Thrombotic microangiopathic antiphospholipid syndromes: a continuum of conditions?

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The original description and definition of the antiphospholipid syndrome (APS) included predominantly thromboses of large veins and large arteries (deep vein thromboses (DVT) and strokes), fetal losses and thrombocytopenia (mild to moderate). The thromboses and fetal losses were often recurrent. Small vessel occlusions did occur (affecting renal and retinal skin vessels, etc.) but these did not dominate the clinical picture. The systemic nature of the syndrome was recognized in 1992 and is referred to as Hughes' Syndrome. In 1992, a new subset consisting predominantly of small vessel microangiopathy, with considerably less large vessel occlusive disease, was defined as the catastrophic antiphospholipid syndrome (CAPS) and the eponym Asherson's Syndrome has been attached. Severe thrombocytopenia and features of the systemic inflammatory response syndrome appear to accompany this very often fatal condition. Recurrences were very rare. A new subset is highlighted and reviewed in this paper and is termed the microangiopathic antiphospholipid syndrome. Patients do not suffer from large vessel occlusions. Hemolytic anemia and, often, severe thrombocytopenias are seen. Included in this subset are thrombotic thrombocytopenic purpura (TTP)-like syndrome, the hemolysis, elevated liver enzyme and low platelet count syndrome and patients with CAPS who do not demonstrate large vessel occlusions. The authors suggest that a continuum may exist between all these conditions, with similar but not identical triggering factors (e.g., infections and drugs), clinical features and treatment (e.g., plasma exchange).

With the increasing literature and knowledge over the last 10 years pertaining to the often fatal variant of the antiphospholipid syndrome (APS), termed the catastrophic APS (CAPS) (also known as Asherson's syndrome) [1], it is appropriate to review this specific variant together with the several autoimmune thrombotic conditions that have, until now, been integrated under the descriptive term thrombotic microangiopathic hemolytic anemia (TMHA) and that include thrombotic thrombocytopenic purpura (TTP), hemolytic–uremic syndrome (HUS) and hemolysis, elevated liver enzyme and low platelet count (HELLP) syndrome. Although the underlying causes for these disorders may vary, they share common, although not identical, 'triggering' factors and clinical manifestations (i.e., thromboses affecting small vessels accompanied in many cases by hemolytic anemia and severe thrombocytopenias), and they may also require similar therapies.

Early insight into the commonality of these conditions was provided in a review entitled 'Multiorgan thrombotic disorders in systemic lupus erythematosus (SLE): a common link?' published in 1992 [2]. Since then, it has become clear that these conditions may also occur in the absence of SLE and may also, not infrequently, be accompanied by the presence of antiphospholipid antibodies (aPL) or a prior history of APS. A recent, comprehensive, review of thrombotic thrombocytopenic purpura (TTP) by Lammle and colleagues has also attempted to unravel the major features of this condition and TMHA [3].

The authors of this review propose that a continuum may exist between all of the conditions reviewed here, in that they share common overlapping triggering factors (infections, drugs, carcinoma, occurrence during pregnancy and the puerperium), similar clinical manifestations and they all seem to respond to the same therapies (e.g., plasma exchange). There may indeed be some overlap with other conditions in which thrombotic microangiopathic may be encountered, including malignant hypertension and scleroderma renal crisis. The aPL may also be demonstrable in patients with idiopathic thrombocytopenic purpura (ITP) and with pre-eclampsia, but these latter conditions do not appear to be associated with small vessel occlusive disease. There are also two other conditions where the association of aPL and microvascular thromboses coexist. These are disseminated intravascular coagulation (DIC) and the heparin-induced thrombosis–thrombocytopenia syndrome (HITT). In both there may also be

severe thrombocytopenia. These conditions are not discussed in the present paper but should also be considered in the differential diagnosis under special clinical circumstances (e.g., following the administration of heparin). Serological DIC itself may complicate the course of the CAPS, further complicating an accurate diagnosis. Anecdotally, TMHA has been described as an unusual complication of diabetes mellitus [4], and one patient with a 12-year history of insulin-dependent diabetes mellitus and rapidly developing diabetic complications who developed TMHA associated with aPL was reported by Morita and colleagues in 1996 [5].

