Unusual manifestations of the antiphospholipid syndrome

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses (often multiple), recurrent fetal losses and is frequently accompanied by a moderate thrombocytopenia in the presence of antiphospholipid antibodies, namely lupus anticoagulant, anticardiolipin antibodies or anti-β2 glycoprotein-I antibodies. The APS can be found in patients with no clinical or laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly systemic lupus erythematosus. Rapid chronological occlusive events, occuring over days to weeks, have been termed the catastrophic APS. Deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation in this syndrome. Conversely, cerebrovascular accidents – either stroke or transient ischemic attacks – are the most common arterial thrombotic manifestations. Early and late fetal losses, premature births and preeclampsia are the most frequent fetal and obstetric manifestations. In addition, several other clinical features are relatively common in these patients, including thrombocytopenia, livedo reticularis, heart valve lesions, hemolytic anemia, epilepsy, myocardial infarction, leg ulcers and amaurosis fugax. However, a large variety of other clinical manifestations have been less frequently described in patients with the APS, with prevalences lower than 5%. In this article we will review some of these 'unusual' manifestations

KEYWORDS: anticardiolipin antibodies ■ antiphospholipid antibodies ■ antiphospholipid syndrome ■ lupus anticoagulant

Ricard Cervera† & Gerard Espinosa

†Author for correspondence: Servei de Malalties Autoimmunes, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain Tel.: +34 932 275 774; Fax: +34 932 271 707; rcervera@clinic.ub.es

The classical clinical picture of the antiphospholipid syndrome (APS) is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant, anticardiolipin antibodies (aCL) or antibodies targeting β_2-glycoprotein-I. The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition ('primary' APS), or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE). Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. Rapid chronological occlusive events, occuring over days to weeks, have been termed the 'catastrophic' APS [1].

According to the largest survey of APS patients – the Europhospholipid project [2] – deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation in this syndrome (38.9%). Conversely, cerebrovascular accidents – either stroke (19.8%) or transient ischemic attacks (11.1%) – are the most common arterial thrombotic manifestations. Early fetal loss (35.4%), late fetal loss (16.9%), premature births (10.6%) and preeclampsia (9.5%) are the most frequent fetal and obstetric manifestations. In addition, several other clinical features are relatively common in these patients, including thrombocytopenia (29.6%), livedo reticularis (24.1%), heart valve lesions (11.6%), hemolytic anemia (9.7%), epilepsy (7%), myocardial infarction (5.5%), leg ulcers (5.5%) and amaurosis fugax (5.4%). However, a large variety of other clinical manifestations have been less frequently described in patients with the APS, with prevalences lower than 5% (Table 1). The majority of these 'unusual' manifestations are case reports or short series and, therefore, it is not possible to create a table of real prevalences. In this article, we will review some of these unusual manifestations, the majority of which have been described in patients with primary APS without an inflammatory background.

Large-vessel manifestations

■ Large peripheral arterial occlusions

The first paper to describe large peripheral arterial occlusions in detail in SLE patients was published in 1965 [3]. Several other reports of

Table 1. Cumulative clinical features during the evolution of the disease in 1000 patients with antiphospholipid syndrome.

Manifestations	No.	%
Peripheral thrombosis		
Deep vein thrombosis	389	38.9
Superficial thrombophlebitis in legs	117	11.7
Arterial thrombosis in legs	43	4.3
Venous thrombosis in arms	34	3.4
Arterial thrombosis in arms	27	2.7
Subclavian vein thrombosis	18	1.8
Jugular vein thrombosis	9	0.9
Neurologic manifestations		
Migraine	202	20.2
Stroke	198	19.8
Transient ischemic attack	111	11.1
Epilepsy	70	7
Multi-infarct dementia	25	2.5
Chorea	13	1.3
Acute encephalopathy	11	1.1
Transient amnesia	7	0.7
Cerebral venous thrombosis	7	0.7
Cerebellar ataxia	7	0.7
Transverse myelopathy	4	0.4
Hemiballismus	3	0.3
Pulmonary manifestations		
Pulmonary embolism	141	14.1
Pulmonary hypertension	22	2.2
Pulmonary microthrombosis	15	1.5
Fibrosant alveolitis	12	1.2
Other (adult respiratory distress syndrome, pulmonary hemorrhage, pulmonary artery thrombosis)	7	0.7
Cardiac manifestations		
Valve thickening/dysfunction	116	11.6
Myocardial infarction	55	5.5
Angina	27	2.7
Myocardiopathy	29	2.9
Vegetations	27	2.7
Coronary bypass rethrombosis	11	1.1
Intracardiac thrombus	4	0.4
Intra-abdominal manifestations		
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	27	2.7
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	15	1.5
Splenic infaction	11	1.1
Pancreatic infarction	5	0.5
Addison´s syndrome	4	0.4
Hepatic manifestations (Budd–Chiari syndrome, small hepatic vein thrombosis)	7	0.7
Cutaneous manifestations		
Livedo reticularis	241	24.1
Ulcers	55	5.5
Pseudovasculitic lesions	39	3.9
Digital gangrene	33	3.3

Data taken from [2].

Table 1. Cumulative clinical features during the evolution of the disease in 1000 patients with antiphospholipid syndrome (cont.).

