# 16 Catastrophic Antiphospholipid Syndrome

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## Introduction

The syndrome of multiple vascular occlusions associated with high titer antiphospholipid antibodies (aPL) is known as catastrophic antiphospholipid syndrome (CAPS). Although antiphospholipid syndrome (APS) is typically characterized by thrombotic events that either occur singly or, when recurrent, are seen many months or even years apart, some patients with this syndrome may develop widespread, non-inflammatory vascular occlusions.

The first reports of patients with multiple non-inflammatory vascular occlusions appeared in 1974, by Dosekun [1], and in 1987, by Ingram [2]. However, it was not until Greisman reported in 1991 on two patients with *"acute, catastrophic, widespread non-inflammatory visceral vascular occlusions associated with high titer antiphospholipid antibodies"* that the full spectrum of clinical features associated with aPL became appreciated [3]. This spectrum was outlined in an editorial by Harris and Bos [4] that accompanied the Greissman report [3]. The authors described two additional patients with "acute disseminated coagulopathy–vasculopathy associated with antiphospholipid syndrome" and identified three cohorts of patients with these antibodies. They recognized that aPL may be "asymptomatic" and observed in patients free of thrombosis or associated with one or two episodes of thrombosis typically involving only one artery or vein at a time with long periods (months to years) free of occlusive events. Alternatively, aPL may confer a risk for an ominous disorder characterized by multiple, typically three or more, wide-spread thrombotic occlusions often with marked ischemic changes in the extremities, livido reticularis, as well as renal, cerebral, myocardial, pulmonary, and other visceral organ thrombotic vasculopathy. Asherson, describing 10 such patients in an article published in 1992, first proposed the term *catastrophic APS* [5].

Over the past 12 years, several reviews of CAPS have been published [6–9]. It is estimated that CAPS comprises 1% of cases of APS syndrome. To date, approximately 250 cases are described in the literature. In 2000, an international registry of patients with CAPS was created by the European Forum on Antiphospholipid Antibodies and can be referenced via the internet at http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM, consisting of 220 patients as of August 1, 2004 [10]. Additionally, a set of classification criteria for CAPS was presented at the 10th International Congress on Antiphospholipid Antibodies in 2002 at Taormina, Sicily (Table 16.1) [11–13].This chapter will describe the clinical, therapeutic, and pathogenic aspects of this condition.

**Table 16.1.** Criteria for the classification of catastrophic antiphospholipid antibody syndrome.

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| Criteria for the classification of catastrophic antiphospholipid antibody syndrome: |
| 1. Evidence of involvement of three or more organs, systems, or tissues. |
| 2. Development of manifestations simultaneously or in less than a week. |
| 3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.[†] |
| 4. Laboratory confirmation of the presence of aPL (lupus anticoagulant or aCL). |
| Definite catastrophic antiphospholipid antibody syndrome |
| All four criteria. |
| Probable catastrophic antiphospholipid antibody syndrome |
| All four criteria, except only two organs, systems, or tissues are involved. |
| All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart because of the early death of a patient never previously tested for aPL before the catastrophic event. |
| Criteria 1, 2, and 4 antiphospholipid. |
| Criteria 1, 3, and 4, and the development of a third event in more than a week, but less than a month, despite anticoagulation. |

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 (greater than 190/110 mm Hg), or proteinuria (greater than 500 mg/24 hours).

[†]For histopathologic confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally. If the patient has not been previously diagnosed as having APS, the laboratory confirmation requires that the presence of aPL must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed clinical criteria for the classification of definite APS.

## Clinical Aspects

Patients with catastrophic APS can be broadly categorized into those with systemic lupus erythematosus (SLE), "lupus-like" illness satisfying two to three of the modified ACR criteria, primary APS, or secondary to an another autoimmune, connective tissue disease such as rheumatoid arthritis, scleroderma, dermatomyositis, polychondritis, primary, systemic necrotizing vasculitis, inflammatory bowel disease, or Behcet's syndrome [14–21].