TTP & hemolytic–uremic syndrome

TTP and hemolytic–uremic syndrome (HUS) are characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura (usually severe), neurological abnormalities, renal dysfunction and fever [6]. In the variant associated with TTP, neurological manifestations may dominate the clinical picture, whereas in the HUS the predominant organ affected is the kidney. However, there is a degree of overlap, with renal abnormalities encountered in 50–75% of TTP patients and extra-renal manifestations common in patients with HUS. The classic pentad of manifestations of TTP – viz, fever, fluctuating neurological signs, renal dysfunction, microangiopathic hemolytic anemia with fragmented erythrocytes (schistocytes) and thrombocytopenia: – is only present in 40% of TTP patients. However, a triad consisting of fewer signs – anemia, thrombocytopenia and neurological abnormalities – may be seen in 75% of cases [7,8]. Both conditions may be relapsing [9,10].

Classic idiopathic TTP is now understood to result from severe deficiency of the metalloprotease enzyme ADAM metallopeptidase with thrombospondin type 1 motif (ADAMTS)-13, which is an essential regulator and prevents microvascular platelet aggregation by the cleaving of the extremely adhesive von Willebrand factor (VWF) secreted by endothelial cells between Tyr 1605 and Met 1606. Unusually, large multimers of circulating VWF result. These react with platelet glycoprotein and the subendothelial matrix, triggering pathologic aggregation of platelets at intravascular sites with high shear stress. The result is the formation of platelet and VWF-rich microvascular thrombi. Hereditary TTP is caused by homozygous or double heterozygous ADAMTS-13 mutations. Acquired TTP is usually associated with severe antibody-mediated ADAMTS-13 deficiencies [11,12].

The key initiating event in TTP may be endothelial cell activation [13–15], which may be due to bacterial endotoxins, antibodies (e.g., aPL), immune complexes, oxidative injury and/or drugs (such as ticlopidine or clopidrogel) [16,17]. However, the pathology of this disorder can be complicated. Immunoglobulin (Ig)G and IgM autoantibodies have been identified that are directed against ADAMTS-13 [11,12]. Antiendothelial cell antibodies can also be demonstrated in patients with TTP and these might contribute to the endothelial cell injury [14]. Conversely, Romani and colleagues proposed that vascular perturbation is a consequence, not a cause, of TTP [15].

Classic TTP manifestations have repeatedly been documented in patients with SLE, the usual sequence being that patients with diagnosed SLE develop TTP during the course of their illness (73%). The reverse pattern, TTP being followed by SLE, is more unusual, encountered in 12% of cases, with the two conditions occuring simultaneously in 15% [18].

The association of TTP with aPL was first described by Jain and colleagues in 1991 in a description of seven patients (one with primary APS and six with SLE) who had TTP-like manifestations in the absence of purpura and with elevated aPL levels [19]. These patients were referred to as having 'thrombotic microangiopathy'. Durand and colleagues reported a similar case in the same year [20]. Further association of TTP, SLE and aPL was reported in 1992 by Hess and colleagues, reporting two patients who fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SLE and four out of five criteria for TTP [21]. Both patients had mucocutaneous bleeding. Nesher and colleagues documented four cases in 1994 and reviewed an additional group of 24 patients compiled from the literature [22]. All patients were female, 50% had active SLE, 89% presented with TTP and 11% presented with HUS. The aPL positivity was present in five out of eight cases, where tested. They stressed that TMHA should be strongly considered in any SLE patient presenting with neurological symptoms or renal failure associated with fever, hemolytic anemia and thrombocytopenia. Patients treated with plasma infusions or plasma exchange had a lower mortality than those not receiving this therapy (25 vs 57%). In 1997, Trent and colleagues reported two cases with chronic relapsing TTP and aPL and suggested an association between these two conditions [23]. In 1994, Umibe and colleagues, described a single

patient with primary APS and TTP [24]. In 2000, Musa and colleagues, again documented the association between TTP (fulminant in their two patients), SLE and aPL [25].