Manifestations	No.	%
Cutaneous manifestations (cont.)		
Cutaneous necrosis	21	2.1
Splinter hemorrhages	7	0.7
Osteo-articular manifestations		
Arthralgia	387	38.7
Arthritis	271	27.1
Avascular necrosis of bone	24	2.4
Ophthalmologic manifestations		
Amaurosis fugax	54	5.4
Retinal artery thrombosis	15	1.5
Retinal vein thrombosis	9	0.9
Optic neuropathy	10	1
Ear, nose and throat manifestations		
Nasal septum perforation	8	0.8
Hematological manifestations		
Thrombocytopenia (<100,000/µl)	296	29.6
Hemolytic anemia	97	9.7
Obstetric manifestations (pregnant female = 590)		
Preeclampsia	56	9.5
Eclampsia	26	4.4
Abruptio placentae	12	2
Post-partum cardio–pulmonary syndrome	3	0.5
Fetal manifestations (pregnancies = 1580)		
Early fetal losses (<10 weeks)	560	35.4
Late fetal losses (≥10 weeks)	267	16.9
Live births	753	47.7
Premature births	80/753	10.6

Data taken from [2].

large arterial occlusions and gangrene in SLE and 'lupus-like' patients who demonstrated aPL at some point during the course of their illness have subsequently been published [4–7].

Aortic occlusions

Several patients with an aortic arch syndrome and SLE have been reported [8–11], most of whom demonstrated aPL [9,10]. Occlusions of the abdominal aorta have also been documented [12,13].

Neurologic manifestations

Sneddon's syndrome

The association of livedo reticularis with ischemic stroke and, on occasion, accompanied by hypertension, has been known as Sneddon's syndrome since 1965 [14]. This may clearly be a manifestation of the primary APS [15,16]. However, the majority of these patients test 'negative' for aPL and Sneddon's syndrome may well be a condition with an alternative pathogenesis, perhaps related to endothelial cell perturbation and dysfunction, leading to thrombotic lesions affecting vessels of the dermis and cerebral vasculature [17–19].

Acute ischemic encephalopathy

Acute ischemic encephalopathy has been observed in several patients with aPL [20,21]. Patients are acutely ill, confused and obtunded with an asymmetrical quadriparesis, hyperreflexia and bilateral extensor plantar responses. Seizures may also occur. Small cortical hypodensities are discernible on MRI scanning.

Cerebral venous & dural sinus thrombosis

Cerebral venous and dural sinus thrombosis have a diverse spectrum of clinical manifestations, the most common being headaches accompanied by

papilledema, nausea, vomiting and visual field loss. Several such cases have been reported with aPL [21–26].

Psychosis

Several cases have been recorded where the APS is preceded by psychosis many years prior to the occurrence of thrombotic symptoms [27]. Increased aPL have indeed been documented in schizophrenic patients [28], as well as in patients suffering from major depressive illness [29–31].

Cognitive defects

Experimental work has found that neurologic and behavioural deficits in animal models are effects of the aPL. On immunofluorescence staining, immunoglobulin deposits have been observed in vessel walls of brain derived from these animals [32]. Four patients with APS who presented with rapidly progressive change in mental status, confusion, memory disturbance and emotional lability have also been reported [33].

Transient global amnesia

Transient global amnesia has been linked to aPL in one patient [34], and the authors suggested that aPL-linked ischemia may underlie the process.

'Pseudo-multiple sclerosis'

Reports of several aPL-positive patients who were young and had fluctuating and recurrent neurologic events with focal and visual neurologic symptoms have been published. High signal lesions in the periventricular white matter on T2-weighted images resembled multiple sclerosis [35,36].

Movement disorders

Chorea

In a review of 50 cases of chorea in the APS [37], we found that 96% were female and that the mean age was 23 years. One episode of chorea was seen in 66% of the patients, while in 34% it was recurrent. Oral contraceptive-induced chorea, chorea gravidarium and post partum chorea occurred in 2–6% of patients. It was seen bilaterally or unilaterally, and occasionally commenced on one side, to reappear on the other side within weeks or months. Computed tomography scanning is usually normal, but infarcts outside the basal ganglia themselves might be seen. MRI findings were only reported in 13 of the 50 cases and infarcts in the caudate nuclei were only seen in three individuals. Steroids, haloperidol, aspirin and anticoagulation were used in several patients and all patients recovered, but the time taken for recovery varied from days to as long as a few months. Some authors have suggested that reversible immune-mediated responses, hormonally influenced in some, are the most likely pathogenesis of chorea, rather than a vascular hypothesis with thrombosis and infarction occurring [38–45]. Binding of autoantibodies to striatal interneurons may cause hypermetabolic dysfunction of these cells.

Hemiballismus

Hemiballismus is a rare movement disorder and has been recorded in one aCL-positive patient [46].

Cerebellar ataxia

Cerebellar ataxia may also rarely be related to the presence of aPL [47].

Spinal syndromes

Transverse myelopathy

Several papers have stressed the occurrence of transverse myelitis with the presence of the aPL [47–53]. Optic neuritis may occur simultaneously, presenting with rapid visual loss accompanied by orbital pain [54].