## Demographic Characteristics

Amongst 220 patients with catastrophic APS in the registry, 156 (70%) are females and 64 (30%) males (2.5:1 female:male ratio) with an age range of 9 to 74 years and an average of 36 years. Thirteen (6%) patients developed the clinical picture before the age of 16 and 19 (9%) after the age of 60. Ninety-one (41%) patients who developed acute, multi-organ involvement suffered from primary APS, 79 (36%) from SLE, 12 (5%) from "lupus-like" illness, and 9 (4%) from other connective tissue disease.

## Preceding Thrombotic History

A slight majority (112/220, 50%) of the patients had a prior history of thrombophilia and thrombotic event. A total of 42 (19%) of the 220 patients had a history of venothromboembolic phenomena, including deep venous thrombophlebitis

(DVT), pulmonary embolism, superior and inferior vena cava thrombosis, or Budd-Chian syndrome (hepatic vein thrombosis).

In addition to venous events, previous major arterial occlusions occurred in 29 (13%) of the CAPS patients. Femoral, popliteal, and digital artery peripheral arterial occlusions were reported, as well as myocardial infarctions, cerebral events as transient ischemic attacks or completed cerebral vascular accidents, adrenal infarction, renal infarction, and mesenteric and splenic artery thrombosis. Spontaneous fetal losses had occurred in only 18 (8%) of the 156 female patients and thrombocytopenia in 28 (13%). One patient 31 years before developing CAPS had experienced an atypical pre-eclampsia – eclampsia presentation known as the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) [19]. Other potential thrombotic manifestations of pre-existing hypercoagulability include non-healing cutaneous ulcers.

## Potential Precipitating Factors

In 130 (59%) of the patients, precipitating factors may have contributed to the development of CAPS. These included infections in 33 (15%) patients, postpartum or recent fetal loss in 7 (3%), and minor surgical procedures or surgery in 19 (9%). Additional precipitating clinical features include malignancy, medication, anticoagulation withdrawal, and SLE exacerbation. The biological significance of these risks is uncertain. As this summary data was culled from numerous investigators' published reports, it may contain biases. The likelihood that the authors ascertained potential risks and chose to include the information can not be certain. Only a prospective study which is designed to audit all identified, hypothetical risk factors could reveal which are statistically significant associations reflective of causal biologic etiologies of CAPS.

## Clinical Presentation

Presentation of CAPS is often complex as it involves multiple organs concurrently over a short period of time, typically days to weeks. Figure 16.1 shows the clinical manifestations attributed to thrombotic events at the time of CAPS.

In CAPS, the most characteristic involvement is of renal, pulmonary, cerebral, gastrointestinal, and cerebral vessels. In contrast to the non-catastrophic APS, DVT is uncommon. However, atypical occlusive events such as of adrenal, pancreatic, splenic, testicular, and cutaneous vessels typify CAPS.

In the 220 patients, 152 (70%) had renal involvement usually accompanied by hypertension. Pathological material revealed renal microangiopathy with small vessel occlusive disease.

Pulmonary involvement occurred in 142 (65%) of the patients. The spectrum of features included severe dyspnea, frank adult respiratory distress syndrome (ARDS), pulmonary emboli, sometimes multiple, pulmonary infarction, interstitial infiltrates, and intra-alveolar hemorrhage.

The central nervous system was involved in 122 (55%) of patients, often as major cerebral infarctions on computerized tomography (CT) or magnetic resonance