ADAMTS-13 deficiencies may be detected in patients with aPL complicated by TTP with underlying SLE, as well as in primary APS patients. In 2005 Rieger and colleagues, detected prevalences of IgG ADAMTS-13 antibodies in 13% of 40 SLE patients and in 5% of 55 APS patients [26]. The frequency of IgM antibodies was much higher (18% in these two groups). However, in some patients, a primary ADAMTS-13 deficiency may be undetectable [27,28], while ADAMTS-13 inhibiting antibodies are present [29,30].

Kincaid-Smith and colleagues [31] and Kniaz and colleagues [32] were the first to suggest a potential association between aPL and the renal vascular thromboses observed in the adult, obstetric form of HUS. Ardiles and colleagues, had examined this association in patients with pediatric HUS and found elevated anticardiolipin antibody titers in 8 out of 17 of these patients [33]. That people with extended rheumatic conditions may develop TTP–HUS in association with aPL is evidenced by a patient with paraneoplastic systemic sclerosis, who developed typical thrombotic microangiopathy of the kidney [34].

HELLP syndrome

The association of hemolysis, elevated liver enzymes and low platelet count is known as the HELLP syndrome and is a thrombotic microangiopathic state complicating pregnancy. It may occur prior to the 32nd week of gestation and usually resolves with delivery of the fetus, without any sequelae. The diagnosis of HELLP is based on the presence of hemolysis (anemia with characteristic blood smear), lactic dehydrogenase (LDH) over the upper normal value or total bilirubin levels of more than 12 mg/l, elevated alanine aminotransferase (AAT) higher than twice the upper normal value and nadir platelet counts below 125×10^9/l. Complete HELLP is defined by the presence of all four criteria and partial HELLP by the presence of two criteria [35].

The association of HELLP with aPL extends back to 1994. Two cases of HELLP syndrome with demonstrable aPL were first reported by Ornstein and Rand in 1994 [36]. These cases were refractory to the delivery of the fetus and corticosteroids, as well as to anticoagulation. Plasma exchange resulted in recovery and resolution of the condition. The authors hypothesized whether an association between this refractory microangiopathic condition and the presence of the aPL existed and accounted for the unusually difficult course. Both patients had demonstrated positive tests for aPL prior to the onset of the HELLP syndrome; one had an APS with multiple thrombotic events and the second had a false positive serological test for syphilis and thrombocytopenia.

In 1995, Ilbery and colleagues reported a patient with positive lupus anticoagulant and HELLP complicated by hepatic and dermal, adrenal infarction, as well as placental abruption [37]. Alsulyman and colleagues in 1996 reported three cases, all of whom had developed severe pre-eclampsia complicated by the syndrome prior to 20 weeks gestation, together with demonstrable aPL in two who both had complicating hepatic infarctions on abdominal computed tomography scanning [38]. Nagayama and colleagues then documented in 1997 a patient with a history of one spontaneous abortion who developed HELLP syndrome at the 16th week of her second pregnancy and had demonstrable aPL [39]. She responded well to an induced abortion, plasma exchange and corticosteroid therapy. McMahon and Smith [40] and Amant and colleagues [41] also reported similar cases in the same year. The two patients described by Amant and colleagues had developed hepatic necrosis and hemorrhage [41].

In 2003, Roberts and colleagues documented an SLE patient with both HELLP and APS with acute renal failure who responded to plasma exchange [42]. Several patients with HELLP syndrome who developed a variety of thrombotic events and infarctions have also been documented. Hepatic infarcts occurring in HELLP syndrome were reported by Zissin and colleagues in 1999 [43]. Both patients were pre-eclamptic. However, this article makes no mention of aPL. Central retinal vein occlusion was reported in one patient [44], while thrombosis of the inferior vena cava was reported by Paternoster and colleagues [45]. This latter patient, however, had also developed pancreatitis (possibly thrombotic) and had a demonstrable R506Q factor V Leiden mutation.

