Editorial

Catastrophic Antiphospholipid Syndrome and Sepsis. A Common Link?



Antiphospholipid syndrome (APS) is an autoimmune condition characterized by vascular thromboses and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL)[1]. In 1992, the "catastrophic" variant of the APS was first defined as a potential life-threatening variant, characterized by multiple small vessel thromboses that can lead to multiorgan failure[2]. In 2003, the eponym "Asherson's syndrome" was attached[3].

Several large series have been reported demonstrating increased numbers of patients with this condition, or perhaps increased awareness of the existence of APS following many recent reports[4]. Due to the diversity of clinical and serological presentations, an international consensus on classification for catastrophic APS (CAPS) has been developed[5].

Fortunately, CAPS is an unusual form of presentation that represents less than 1% of the APS cases[4]. However, patients with CAPS usually face a life-threatening situation. The mortality rate was about 50% in the largest published series[4]. However, in a recent article by Bucciarelli, *et al*[6], mortality has clearly fallen by some 20%, due in all probability to the aggressive early therapies such as plasma exchange, intravenous immunoglobulin, full anticoagulation, parenteral steroid, and, if necessary, antibiotic.

CAPS is characterized by a diffuse thrombotic microvasculopathy with a predilection for lung, brain, heart, kidney, skin, and gastrointestinal tract. In contrast to classic APS, single venous or arterial medium to large blood vessel occlusions are uncommon. However, atypical occlusive events involving adrenal, pancreatic, splenic, and testicular vessels characterize CAPS[6].

The main finding of necropsy studies was microthrombosis, present in 84.5% of patients[6]. This is one of the features that differentiates classic APS from CAPS. CAPS is said to affect small vessels primarily, whereas APS predominantly affects large vessels. In CAPS, thrombotic events occur simultaneously or over a short period of time and at multiple sites. In APS, thrombotic events are sporadic and often confined to a single site. In addition, in CAPS, severe multiple organ dysfunction characterized by diffuse small-vessel ischemia and thromboses predominantly affecting the parenchymal organs dominates the clinical picture[6].

The mechanisms of causation and pathogenesis of CAPS are not completely understood. It is still unclear why some patients will develop recurrent thromboses, mainly affecting large vessels, while others (sometimes following essentially similar "triggering" factors, e.g., anticoagulation withdrawal) develop rapidly recurring vascular occlusions, predominantly affecting small vessels.

The pathogenesis and clinical manifestations of CAPS have received insufficient attention. At present, there are no studies on the pathophysiological mechanisms of CAPS. One reason is the difficulty collecting blood and serum samples during an episode due to the low prevalence of the condition, the high rate of mortality, the wide and sporadic distribution of cases, and lack of knowledge of physicians in intensive care units, where most patients are admitted.

There are 2 possible explanations for the clinical manifestations of CAPS. First, as to the organs affected by the thrombotic events and the extent of the thromboses, Kitchens has suggested that the vascular occlusions in these patients are themselves responsible for the ongoing thrombosis. Clots continue to generate thrombin, fibrinolysis is depressed by an increase in plasminogen activator inhibitor type-1 (PAI-1), and there is consumption of the natural anticoagulant proteins such as protein C and antithrombin[7]. Second, manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues. At present, these 2 explanations remain theoretical.

It is now recognized that SIRS may arise both from sepsis and from noninfectious causes, such as immune-mediated organ injury. The acute respiratory distress syndrome (ARDS), encephalopathy, and myocardial dysfunction, clinical manifestations present in patients with CAPS, have all been related to the development of SIRS[8].

Another specific characteristic of CAPS is that 60% of patients appear to have a triggering factor, especially infections, the commonest identifiable trigger for CAPS, present in about 25% of cases[4]. Multiple triggering factors may be present in the same patient (for example, infection, anticoagulation withdrawal followed by a surgical procedure, or biopsy in patients with neoplasia and aPL). This so-called (double- or treble-hit) hypothesis applies to any patient with

multiorgan failure. Specific triggering infections encountered to date include malaria, Dengue, typhoid fever, viral infections of upper respiratory tract, urinary infections, and sepsis. CAPS has also been triggered by immunization.