Guillain–Barré syndrome

A few patients with Guillain–Barré syndrome have been documented [55,56]. It has been suggested that aCL of the IgA isotype are associated with peak disease activity [57].

Anterior spinal artery syndrome

Sparing of the posterior columns occurs in anterior spinal artery syndrome, with the patient presenting with a flaccid paraplegia, sphincter disturbances and dissociated sensory impairment. Several cases with positive aCL have been documented [58–60].

Ophthalmic complications

Several reports have estimated the occurence of retinal vascular occlusions in 8–12% of patients with aPL [61–64]. Optic neuropathy (acute retrobulbar optic neuritis, ischemic optic atrophy and progressive optic atrophy) has also been linked to the presence of the aPL [65–67].

Cardiac manifestations

Coronary bypass graft & angioplasty occlusions

Elevated aCL levels in patients who developed late bypass vein graft occlusions have been detected [68]. Another study reported increased IgA aCL levels in men with coronary artery disease who were treated with percutaneous transluminal coronary angioplasty and restenosed [69].

Cardiomyopathy

Multiple small vascular occlusions ('thrombotic microvasculopathy') are responsible for both acute and chronic cardiomyopathy seen in patients with aPL. Acute cardiac collapse (often together with respiratory decompensation) is frequent in patients with the catastrophic APS, and is one of the most common causes of death in this group of patients. Circulatory failure, as an isolated event, has also been reported [70,71], analagous to that seen with renal thrombotic microangiopathy. Chronic cardiomyopathy may be global or localised. Segmental ventricular dysfunction can supervene [72–74].

Intracardiac thrombus

Several patients with aPL have been reported who developed thrombi in the ventricular cavities [75–79]. Atrial thrombus might mimic atrial myxoma [80]. Occasionally, a clot may form on a normal mitral valve [81].

Complications of cardiovascular surgery

A 10% prevalence of a hypercoagulable condition has been detected on screening 158 patients with cardiovascular surgical procedures and these patients had a significantly higher incidence of early graft thrombosis [82]. Other authors identified 19 patients with aPL among 1078 treated for vascular surgical problems, while in a survey over a 2-year period [83], another group found that 26% of their patients were aPL positive and that they were 1.8 times more likely to have undergone previous lower-extremity vascular surgical procedures and 5.6 times more likely to have suffered occlusion of previous reconstructions [84]. In 1995, in a 5-year study, the authors identified 71 aPL-positive patients, of whom 19 had cardiovascular surgical procedures [85].

Pulmonary manifestations

Pulmonary arterial occlusions

Major pulmonary arterial thrombosis

Major pulmonary arterial thrombosis is distinctly rare and few such cases have been reported [86].

Pulmonary microthromboses

Unexpectedly, pulmonary microthromboses are also very uncommon in the APS, although originally suspected as being etiologically important in the pathogenesis of pulmonary hypertension in the presence of the aPL [87–89].

Acute respiratory distress syndrome

Several patients with the APS and acute respiratory distress syndrome (ARDS) have been reported [90,91]. A high frequency of ARDS in patients with catastrophic APS has also been described. It may be as a result of excessive cytokine production due to tissue damage seen in the catastrophic APS and is also part of the systemic inflammatory response syndrome, both in the context of infection and unrelated to precipitating factors. It has been described in patients with SLE-related APS and in primary APS.

Intra-alveolar pulmonary hemorrhage

Intra-alveolar pulmonary hemorrhage has been documented by several authors [88,92–96]. Coexisting pulmonary pathology such as pulmonary capillaritis, ARDS, microvascular thrombi and bronchiolitis obliterans was present in several patients simultaneously.

Post-partum syndrome

A post-partum syndrome comprising spiking fevers and pleurtic chest pain associated with pleural effusion and patchy infiltration of the lungs on chest x-ray has been described [97,98].

Renal manifestations

Intrarenal vascular lesions ('thrombotic microangiopathy')

Termed 'noninflammatory renal microangiopathy' by some authors [99], intrarenal vascular lesions closely resemble those seen in malignant hypertension and other thrombotic microangiopathies such as those found in patients with systemic sclerosis, eclampsia, the thrombotic thrombocytopenic purpura–hemolytic uremic syndrome group of conditions and in patients with transplant rejection [100–103] (**Figure 1**).

Renal artery occlusions

Renal artery trunk lesions have been documented in several patients with APS. Severe hypertension is common and renal failure may result. Unilateral or bilateral renal artery occlusions have been documented. Renal infarction may develop [104–106].

Renal vein thrombosis

A relationship between thrombosis of the renal veins and the aPL has been suggested despite the fact that renal vein thrombosis is not uncommon in patients with a nephrotic syndrome, regardless of etiology [107–110].