The topic of hepatic infarcts in pregnancy accompanied by aPL was reviewed extensively by Pauzner and colleagues in 2003 [46]. They presented four patients with primary APS whose pregnancies were complicated by hepatic infarcts and also reviewed 20 pregnancies in 28 women with pregnancy-associated hepatic infarcts. The

aPL were present in 14 out of 15 patients in whom their presence was assessed. Of 22 patients with available data, 16 had typical HELLP syndrome. The authors concluded that almost all patients with hepatic infarcts associated with pregnancy had aPL in addition to complete or atypical HELLP syndrome. Hepatic infarcts occurred at all stages of pregnancy, from as early as the 7th week of gestation and up to the postpartum period. They concluded that hepatic infarction during pregnancy was almost always associated with aPL, but in a few cases had been reported with other thrombophilic defects, for example, factor V Leiden mutation. They also suggested that the term HELLP syndromes be used to include hepatic infarcts among the manifestation of the condition.

Le Thi Thuong and colleagues recently reviewed 16 cases of HELLP syndrome associated with aPL [47]. HELLP recurred in one patient with SLE. They concluded that the risk of HELLP syndrome was probably increased in the APS and stated that the number of such cases was more than 30 in the English literature. HELLP syndrome appeared to be more severe in the APS than in the general population and more than two thirds of their cases were associated with pre-eclampsia or eclampsia. Such patients might be refractory to corticosteroid administration, thus anticoagulation and plasma exchange may be required. Two cases were complicated by micro-angiopathic coagulopathy. In one case, hepatic involvement was due to complete thrombosis of the hepatic veins.

An interface between HELLP syndrome and the CAPS exists. This is illustrated by the patient reported by Hochfeld and colleagues [48] and the unusual case documented by Sinha and colleagues of a patient with refractory HELLP syndrome, bone marrow necrosis and features of CAPS [49]. This case also emphasizes the point that the HELLP syndrome may be refractory in patients who demonstrate aPL, as was stressed by Ornstein and Rand in their early report [36]. In 2005, Koenig and colleagues [50] also documented a similar patient to the one reported by Sinha and colleagues [49]. Their patient, a 16-year-old female with a known case of primary APS, developed HELLP syndrome during the 17th week of pregnancy at the age of 19 years, followed by CAPS with complicating hepatic and intestinal infarctions, bone marrow necrosis and severe thrombocytopenia in the puerperium. She recovered following the administration of Igs together with anticoagulation. There was no response to the administration of fresh frozen plasma (FFP), proving that the response to plasma exchange in these patients is due to removal of aPL and perhaps other factors as yet unknown, rather than addition of the natural anticoagulants (protein C, S and antithrombin) present in FFP. FFP also contains VWF and high-molecular-weight multimers of VWF, which have been implicated in the pathogenesis of TTP. These have an enhanced ability to cause platelet aggregation.

Catastrophic antiphospholipid syndrome

This rapidly progressive, often fatal variant of the APS was first defined in 1992 with the publication of ten representative cases [51]. Many more cases have been documented over the past 14 years, due primarily to the establishment of a website based in Barcelona [101] and a major effort by several key collaborators. Almost 300 patients with this condition have been documented and many reviews have been published [52–55]. The characteristic features of the condition are:

- Rapid onset, resulting in multiple organ dysfunction syndrome;
- Small vessel disease predominating;
- Pathological evidence of thrombotic microangiopathy;
- Fulminant tissue necrosis, particularly involving the gastrointestinal tract, which may result in evidence of the systemic inflammatory response syndrome manifest particularly as an acute respiratory distress syndrome [54];
- High frequency of unusual organ involvement, such as reproductive organ infarctions, bone marrow necrosis, acalculous cholecystitis, polyneuropathy or splenic, hepatic and adrenal infarctions.

Serological evidence of DIC is present in a significant proportion of patients (20%) [55].