Both sepsis and CAPS have SIRS in common, which is marked by presence of 2 or more of the following: (1) temperature > 38ºC or < 36ºC; (2) heart rate > 90 beats/min; (3) respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg; and (d) white blood cell count > 12,000 cells/mm^3 or with > 10% immature (band) forms. Sepsis has been defined as the systemic inflammatory response to infection, and when it is severe, there is evidence of organ dysfunction with resulting hypoperfusion and hypoxia, lactic acidosis, oliguria, and cerebral dysfunction mainly[9].

This evident relationship between APS and infection may explain the development of CAPS using the sepsis model. Aberrant neutrophil activity has been implicated in the organ failure of severe sepsis, and it is likely that a similar situation exists in patients with CAPS. Examination of autopsy specimens from patients with multiple organ failure and severe sepsis shows sequestration and aggregation of neutrophils in renal blood vessels and large-scale infiltration in the lungs, resulting in ARDS[10]. In the latter condition, the intensity of the neutrophil response has been correlated with the impairment of lung function and with the high concentration of neutrophil-derived proteolytic enzymes found in bronchoalveolar lavage fluid. There is a high frequency of ARDS in CAPS as well as in patients with severe sepsis. The role of neutrophils in multiple organ failure has recently been reviewed[10].

Catastrophic APS is characterized by multiple microvascular thrombotic events of rapid onset, causing multiorgan failure, a picture suggestive of septic shock in which there is a massive, acute inflammatory response. Studies supporting this hypothesis have appeared in the last 5 years, most notably Asherson and Shoenfeld, who proposed a theory of "molecular mimicry"[11]. Pathogenic aPL and anti-$ß_2$-glycoprotein I (anti-$ß_2$-GPI) can be generated with peptides of bacterial and viral origin that mimic various regions of $ß_2$-GPI[12]. These data strongly suggest molecular mimicry between bacterial/viral antigens and self-proteins in APS. Based on these *in vitro* data, molecular mimicry has also been proposed for the development of CAPS following infection. Despite potential ascertainment bias, in a recent review of patients with APS triggered by an infection, 40% developed CAPS[13].

In sepsis, SIRS affects coagulation. Specifically, proinflammatory cytokines [tumor necrosis factor-α (TNF-α), interferon-γ, and interleukin 1 (IL-1)] induce tissue factor expression on monocytes and endothelial cells, downregulate physiological anticoagulant pathways, and inhibit fibrinolysis[14]. This leads to microvascular thrombosis and influences and modulates the inflammatory response.

The sepsis response begins with the activation of host cells by recognition of lipopolysaccharide (LPS). The main mechanism by which LPS is sensed is via an LPS-binding protein (LBP) and then signaling through the Toll-like receptor 4 (TLR4). TLR are a key component of innate immune response recognition of specific microbial products including LPS. Intracellular signaling depends on binding of the intracellular TLR domain to IL-1 receptor-associated kinase (IRAK), a process that is facilitated by an adapter protein MyD88 (myeloid differentiation protein 88). The activation of IRAK induces the nuclear translocation of nuclear factor-κB (NF-κB) and ultimately the activation of cytokine gene promoters such as IL-1, IL-6, and TNF-α[14].

There is some evidence that anti-$ß_2$-GPI antibodies trigger an endothelial-signalling cascade comparable to that activated by LPS. Anti-$ß_2$-GPI antibodies and LPS induce a comparable phosphorylation of the IRAK. Activation of endothelial cells by anti-$ß_2$-GPI antibodies has been demonstrated. Meroni, *et al* have shown that this activation may induce a proinflammatory phenotype of endothelial cells and that *in vitro* activation of endothelial cells is associated with NF-κB nuclear translocation[15]. In addition, this group recently reported that anti-$ß_2$-GPI antibodies activate endothelial cells through the MyD88-dependent pathway[15]. These findings raise the possibility that the autoantibodies activate endothelial cells through the TLR-4 involved in LPS pathway.

