25]. Thus, unless an absolute contraindication exists, corticosteroids should be considered in catastrophic APS patients.

Second-line Therapies

Plasma exchanges remove aPL (most likely transiently) as well as cytokines, TNF- α , and complement products. Based on a literature search of plasma exchange use in patients with catastrophic APS [26], as well as the CAPS Registry analysis [5], the use of plasma exchanges clearly improves patient survival. It is important to note that most, but not all, of reported patients with catastrophic APS received plasma exchanges together with fresh frozen plasma (FFP) as the replacement fluid (FFP contains natural anticoagulants, such as antithrombin III, and also clotting factors). It is unknown if plasma exchanges with a different replacement fluid, such as human albumin solution, would result in different outcomes. It should be noted that plasma exchanges should be the treatment of choice in patients with features of microangiopathic hemolytic anemia in which small-vessel occlusive disease is emphasized. The most often used procedure is removal of 2 to 3 liters of plasma for a minimum of 3 to 5 days [19].

The recommended daily dose of intravenous immunoglobulin (IVIg) is 0.4 gm/d/kg body weight for 4 to 5 days. It may be specifically helpful in those patients who have severe thrombocytopenia but also possibly decreases antibody synthesis and increases the catabolism of circulating immunoglobulins in others [27]. IVIg is usually well tolerated, but a few reports exist of thromboembolic events after IVIg infusions and a few cases have been described regarding the association of acute renal failure with IVIg therapy. There is no evidence, judging from the analysis of treated patients with catastrophic APS, that IVIg on its own improves survival, although its combination with plasma exchanges may be more effective and can be recommended for the most severe cases. However, physicians should be aware that thrombosis with IVIg use has been reported when high doses of IVIg are delivered rapidly, especially in elderly patients with comorbidities such as diabetes, hypertension, or hypercholesterolemia [27]. Thus, when anticoagulation needs to be interrupted (e.g., for bleeding), physicians should be cautious with IVIg use. Avoiding other products with high osmolality, reducing the rate of IVIg infusion to avoid large osmolar load delivery, hydration, and using nonsucrose IVIg products (especially in patients with renal failure) are strategies that can reduce thrombosis risk [27]. When IVIg and plasma exchanges are used simultaneously in the same patient, usually IVIg is

administered after the last day of the plasma exchange to prevent the removal of IVIg by plasma exchange.

Third-line Therapies

Third-line therapies comprise several compounds that have either been used fairly often (cyclophosphamide) or only in a few cases (rituximab, prostacyclines, ancrod, defibrotide) and may have contributed to the recovery of the patient.

Cyclophosphamide may be beneficial in catastrophic APS patients with SLE but not in primary APS patients, which has been demonstrated in a recent multivariate analysis of the CAPS Registry [28]. Of note, these results can be confounded because the timing of cyclophosphamide was earlier in the course of SLE-associated catastrophic APS management than in primary catastrophic APS. Nevertheless, physicians should have a lower threshold to use cyclophosphamide in catastrophic APS patients with SLE, especially in the presence of active lupus disease.

Rituximab is an anti-CD20 monoclonal antibody that has been successfully used in a limited number of APS patients with thrombocytopenia [29–31] or autoimmune hemolytic anemia [30]. However, it is not possible to evaluate the antithrombotic effects of rituximab because rituximab-treated catastrophic APS patients also received anticoagulants and multiple immunosuppressive agents.

Prostacyclin, a potent inhibitor of platelet aggregation, would theoretically be of benefit in the ongoing clotting process. It is also a vasodilator. The dose is 5 ng/kg/min for 7 days. Ancrod is a powerful fibrinolytic that also corrects plasminogen activator deficiencies. It is seldom used today [32]. Defibrotide is an alkali metal salt of single-stranded DNA that has been shown to act as potent inhibitor of endothelin I, thrombin-induced platelet aggregation, and thromboxane synthesis, as well as a potent inhibitor of fibrin clot formation. Because of its polypharmacologic properties, it may have an important future role in the management of refractory patients with catastrophic APS and has been used successfully in one patient [33].