Most patients end up in intensive care units (ICU) with a plethora of physicians in attendance. However, unfortunately, it seems that many attending physicians often miss the diagnosis.

The condition is most frequently encountered in patients with a primary APS (49.9%), with SLE and 'lupus-like' disease being slightly less frequent (45%). Other uncommon associations include rheumatoid arthritis, systemic sclerosis, dermatomyositis, Crohn's disease, ulcerative colitis and vasculitides (e.g., polychondritis and Behçet's disease). Clearly, some patients have

already been identified as suffering from a simple or classic APS and may already have been receiving long-term steroids or anticoagulation. However, the condition may arise *de novo* in others. A previous history of vascular occlusive events is, therefore, of great importance.

Triggering factors may be present in 60% of patients. These are infections (22%), trauma (13%), anticoagulation withdrawal (7.2%), neoplasia (6.8%), obstetric related (4.2%), lupus 'flares' (3%) and others (i.e., drugs such as captopril, oral contraceptives, danazol or thiazide diuretics, ovulation induction and postimmunization) (4%). Specific infections (e.g., typhoid fever, malaria and Dengue fever, among others) have been encountered; most have had a variety of infectious triggers that include viral upper respiratory, unidentified urinary tract or bacterial infections. Infected leg ulcers have featured prominently among the latter etiological triggers encountered. Immunization against yellow fever, Japanese B encephalitis and influenza have been followed by CAPS in isolated cases. The trauma may be major, or even minor, surgical (e.g., biopsy), or a simple fracture. In a percentage of patients multiple trigger factors may be present in the same patient (e.g., infection, anticoagulation withdrawal followed by a surgical procedure, or biopsy in patients with neoplasia who have aPL). This is the so-called 'double' or 'treble' hit hypothesis, common in other patients who present with multiorgan failure.

The predominant organs involved clinically are the kidneys (70%), lungs (66%), brain (60%), heart (52%), and skin (47%). Cardiac and pulmonary complications are most likely to be associated with poorer prognosis and death [56]. A recent paper has examined and reported on the histopathological findings taken from the CAPS registry, in those cases where these have been available [57] and confirmed the previous clinical study [56]. However, patients do not die from renal failure but either stroke or a cardiopulmonary death is usual.

The pathogenesis of this condition has not received as much attention as the clinical manifestations. The rarity of the condition, its high mortality, sporadic cases encountered in many different geographical areas and hospitals and a lack of education of ICU physicians have undoubtedly led to difficulties in collecting blood and serum samples from affected patients both during the episode and, if they survive, later as well. It is hoped that this situation will be remedied in 2006/2007 with the formation of the CAPS Research Committee and the issuing of appropriate guidelines.

Asherson and Shoenfeld proposed a theory of 'molecular mimicry' in 2000 [58]. Kitchens referred to the condition as a 'thrombotic storm', and hypothesized that the vascular occlusions in these patients themselves were responsible for the ongoing thrombosis [59]. 'Thrombosis begets thrombosis' was included in the title of his paper.

The role of complement in aPL-induced thrombosis has received a great deal of attention recently. Pierangeli and colleagues stressed the role of complement fractions C3 and C5 in aPL-mediated thrombosis [60]. The recent outstanding work on the role of complement in the etiopathogenesis of fetal loss from the Salmon group in New York has been extended by the group from Harvard University in Boston MA, USA, and their research may perhaps explain some of the odd features of CAPS [60–63]. Hart and colleagues [62] and Fleming and colleagues [63] recently published two important papers that demonstrated clearly that complement activation plays an important role, not only in local tissue injury, but also in remote injury. Gut barrier dysfunction, for example from ischemia induced by small vessel occlusive disease in CAPS, may lead to bacterial translocation to the lung, resulting in increased complement neutrophil infiltration as a result of lectin complement pathway activation via ficolins. Manose binding lectin (MBL) activates the lectin complement in the intestines; ficolins may be activating complement in the lungs. This hypothesis explains why, with neutrophilic infiltration initially, secondary disruption of alveolar blood vessels might take place, resulting in diffuse alveolar hemorrhage, a not infrequent accompaniment of CAPS. The high frequency of abdominal symptomatology in CAPS patients and the increased frequency of pulmonary complications such as alveolar hemorrhage in the group of patients with CAPS lends credence to this link. The ficolin hypothesis also ties in well with the high frequency of infections as triggering mechanisms for catastrophic APS. The second paper from this group led them to conclude that aPL could bind to tissues subjected to ischemia/reperfusion insult and mediated tissue damage, just as they had been shown to mediate fetal growth retardation and loss when injected into pregnant mice [63].