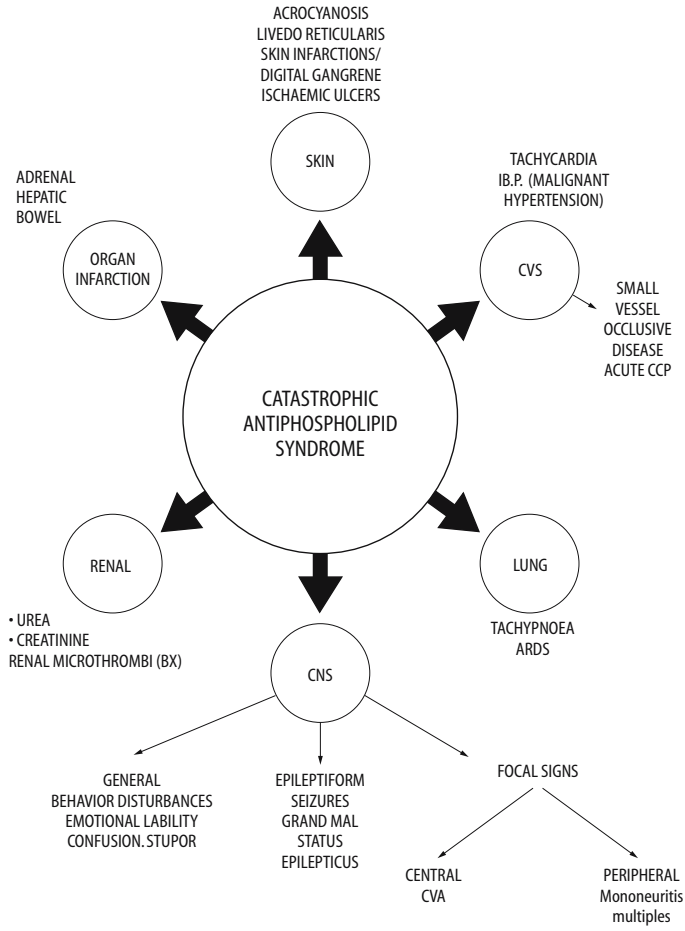


**Figure 16.1.** Clinical manifestations of catastrophic antiphospholipid syndrome.

imaging (MRI) scans. Additional manifestations include cerebral sinus thrombosis and seizures. Microthrombi and microinfarctions in pathological material obtained from patients suggests that the thrombophilia that characterizes CAPS results in thrombotic events involving the micro-circulation.

Cardiac manifestations were described in 108 (50%) patients, although typical myocardial infarction occurred no more often than diffuse myocardial involvement with congestive heart failure or vale lesions. Again, pathological material revealed multiple myocardial microthrombi.

Ninety-seven (44%) patients had gastrointestinal involvement. Vascular occlusions of mesenteric, portal, and inferior vena cava were common and arterial occlusions were accompanied by gangrene of the bowels and splenic infarctions. Hepatic involvement and pancreatitis were not uncommon. Microthrombi characterized the organs examined at autopsy.

Adrenal thrombosis was present in 23 (11%) patients. Additional unusual features of CAPS include testicular infarction and necrosis of the prostate gland. Another characteristic feature was skin involvement, with 93 (42%) demonstrating livedo reticularis, ulcerations, gangrene, purpura, acrocyanosis, or digital ischemia.

## Laboratory Findings

Thrombocytopenia (< 100,000/mm) was reported in 100 (46%) patients, hemolytic anemia in 60 (27%), findings consistent with disseminated intravascular coagulation (DIC) (prolonged coagulation tests with increased fibrinogen degradation factors and hypofibrinogenemia) in 36 (16%), and evidence of microangiopathy with schistocytes (fragmented erythrocytes) reported in peripheral blood smears in 23 (13%) patients. Lupus anticoagulant was detected in 173 (79%) of the patients and anticardiolipin antibodies (aCL) were positive in 190 (86%) patients. The antinuclear antibodies (ANA) was positive in 105 (48%) patients including in high titer.

## Outcome

Death occurred in 104 of the 220 (47%) patients and most commonly from cardiac events, predominately from myocardial microthrombi producing cardiac failure, or less often acute myocardial infarction. Respiratory failure especially with ARDS or diffuse alveolar hemorrhage was often a complicating feature in fatal cases. Cerebrovascular involvement was a less common cause of death, although coma, large vessel strokes, multiple small vessel strokes, seizures, and cerebral hemorrhage contributed to significant morbidity. Renal involvement, although a common clinical feature, was not a usual cause of death. Death occurred from gastrointestinal involvement in patients related to esophageal perforation and bowel infarction. Surviving an episode of CAPS is typically associated with a good prognosis, as only 26% develop further APS-related episodes [22], but without features of the catastrophic syndrome. Only a single example of recurrent CAPS has appeared in the literature.