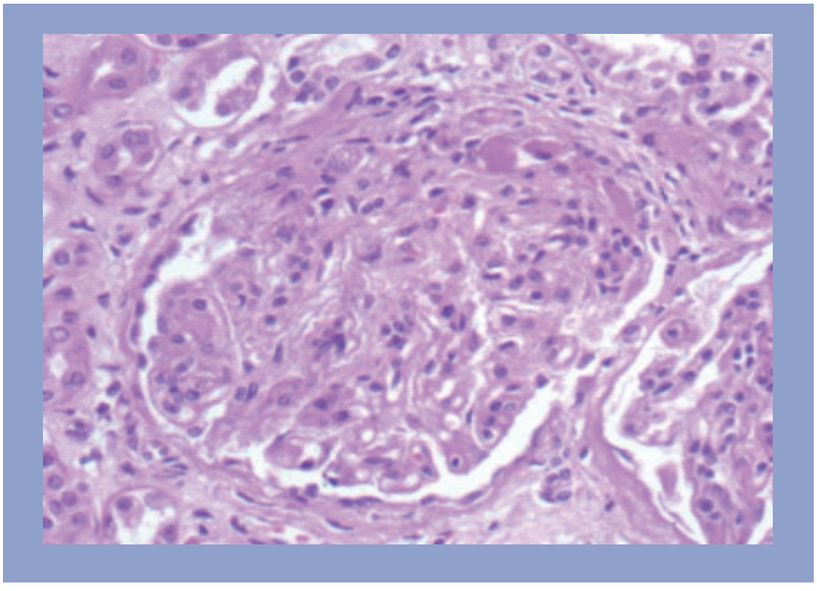

Figure 1. Glomerular microthrombosis in a patient with catastrophic antiphospholipid syndrome.

End-stage renal failure & hemodialysis

A total of 146 patients receiving dialysis for end-stage renal failure have been analyzed and it was found that having positive aCL predisposes to thrombotic events [111], in contrast to the bleeding tendency of end-stage renal patients. The association with repeated clotting of arteriovenous grafts has also been stressed by several authors [112–114].

Renal transplantation

Post-renal transplant thrombotic complications, including thrombotic microangiopathy, have been reported in some patients with aPL [115,116].

Pregnancy & post-partum syndromes

Renal failure occurring during pregnancy and, in particular, the post-partum period, may also be due to thrombotic microangiopathy. Several cases associated with aPL have now appeared in the literature [117–119].

Adrenal manifestations

Adrenal insufficiency is being increasingly recognized within the APS [120–132] and, although mainly reported in the adult literature [120–122], has also been documented in children and teenagers, the youngest being 10 years of age [123]. The mechanism for development of adrenal insufficiency seems to be a combination of adrenal vein thrombosis and/or hemorrhagic infarction and is usually bilateral. It has been proposed that any rise in adrenal venous pressure (e.g., such as occurs with venous thrombosis) would result in hemorrhage into the gland [127].

Hepatic manifestations

Budd–Chiari syndrome

Budd–Chiari syndrome is characterized by obstruction of large hepatic veins. Hepatic congestion and liver cell necrosis results [133–134]. Several case reports in patients with aPL have appeared [135–138].

Portal hypertension

The existence of portal hypertension in association with the aPL has been documented [139–143]. Several patients reported had a combination of both portal and pulmonary hypertension [139,141].

Obstruction of small hepatic veins (hepatic veno-occlusive disease)

Hepatic veno-occlusive disease is a condition characterized by nonthrombotic concentric narrowing of the lumen of small centrilobular veins by loose connective tissue and results in congestion and liver cell necrosis in the centrilobular areas [133]. Several patients with hepatic veno-occlusive disease and aPL have been reported. The condition is often associated with nodular hyperplasia of the liver and has also been reported in patients following bone marrow transplantation [144–146].

Nodular regenerative hyperplasia

A role for the aPL in the pathogenesis of nodular regenerative hyperplasia of the liver has been suggested [147,148] (Figure 2).

Hepatic infarction

Overt clinical hepatic infarction is rare but has occasionally been reported in the APS [148]. It seems to be not uncommon during pregnancy [149–151].

Digestive manifestations

Esophageal necrosis

A patient with a primary APS who thrombosed vessels at the lower end of the esophagus, resulting in necrosis, septic mediastinitis and death, has been documented [152].

Gastric ulceration

Progressive gastric ulceration with necrosis in a patient presenting with severe abdominal pain was found to be due to widespread occlusive vascular disease involving veins, small arteries and arterioles in one patient [153].

Small and large bowel vascular occlusions

Several cases of large bowel and intestinal infarctions in patients with aPL have been reported [154–161].

Mesenteric inflammatory vaso-occlusive disease

One patient with an unusual form of vasculitis involving the mesenteric vessels – mesenteric inflammatory vaso-occlusive disease – has been reported, who also developed an APS with deep vein thrombosis, thrombocytopenia and high titres of aCL [162]. The association of idiopathic mesenteric thrombosis and peripheral thrombosis has, in fact, been known for a long time [163].

Inflammatory bowel disease

Thromboembolic disease is a well recognized, although uncommon, complication of inflammatory bowel disease [164,165]. It has recently been reported that the presence of aPL may be associated with thrombosis in patients with ulcerative colitis and Crohn's disease [166–170].

Occlusion of splenic vessels

Occlusion of splenic vessels has been reported in combination with other vascular occlusions and splenic infarction may supervene [154,171,172].

Obstetric manifestations

Maternal complications

Several reports have suggested that women with aPL are more likely to develop a post-partum cardio–pulmonary syndrome [97,98], chorea gravidarum [37], post-partum cerebral infarct following aspirin withdrawal [173] and maternal death [174].