Additionally, the disruption of annexin A5 homeostasis may also be important in the pathogenesis of the APS [64–66]. The role of the complement system and of annexin A5 may not be mutually exclusive. Discovering the links

between them may be the next breakthrough waiting to be achieved.

The treatment of the CAPS remains unsatisfactory, but it is clear that many patients have not been given the benefit of intravenous γ-globulins and repeated plasma exchanges, which have been strongly recommended [67]. High-dose steroids and parenteral anticoagulation should be supplemented by intravenous γ–globulins and repeated plasma exchanges early on in the course of CAPS and should not be withheld. The use of rituximab in patients who demonstrate severe thrombocytopenia has been successful in those few cases to whom it has been administered [68]. Antibiotics should also be administered if an infection is present or suspected.

Relapsing CAPS is rare; few such patients have been reported to date. In one patient, two relapses were triggered by infections; in another, trauma was responsible; while in a third, no obvious precipitating factors were detectable prior to two relapses. However, simple cataract surgery was responsible for a third relapse, which the patient survived.

Relationship between TMHA & CAPS

Merrill and Asherson recently pointed out that perhaps a commonality exists in these conditions with the occurrence of diffuse microvascular thrombosis in all [69]. Essentially, similar complications, such as severe thrombocytopenia, microangiopathic hemolytic anemia, fever, renal and neurological complications (mainly in TTP–HUS and CAPS, but not in the HELLP syndrome) may be encountered. The aPL have indeed been reported in all, with or without the presence of SLE.

Certainly, endothelial cell activation plays an important and putative role, which was pointed out several years ago by Meroni and colleagues [70]. In 2003, Raschi and colleagues further explored the relationship between aPL (particularly antibodies to β2 glycoprotein I [β2GPI] and endothelial cell activation [71]. Their findings demonstrated that anti-β2GPI antibodies reacted with their antigen probably associated with a member of the T-lymphocyte receptor (TLR)/IL-1 receptor family, on the endothelial cell surface, directly inducing activation. This anti-β2GPI binding to the endothelial cell surface induces nuclear factor-κB translocation, leading to a proinflammatory endothelial cell phenotype similar to that elicited by interaction with microbial products (e.g., lipopolysaccharide). Involvement of the TLR family is, therefore, of great importance in this process. Since these receptors are intimately involved with innate immunity, directed especially towards infections so prevalent as triggering factors in several of the conditions reviewed, their role remains to be further explored and studies looking at differing phenotypes, for example in those patients manifesting CAPS are planned.

Table 1. Differential diagnosis of thrombotic microangiopathic antiphospholipid syndromes.				
	TTP	**HUS**	**HELLP syndrome**	**Catastrophic APS**
Clinical manifestations				
Fever	++	+	-	+/-
CNS involvement	+++	+	-	++
Renal involvement	+	+++	-	++
Hepatic involvement	-	-	+	+
Laboratory features				
Thrombocytopenia	+++	+	+	++
Microangiopathic hemolytic anemia	+	+	+/-	+
ADAMTS-13 activity	Very low	Low	Low	Unknown
Therapy				
Anticoagulation	-	-	-	+
Steroids	-	-	-	+
Plasma exchange	+	+	+	+
IVIg	-	-	-	+

ADAMTS: ADAM metallopeptidase with thrombospondin ; APS: Antiphospholipid syndrome; HELLP: Hemolysis, elevated liver enzymes and low platelet count; HUS: Hemolytic–uremic syndrome; IVIg: Intravenous immunoglobulins; TTP: Thrombotic thrombocytopenic purpura.