## Therapeutic Aspects

In the absence of randomized controlled trials, optimal therapy for patients with catastrophic APS is uncertain. In contrast to the experience with APS where Khamashta [23] reviewed retrospectively, in 147 patients, the efficacy of warfarin, low-dose aspirin, or both in the secondary prevention of thrombosis, no single center, large series of patients with CAPS exists. A more recent prospective randomized trial of 114 APS patients suggested that more moderate-intensity warfarin anticoagulation was no less effective in preventing thrombotic recurrences as compared to high intensity [24]. Treatment is therefore empiric. Because catastrophic APS is a thrombophilic disorder characterized by wide-spread microvasculopathy, the rationale of treatment is to prevent thrombosis by anticoagulation, to prevent the production and circulation of mediators (i.e., aPL, cytokines, complement

degradation products, anti-endothelial cell antibodies, etc.) which generate the hypercoagulable state, or to prevent both. In other words, treatment may consist of anticoagulation, immunosuppressives, such as corticosteroids or cytotoxics, or plasmapheresis. The role of antiplatelet agents, prostacyclin, intravenous immunoglobulin, ancrod, defibrotide, and other fibrinolytic treatment is less certain.

Patients treated with the combination of anticoagulation in addition to steroids plus a therapy which can achieve a prompt reduction in aPL titer, either plasmapheresis [25] or intravenous gammaglobulin [26], had the highest survival rate of almost 70% [6–9]. A role for cyclophosphamide is suggested by its use in many of the most severe cases, CAPS accompanying SLE, and knowledge it prevents the rebound production of pathogenic autoantibodies by autoaggresive lymphocytes. Patients have received ancrod, purified fraction of Malayan snake pit viper venom, as well as defibrotide [6–9] and fibrinolytics such as streptokinase [27] with uncertain benefit.

## Pathogenic Aspects

Catastrophic APS occurs in a minority of patients with aPL, is characterized by acute, vascular occlusions involving multiple organs, and is an example of a non-inflammatory thrombotic microvasculopathy. The pathogenesis of microvasculopathy in autoimmune disease includes: (1) classic leukocytoclastic vasculitis secondary to subendothelial immune complex deposition in vessel walls; (2) leukothrombosis secondary to intravascular activation of complement, neutrophils, and endothelium in the absence of local immune complex deposition; or (3) thrombosis of vessels secondary to a non-inflammatory vasculopathy [28–30].

Besides APS, other thrombotic microangiopathic syndromes include thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), DIC, and HELLP syndrome. The latter is an uncommon complication of pregnancy and, interestingly, Neuwelt described a woman who developed catastrophic APS 31 years after a pregnancy accompanied by HELLP, suggesting a unifying pathophysiologic mechanism [25]. On the other hand, evidence suggests that an inhibitor of von Willebrand factor-cleaving protease (ADAMTS-13) causes the thrombotic microangiopathic hemolytic anemia that characterizes autoimmune associated TTP [31]. The uncatabolized von Willebrand multimers promote disseminated intravascular platelet aggregation.

The diffuse and multiorgan, yet episodic, nature of CAPS occurring in only a minority of patients with likely long-standing circulating aPL is consistent with the hypothesis that an additional biological factor is required for wide-spread microvasculopathy. A candidate target for activation that would then be permissive for the development of APS is endothelial cells [28, 30]. There are groups of immune stimuli that activate endothelial cells and likely contribute to providing preparatory signals for CAPS. These stimuli include cytokines, complement components, and autoantibodies.

Cytokines are likely to be important mediators of endothelial cell activation required for the development of catastrophic APS. Tumor necrosis factor α (TNF-α), interferon α (INF-α), and interleukin-1 (IL-1) each stimulate endothelial cells [32].

It should be noted that while endothelial cells may be acted upon by cytokines produced by other inflammatory cells, they also can be stimulated to produce cytokines such as IL-1, IL-6, IL-8, and TNF-α, which can act as autacoids to upregulate adhesion molecule expression [34].

Several products of the activated complement system (e.g., C3b, iC3b, and C5a) are known to activate the endothelium [33]. Additionally, assembly of the membrane attack complex (MAC), consisting of C5b-9, on endothelial cells results in the up-regulation of adhesion molecules [32]. Specifically, MAC has been shown to participate in the upregulation of endothelial cell tissue factor activity and this expression of tissue factor by the endothelium promotes a procoagulant state that is likely to contribute to the vascular injury typical of catastrophic APS [35]. There is also evidence that Clq is a cofactor required for immune complexes to stimulate endothelial expression of E-selectin, ICAM-1, and VCAM-1 [36]. Finally, the essential role for complement components and neutrophils in APS, especially in the circumstance of placental vasculopathy that underlies fetal loss, is supported by experimental studies where antibodies that block C5a-polymorphonuclear leukocyte C5a receptor interactions prevent complications in pregnant mice which receive human IgG containing aPL antibodies [37–39]. These findings are further confirmed by experience with using C3 convertase inhibitor complement receptor 1–related gene, as well as C3 deficient mice, both of which mitigates fetal loss [38].