HELLP syndrome

A group of preeclamptic patients have been defined with hemolysis, elevated liver enzymes and a low platelet count (HELLP) syndrome. Reports of an association between this syndrome and the aPL appeared in 1994 with a documentation of two cases [175], which both demonstrated aCL and appeared to be refractory despite delivery, corticosteroids and anticoagulation. Placental pathology and skin biopsy revealed diffuse deposition of fibrin with small-vessel thrombi. Plasma exchange resulted in resolution of the syndrome in these patients.

Osteoarticular manifestations

Avascular necrosis of bone

A possible link between avascular necrosis of bone and aPL has been postulated [176], and this has been strengthened by reports of avascular necrosis of bone in patients with the primary APS who had not been exposed to glucocorticoid therapy at all [177–191].

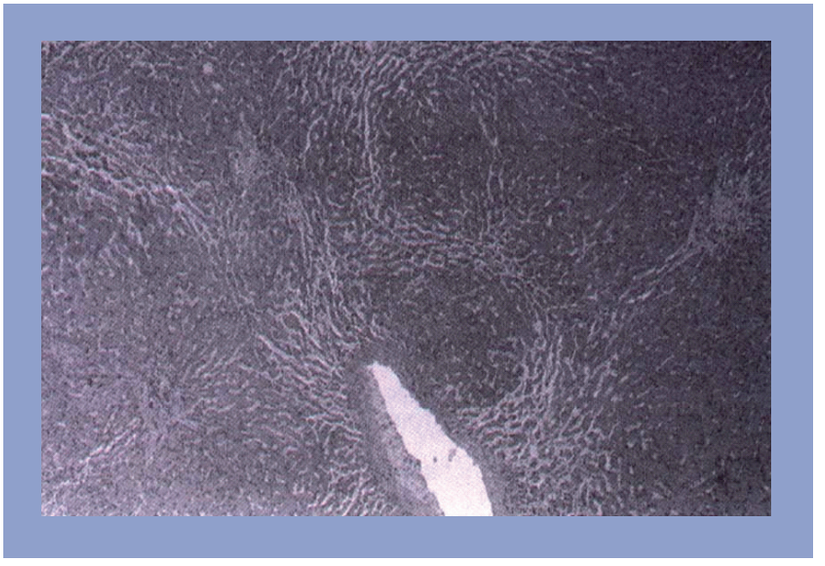

Figure 2. Hepatic nodular regenerative hyperplasia.

Dermatologic manifestations

Cutaneous necrosis

Superficial skin necrosis has been reported by several investigators [192–195]. Necrosing livedo reticularis of the legs has been described in a patient with pulmonary hemorrhage [196] and widespread skin necrosis in a patient with AIDS and aPL has been documented [197]. Widespread cutaneous necrosis is associated with massive thrombosis of small and medium-sized dermal vessels and has also been reported with the primary APS [198], with SLE [193,199], with rheumatoid arthritis [200] and in mycosis fungoides [201]. Painful cutaneous necrosis has been described on the cheeks and earlobes of a patient with lupus anticoagulant [202]. A patient with skin necrosis occurring during coumadin therapy who additionally had an acquired protein S deficiency and primary APS has also been documented [203].

Macules & nodules

Erythematous macules and painful skin nodules occurring in aPL-positive patients have been reported. These lesions are due to thrombotic skin disease, are located on the palms, soles and fingers and do not disappear on pressure [202,204]. These painful lesions have been reported as improving with salicylate therapy [205]. One patient with lymphocyte vasculitis, thrombosis and aCL was also documented [206].

Multiple subungual hemorrhages

Multiple subungual hemorrhages have been reported in the APS [207], in the absence of infective bacterial endocarditis (pseudo-infective endocarditis) [208], dependent on warfarin withdrawal and the appearance of catastrophic APS [209], with the administration of oral contraceptives and during pregnancy [207], and with amaurosis fugax [210,211].

Gangrene & digital necrosis

Cutaneous ischemic symptoms may culminate in digital gangrene and aPL-associated gangrene [7].

Conclusion

The many manifestations summarized in this article may not be statistically significantly related to the presence of the aPL or indeed be considered as 'definite' manifestations of the APS according to the classification criteria. However, as more cases are reported, the statistical evidence for these associations may become more definite. Many of these conditions are themselves uncommon and the demonstration of aPL has enabled us to more easily understand their pathogenesis, until now unexplained and complex.

The expanding spectrum of the association of a large variety of clinical events with the presence of the aPL, not all of which are associated with the presence of underlying thrombotic lesions (e.g., chorea), is evidence of the multifactorial actions of this group of antibodies and doubtless, as more cases are reported and published in the future, the unravelling of this unique group of disorders will take place. Therapy, with the introduction of novel compounds affecting different phases of the coagulation cascade, will also be refined and hopefully the need for long-term anticoagulation therapy with all its difficulties and attendant complications will fall away.