In their recent review, Espinosa and colleagues pointed out that the association of the aPL with these TMHA-like disorders might in fact be higher than previously appreciated [72] and it now appears, with the several publications and recent case reports alluded to in this paper, that there may in fact be a 'continuum' of illness leading up to CAPS or a significant overlapping of these disorders with CAPS itself. This is perhaps exemplified by the association of the HELLP syndrome with CAPS in the case reports by Hochfeld and colleagues [48], Sinha and colleagues [49] and Koenig and colleagues [50]. The presence of schistocytes in CAPS patients makes the differential diagnosis between this condition and TTP difficult in those patients with predominantly renal and neurological involvement and who also have demonstrable titers of aPL. However, it is important to emphasize that there is little knowledge of how many of these patients share any of the molecular mechanisms recently identified in patients with TTP or atypical HUS.

Relationship of these conditions to common triggers

This topic has recently been reviewed by Kravitz and Shoenfeld [73]. TTP may develop after a variety of infections, including *Escherichia coli, Salmonella typhi, Campylobacter jejuni, Streptococcus pneumonia* and *Yersinia* [74,75]. Its variant, HUS (particularly childhood HUS), is often associated with preceding hemorrhagic colitis caused by verocytotoxin-producing *Escherichia coli* 0157:H7 infection [76]. Several case reports have also documented the association of TTP with viral infections, including HIV [77], cytomegalovirus [78], parvovirus B19 [76] and adenovirus [79], especially among immunosuppressed patients, as well as with *Mycoplasma pneumoniae* [80]. Cases of TTP relapse have been associated with *Staphylococcus aureus* bacteremia [812] and *Acinetobacter anitratus* [82]. The hypothesis that an infectious agent may be the inciting factor is reinforced by a report from Watson and colleagues describing a fatal case of TTP in a man whose wife died 6 months later of a similar illness [83]. Other conditions associated with the development of TTP include pregnancy, drugs, cancer, chemotherapy and bone marrow transplantation. In the latest analysis of the CAPS registry, no fewer than 16 patients have developed this condition as a complication of carcinoma or lymphoma and it is also now well described complicating pregnancy and the puerperium.

Future perspective

The issue of whether thrombotic microangiopathic APS has a distinct pathogenesis that separates it from classic APS or CAPS should be further considered in the future in order to find out what determines the size of the vessels affected in individual cases and what the therapeutic recommendations to such patients should be.

Executive summary

- The antiphospholipid syndrome (APS) remains an all-embracing term to cover several 'subsets'.

- In patients suffering from the simple/classic APS, large vessel occlusions affecting deep veins and large arterial vessels supplying the brain dominate, with a minority of patients demonstrating small vessel occlusions (e.g., renal, retinal and nail bed vasculature).

- In the recently defined catastrophic APS (Asherson's syndrome), small vessel occlusions involving the gastrointestinal tract or brain predominate, with large vessel occlusions causing deep vein thromboses, pulmonary embolism and arterial thromboses causing strokes in only 20–30% of patients.

- It is suggested that a smaller subset comprising patients with only small vessel occlusions accompanied by antiphospholipid antibodies may exist. This group comprises thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome-like syndromes and hemolytsis, elevated liver enzymes and low platelet count (HELLP) syndrome.

- A continuum may exist between these conditions and catastrophic APS; several patients have now been documented with HELLP syndromes who have later developed catastrophic APS.

- These patients may have essentially similar triggering factors (e.g., infections, drug administration, carcinomas or they are related to pregnancy/puerperium), demonstrate hemolytic anemia and may require and respond favorably to similar therapies (e.g., plasma exchanges using fresh frozen plasma, or intravenous immunoglobulins).

- These microangiopathic syndromes may occur both in the presence or absence of systemic lupus erythematosus.

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Website

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