Anti-$ß_2$-GPI antibodies have been shown to recognize $ß_2$-GPI peptides displaying molecular mimicry with common bacteria and viruses, both at the level of amino acid sequence and conformational structure[12]. Such a homology was suggested to represent the rationale for the possible infectious origin of the syndrome. Because common microbial structures do represent the natural ligand for TLR, it has been speculated that $ß_2$-GPI might interact with TLR and that anti-$ß_2$-GPI antibodies recognizing the molecule might cross-link it together with TLR, eventually triggering the inflammatory cascade. Since these receptors are intimately involved with innate immunity directed especially towards infections as prevalent "triggering" factors in CAPS, their role remains to be further explored, and studies looking at differing phenotypes in those patients manifesting CAPS are needed.

Cytokines are also important in inducing a procoagulant effect in sepsis. Coagulation pathways are initiated by LPS, inducing expression of tissue factor on mononuclear and endothelial cells. Simultaneously, normal regulatory fibrinolytic mechanisms are impaired due to high PAI-1 plasma levels. The net result is enhanced thrombin production and reduced fibrin removal, leading to the deposition of fibrin clots in small blood vessels, inadequate tissue perfusion, and organ failure[14]. There is some evidence that CAPS induced by anti-$ß_2$-GPI antibodies shares with the sepsis response the increased expression of tissue factor and PAI-1 on endothelial cells and monocytes.

Another point in common between sepsis and CAPS should be the role of von Willebrand factor–cleaving protease, 1-5ADAMTS13 (a disintegrin-like metalloprotease with thrombospondin type 1 repeats) in the development of both conditions. A severe deficiency of ADAMTS13 is found in most patients with thrombotic thrombocytopenic purpura (TTP), and this deficiency is thought to be responsible for platelet aggregation and microthrombi formation in the circulation, which in turn cause typical thrombotic microangiopathies (TMA) to develop[16]. The presence of TMA is a hallmark of CAPS. Our group has shown that CAPS is one of the most frequent clinical presentations of patients with TMA associated with aPL[17]. It also is possible that secondary deficiency of ADAMTS13 may account for the development of microthrombi formation in disease states other than TTP, such as sepsis-induced disseminated intravascular coagulation (DIC)[18], and possibly CAPS. Our group has shown that 13% of patients with CAPS presented with DIC features, infections being the most common precipitating factor[19]. The presence of schistocytes in CAPS makes the differential diagnosis between CAPS and TTP difficult in aPL patients with predominantly renal and neurological involvement. However, schistocytes in CAPS patients are scanty. There remains a possibility that, pathologically, CAPS and TTP might be a partially identical syndrome, and it has been recently suggested that a "continuum" between these conditions might exist[20].

What then does the current research in ADAMTS13 deficiency in APS show? Amoura, *et al* described 2 patients with TTP and primary APS[21]. They also described the results of tests for ADAMTS13 activity in 20 patients with primary APS, as well as tests for aPL in 26 patients who had TTP with severe ADAMTS13 deficiency and ADAMTS13-inhibiting antibodies. In both patients with TTP and primary APS, ADAMTS13 activity was undetectable, and ADAMTS13-inhibiting antibodies were present. In 20 patients with primary APS, no severe deficiency of ADAMTS13 was observed. Finally, only one of the 26 patients with TTP had a low level of IgG anticardiolipin antibodies. From this study there is now some evidence that ADAMTS13 deficiency may play a role in some patients with CAPS.

Catastrophic APS resembles severe sepsis in its acute presentation, with features of SIRS leading to multiple organ dysfunction. Further, infections are the best known triggers of CAPS. This emphasizes the need for early diagnosis and aggressive antibiotic treatment as soon as infection is suspected in both classic APS and CAPS patients. However, the benefits of prophylactic antibiotic use in a CAPS patient without a suspected or proven infection should be carefully weighed. The most important future objective is to collect blood and serum samples from patients with CAPS, especially during acute episodes. This will permit laboratory studies on pathophysiology of CAPS, including cytokine profile, complement deficiencies, TLR and mannose-binding lectin polymorphisms, and the possible role of ADAMTS13 deficiency.

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