Future perspective

The etiology of APS has been studied extensively. However, a key question remains unsolved: is the etiology single or multiple? A 'two-hit hypothesis' has been suggested to explain the clinical observation that thrombotic events occur only occasionally in spite of the persistent presence of aPL. The aPL (first hit) increases the thrombophilic risk and the clotting takes place in the presence of another thrombophilic condition (second hit). It has been suggested that infectious processes may be the second hit since they frequently precede the full-blown picture of the syndrome and may be the initiator of the catastrophic subtype. Innate immunity receptors (i.e., toll like receptors) and mediators (complement) involved in sensing microbial agents might synergize and contribute in triggering the clotting event. However, the infectious etiology of APS is not limited to the triggering effect of infectious processes. In fact, it has been shown that antibodies against the main aPL antigenic targets, such as β2 glycoprotein-I, may be synthesized by B cell clones cross-reacting with epitopes expressed on infectious agents as the result of a molecular mimicry between exogenous molecules and β2 glycoprotein-I. Whether an individual will develop APS will depend mainly on his/her genetic predisposition, which might or might not favor the production of the cross-reacting autoantibodies.

Therefore, the questions remains if there are additional etiological factors for APS. Are there other environmental factors that are responsible for inducing APS, such as drugs or tumors? Are there other stimulants of the innate immune system driving it toward an overt APS, such as redox effect? If persistent positivity for aPL represents a condition necessary but not sufficient by itself to induce the clinical manifestations of the syndrome, is there a genetic background for explaining why a positive aPL carrier develops thrombotic events or remains asymptomatic? May the same genetic background explain why the catastrophic variant occurs in some cases only? The presence of aPL, but not the clinical manifestations of the disease, has been associated with *MHC* genes, while concomitant genetic thrombophilic conditions were reported to increase the ultimate risk of thrombotic events.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The classical clinical picture of the antiphospholipid syndrome (APS) is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations.
- Deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation in this syndrome (38.9%). Cerebrovascular accidents – either stroke (19.8%) or transient ischemic attacks (11.1%) – are the most common arterial thrombotic manifestations. Early fetal loss (35.4%), late fetal loss (16.9%), premature birth (10.6%), and preeclampsia (9.5%) are the most frequent fetal and obstetric manifestations.
- Several other clinical features are relatively common in these patients, including thrombocytopenia (29.6%), livedo reticularis (24.1%), heart valve lesions (11.6%), hemolytic anemia (9.7%), epilepsy (7%), myocardial infarction (5.5%), leg ulcers (5.5%) and amaurosis fugax (5.4%).
- However, a large variety of clinical manifestations have been occasionally described in patients with the APS, with prevalences lower than 5%. Virtually any organ, system or tissue of the body can be affected and the APS be manifested in such diverse conditions as chorea, intracardiac thrombus, acute respiratory distress syndrome, Addison´s disease, Budd–Chiari syndrome, avascular necrosis of bone or preeclamptic patients with hemolysis, elevated liver enzymes and a low platelet count (HELLP syndrome), to name just a few.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Asherson RA, Cervera R, Piette JC, Shoenfeld Y: Milestones in the antiphospholipid syndrome. In: *The Antiphospholipid Syndrome II - Autoimmune Thrombosis*. Asherson RA, Cervera R, Piette JC, Shoenfeld Y (Eds). Elsevier, Amsterdam, The Netherlands, 3–9 (2002).

2 Cervera R, Piette JC, Font J *et al.*: Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum.* 46, 1019–1027 (2002).

▪▪ **Largest survey of antiphospholipid syndrome (APS) patients describing the prevalence of the main clinical manifestations of this syndrome.**

3 Alarcón-Segovia D, Osmundson PJ: Peripheral vascular syndromes associated with systemic lupus erythematosus. *Ann. Intern. Med.* 62, 907–919 (1965).

4 Bird AG, Lendrum R, Asherson RA, Hughes GRV: Disseminated intravascular coagulation, antiphospholipid antibodies and ischaemic necrosis of extremities. *Ann. Rheum. Dis.* 46, 251–255 (1987).

5 Asherson RA, Derksen RHWM, Harris EN *et al.*: Large vessel occlusion and gangrene in systemic lupus erythematosus and "lupus-like" disease. A report of six cases. *J. Rheumatol.* 13, 740–747 (1986).

6 Jindal BK, Martin MFR, Gayner A: Gangrene developing after minor surgery in a patients with undiagnosed systemic lupus erythematosus and lupus anticoagulant. *Ann. Rheum. Dis.* 42, 347–349 (1983).

7 Asherson RA, Cervera R, Klumb E *et al.*: Amputation of digits or limbs in patients with antiphospholipid syndrome. *Semin. Arthritis Rheum.* 38, 124–131 (2008).

▪ **Largest series of APS patients with gangrene and amputation of digits or limbs.**

8 Ferrante FM, Myerson GE, Goldman JA: Subclavian artery thrombosis mimicking the aortic arch syndrome in systemic lupus erythematosus. *Arthritis Rheum.* 25, 1501–1504 (1982).

9 Asherson RA, Harris EN, Gharavi AE *et al.*: Aortic arch syndrome associated with anticardiolipin antibodies and the lupus anticoagulant: comment on Ferrante paper. *Arthritis Rheum.* 28, 594–595 (1985).

10 Lessof MH, Glynn LE: The pulseless syndrome. *Lancet* 1, 799–801 (1959).

11 Asherson RA, Ridley MG, Khamashta MA, Hughes GRV: Gangrena en el lupus eritematoso sistémico. *Piel* 3, 409–412 (1988).