Other fibrinolytics (e.g., streptokinase, urokinase, tissue plasminogen activators) theoretically may play an important role in the management of refractory patients with catastrophic APS but may be associated with hemorrhagic complications. Their judicious use is probably justified in difficult cases in which a life-threatening situation is imminent because of ongoing clotting.

Nonspecific Therapies

Most patients present to the ICU because multiorgan failure has supervened. If renal failure is present, hemodialysis may be required. Mechanical ventilation for respiratory failure is often indicated, particularly if ARDS is present. Inotropic

drugs for circulatory failure must be administered. Severe hypertension caused by renal vascular occlusive disease may necessitate aggressive antihypertensive therapy. Parenteral steroids are necessary if hypotension is present that is caused by myocardial depression, microangiopathy of small cardiac vessels, or hemorrhagic infarction of the adrenal glands. Such hypotension is another reason for inotropic drugs.

Additionally, ICU physicians should be aware of the challenges of catastrophic APS management. The limitation of intravascular instrumentation, especially arterial, is crucial as these procedures can increase the risk of new clots. Other ICU-related recommendations include use of low tidal volume ventilation and maintenance of inspiratory plateau pressure less than 30 cm water in patients with ARDS, positioning of the head of the bed for the intubated patients at 45° to reduce the incidence of ventilator-associated pneumonia, tight glyce-mic control, and stress ulcer prophylaxis with H₂-receptor blockers or proton pump inhibitors [34].

Prognosis

Poor Prognostic Factors

To identify the prognostic factors in patients with catastrophic APS, our group recently compared the demographic, clinical, and immunologic features of patients who died with those who survived [35]. Older age (>36 y), SLE, pulmonary and renal involvement, and positive antinuclear antibody titer were associated with higher mortality in patients with catastrophic APS. However, catastrophic APS was usually accompanied by nonthrombotic complications, such as sepsis, that directly affect the prognosis. No risk-stratified prognostic studies exist.

Autopsy Analysis

Based on the analysis of the initial 250 CAPS Registry patients, 114 of 250 patients did not survive and 59 of 114 underwent autopsy. Cerebral involvement was the main cause of death (mainly stroke), followed by cardiac involvement and infection. Microthrombosis was the most common finding at autopsy (89%). Of note, as demonstrated by the autopsy findings, microthrombosis is a major feature that differentiates classic APS from catastrophic APS [5].

Long-term Outcomes

The only study about long-term prognosis of patients who survive the initial catastrophic event demonstrated that 66% of patients remain free of thromboses and 17% develop further APS-related manifestation during a follow-up of about 6 years [36].

Relapsing Catastrophic APS

As opposed to the similar condition of TTP, in which relapses frequently occur, recurrent or “relapsing” catastrophic APS is distinctly uncommon. In the CAPS Registry, relapses were reported in 9 of 280 (3%) patients. A total of 35 episodes of catastrophic APS were described in these patients (6 patients presented 2 recurrences; 2 patients suffered 3 relapses; and 1 patient developed 17 relapses). Mean age of patients was 45±16 years. Five (55%) patients were women and eight (88%) patients suffered from primary APS. A precipitating factor was identified in nine episodes (55% infections; 45% related with anticoagulant treatment). Brain, kidney, heart, and lung were the most common organs involved. Interestingly, laboratory features of microangiopathic hemolytic anemia (schistocytes) were present in 13 of 18 (72%) episodes. The mortality rate was 33%. Therefore, although relapse is a rare complication in patients with catastrophic APS, the presence of schistocytes could be associated with the development of relapses [37].

Conclusions

Catastrophic APS is an uncommon but potentially life-threatening condition requiring a high degree of clinical awareness. It is clear that most patients with this condition manifest microangiopathy (ie, occlusive vascular disease affecting predominantly small vessels of different organs, particularly kidney, lungs, brain, heart, and liver), with a minority of patients only experiencing the typical large-vessel-type occlusions seen in the simple APS. A basic and sudden disturbance of the coagulation or fibrinolytic systems induced by the aPL is highly probable in this group of patients, but precipitating factors remain unknown in most of them. The therapeutic connotation is that this may be corrected with the combination of anticoagulation plus steroids plus attempts at achieving a prompt reduction of aPL titer (ie, plasma exchanges and IVIg).

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