Autoantibodies including aPL, anti-endothelial cell, and anti-dsDNA have each been demonstrated to react with endothelial cells in vitro, provide a stimulatory signal, and upregulate adhesion molecules or tissue factor [40, 41]. Antiendothelial cells, for example, have the capacity to increase tissue factor expression. Anti-DNA antibodies stimulate the release of IL-1 and IL-6 from human endothelial cells. In studies, the incubation of endothelial cells with purified IgG containing anti-dsDNA (compared with those incubated with anti-dsDNA–depleted IgG) caused a significant increase of supernatant IL-1 and IL-6 in association with increased mRNA expression of these cytokines. Moreover, using a similar strategy, the upregulation of adhesion molecule expression on endothelial cells by anti-DNA autoantibodies in patients with SLE was demonstrated. Simanitov showed that IgG from patients with aPL is able to enhance endothelial cell adhesion molecule expression and monocyte adherence [42]. This capacity of aPL to activate endothelial cells may be required in catastrophic APS before aPL interacts with platelets or coagulation proteins to mediate diffuse thrombotic microvasculopathy.

The activation of endothelial cells and accompanying upregulation of adhesion molecules and tissue factor is likely pivotal to the development of CAPS. It is the collaboration of cytokines, activated complement components, and autoantibodies that act on endothelial cells to increase its adhesiveness and procoagulant activity that provides the preparatory signals for aPL in CAPS. These same mediators can act on leukocytes and platelets to increase their adhesion to vascular endothelium and to promote microthrombosis and the local release of toxic mediators, including proteases and oxygen-derived free radicals [28, 30, 32]. This interaction between activated endothelial cells, neutrophils, and platelets in the presence of aPL generates the diffuse microvasculopathy that characterizes CAPS. This widespread, thrombotic microvasculopathy is responsible for the clinical features of catastrophic APS by producing tissue injury, which can include pulmonary capillary leak or ARDS, brain capillary leak or "acute cerebral distress syndrome," myocar-

dial dysfunction and potentially systemic inflammatory response syndrome (SIRS) with multi-organ failure [29].

It is now recognized that SIRS may arise both from sepsis and from non-infectious causes, such as immune-mediated organ injury [43]. SIRS is a reaction characterized by widespread inflammation primarily affecting vascular endothelium, however, the same cascade of mediators have been invoked in catastrophic APS [44]. The main endogenous mediators of both include TNF-á and IL-1 with a prominent role for platelet-activating factor, vasodilator prostaglandins, complement activation, and upregulation of adhesion molecules on leukocytes, platelets, and endothelial cells [45]. CAPS and SIRS share similar clinical consequences with multiorgan failure and manifestations, which include impaired renal function, ARDS, cerebral dysfunction, decreased myocardial contractility, and catecholamine unresponsive hypotension.

## Summary

CAPS develops in a minority (1%) of patients with aPL and is characterized by acute, vascular occlusion involving three or more organs. The disorder is characterized by a diffuse thrombotic microvasculopathy with a predilection for kidney, lung, brain, heart, skin, and gastrointestinal tract. Treatment is empiric and, although mortality may approach 50%, outcomes appear best for patients that receive combinations of heparin anticoagulation, steroids, plasmapheresis, intravenous gammaglobulin, and, in the setting of SLE disease exacerbation, cyclophosphamide. The etiology of CAPS awaits clarification but likely involves the activation of vascular endothelium to express surface adhesion molecules and possibly tissue factor that interact with circulating cellular inflammatory cells, elements of the phospholipid-dependent coagulation factors, and platelets in the presence of aPL. Improved therapy awaits better understanding of the underlying immunologic, coagulation, and vascular pathology.

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