12 Drew P, Asherson RA, Zuk RJ *et al.*: Aortic occlusion in systemic lupus erythematosus associated with antiphospholipid antibodies. *Ann. Rheum. Dis.* 46, 612–616 (1987).

13 Ter Borg EJ, Van Der Meer J, De Wolf JTM *et al.*: Arterial thrombotic manifestations in young women associated with the lupus antocoagulant. *Clin. Rheumatol.* 7, 74–79 (1988).

14 Sneddon IB: Cerebrovascular lesions and livedo reticularis. *Br. J. Dermatol.* 77, 180–185 (1965).

15 Rebollo M, Val FJ, Garijo F *et al.*: Livedo reticularis and cerebro-vascular lesions (Sneddon's syndrome). Clinical, radiological and pathological features in eight cases. *Brain* 106, 965–979 (1983).

16 Brey RL, Escalante A, Futrell N, Asherson RA: Cerebral thrombosis and other neurologic manifestations in the Antiphospholipid Syndrome. In: *The Antiphospholipid Syndrome*. Asherson RA, Cervera R, Piette J-C, Shoenfeld Y (Eds). CRC Press, FL, USA, 133–150 (1996).

17 Asherson RA, Mayou S, Black M *et al.*: Livedo reticularis, connetive tissue disease, anticardiolipin antibodies and CNS complications. *Arthritis Rheum.* 30(Suppl. 4), S69 (1987).

18 Asherson RA, Cervera R: Sneddon's and the "primary" antiphospholipid syndrome: confusion clarified. *J. Stroke Cerebrovasc. Dis.* 3, 121–122 (1993).

19 Uthman IW, Khamashta MA: Livedo racemosa: a striking dermatological sign for the antiphospholipid syndrome. *J. Rheumatol.* 33, 2379–2382 (2006).

20 Briley DP, Coull BM, Goodnight SH: Neurological disease associated with antiphospholipid antibodies. *Ann. Neurol.* 25, 221–227 (1989).

21 Levine SR, Kieran S, Puzio K, Feit H, Patel SC, Welch KYA: Cerebral venous thrombosis with lupus anticoagulant. Report of two cases. *Stroke* 18, 801–804 (1987).

22 Lau SO, Bock GH Edson JR, Michael AF: Sagittal sinus thrombosis in the nephrotic syndrome. *J. Pediatr.* 97, 948–950 (1980).

23 Averback P: Primary cerebral venous thrombosis in young adults. The diverse manifestations of an unrecognised disease. *Ann. Neurol.* 3, 81–86 (1978).

24 Provenzale JM, Loganbill HA: Dural sinus thrombosis and venous infarction associated with antiphospholipid antibodies. MR findings. *J. Comput. Assist. Tomogr.* 18, 719–723 (1994).

25 Mokri B, Jack CRJR, Petty GW: Pseudotumour syndrome associated with cerebral venous sinus occlusion and antiphospholipid antibodies. *Stroke* 24, 469–472 (1993).

26 Khoo KBK, Long FL, Tuck RR, Allen RJ, Tymms KE: Cerebral venous sinus thrombosis associated with the primary antiphospholipid syndrome. *Med. J. Aust.* 162, 30–32 (1995).

27 Jurtz G, Muller N: The antiphospholipid syndrome and psychosis. *Am. J. Psychiatry* 151, 1841–1842 (1994).

28 Sirota P, Schild K, Firer M *et al.*: The diversity of autoantibodies in schizophrenic patients and their first degree relatives : analysis of multiple case families. In: *Abstracts of the First International Congress of the International Society of Neuro-Immune Modulation. Florence.* ISNIM 389 (1991).

29 Maes M, Meltzer H, Jacobs J *et al.*: Autoimmunity in depression: increased antiphospholipid autoantibodies. *Acta Psychiatr. Scand.* 87, 160–166 (1993).

30 Calabrese LV, Stern TA: Neuropsychiatric manifestations of systemic lupus erythematosus. *Psychosomatics* 36, 344–359 (1995).

31 Abel T, Goldman DD, Urowitz MB: Neuropsychiatric lupus. *J. Rheumatol.* 7, 325–333 (1980).

32 Ziporen L, Eilam D, Shoenfeld Y, Korczyn AD: Neurologic dysfunction associated with antiphospholipid antibodies: animal models. *Neurology* 46, A459 (1996).

33 Mikdashi JA, Chase C, Kay GG: Neurocognitive deficits in antiphospholipid syndrome. *Neurology* 46, A359 (1996).

34 Montalban J, Arboix A, Staub H *et al.*: Transient global amnesia and antiphospholipid antibodies. *Clin. Exp. Rheumatol.* 7, 85–87 (1989).

35 Scott TF, Hess D, Brillman J: Antiphospholipid antibody syndrome mimicking multiple sclerosis clinically and by magnetic resonance imaging. *Arch. Intern. Med.* 154, 917–920 (1994).

36 Hughes GRV: The antiphospholipid syndrome and "multiple sclerosis". *Lupus* 8, 89 (1999).

37 Cervera R, Asherson RA, Font J *et al.*: Chorea in the antiphospholipid syndrome. Clinical, neurologic and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore)* 76, 203–212 (1997).

▪ **Largest series of APS patients with chorea.**

38 Asherson RA, Derksen RHWM, Harris EN *et al.*: Chorea in systemic lupus erythematosus and 'lupus-like' disease: association with antiphospholipid antibodies. *Semin. Arthritis Rheum.* 16, 253–259 (1987).

39 Bouchez B, Arnott G, Hatron PY, Wattel A, Devulder B: Choré et lupus érytémateux disséminé avec anticoagulant circulant. Trois cas. *Rev Neurol (Paris)* 141, 571–574 (1985).

40 Khamashta MA, Gil A, Anciones B *et al.*: Chorea in systemic lupus erythematosus: association with antiphospholipid antibodies. *Ann. Rheum. Dis.* 47, 681–683 (1988).

41 Hodges JR: Chorea and the lupus anticoagulant. *J. Neurol. Neurosurg. Psychiatr.* 50, 368–369 (1987).

42 Asherson RA, Harris EN, Gharavi AE, Hughes GRV: Systemic lupus erythematosus, antiphospholipid antibodies, chorea and oral contraceptives. *Arthritis Rheum.* 29, 1535–1536 (1986).

43 Asherson RA, Harris EN, Hughes GRV, Farquharson RG: Complications of oral contraceptives and antiphospholipid antibodies. *Arthritis Rheum.* 31, 575 (1988).

44 Furie R, Ishikawa T, Dhawan V, Eidelberg D: Alternating hemichorea in primary antiphospholipid syndrome. Evidence for contralateral striatal hypermetabolism. *Neurology* 44, 2197–2199 (1994).

45 Sundén-Cullberg J, Tedroff J, Aquilonius S-M: Reversible chorea in primary antiphospholipid syndrome. *Mov. Disord.* 13, 147–149 (1998).

46 Tam L-S, Cohen MG, Li EK: Hemiballismus in systemic lupus erythematosus: possible association with antiphospholipid antibodies. *Lupus* 4, 67–69 (1995).

47 Singh PR, Piasaa K, Qumar A *et al.*: Cerebellar ataxia in systemic lupus erythematosus: three case reports. *Ann. Rheum. Dis.* 97, 954–956 (1988).

48 Propper DJ, Bucknall RC: Acute transverse myelitis complicating lupus erythematosus. *Ann. Rheum. Dis.* 48, 512–515 (1989).

49 Adrianakos AA, Duffy UJ, Suzuki M, Sharp JJ: Transverse myelopathy in systemic lupus erythematosus. A report of three cases and a review of the literature. *Ann. Intern. Med.* 83, 616–624 (1975).

50 Harisdangkul V, Doorenbos D, Subramony SH: Lupus transverse myelopathy: better outcome with early recognition and aggressive high-dose intravenous corticosteroid pulse treatment. *J. Neurol.* 242, 326–331 (1995).

51 Lavalle C, Pizarro S, Drenkard C, Sánchez-Guerrero J, Alarcón-Segovia D: Transverse myelitis: manifestation of systemic lupus erythematosus strongly associated with antiphospholipid antibodies. *J. Rheumatol.* 17, 34–37 (1990).

52 Chang R, Quismorio P Jr: Transverse myelopathy in systemic lupus erythematosus (SLE). *Arthritis Rheum.* 33 (Suppl. 9), S102 (1990).

53 Smyth AE, Bruce IN, McMillan SA, Bell AL: Transverse myelitis : a complication of systemic lupus erythematosus that is associated with the antiphospholipid syndrome. *Ulster Med. J.* 645, 91–94 (1996).

54 Oppenheimer S, Hofbrand BI: Optic neuritis and myelopathy in systemic lupus erythematosus. *Can. J. Neurol. Sci.* 13, 129–132 (1986).

55 Harris EN, Englert H, Derue G, Hughes GRV, Gharavi AE: Antiphospholipid antibodies in acute Guillain-Barré syndrome. *Lancet* 2, 1361–1362 (1983).

56 Palosuo T, Vaarala O, Kinnuren E: Anticardiolipin antibodies in the Guillain-Barré syndrome. *Lancet* 2, 839 (1985).

57 Frampton G, Weiner JB, Cameron JS, Hughes RAC: Severe Guillain-Barré syndrome: an association with IgA anticardiolipin antibodies in a series of 92 patients. *J. Neuro-Immunol.* 19, 133–139 (1988).

58 Marcusse HN, Hahn J, Tan WD, Breedveld FC: Anterior spinal artery syndrome in systemic lupus erythematosus. *Br. J. Rheumatol.* 28, 344–346 (1989).

59 Harris EN, Gharavi AE, Mackworth-Young CG, Patel BM, Derue G, Hughes GRV: Lupoid sclerosis: a possible pathogenetic role for antiphospholipid antibodies. *Ann. Rheum. Dis.* 44, 281–283 (1985).

60 Marullo S, Clauvel JP, Intrator L, Danon F, Brouet JC, Oksenhendler E: Lupoid sclerosis with antiphospholipid and antimyelin antibodies. *J. Rheumatol.* 20, 747–749 (1993).

61 Labutta RJ: Ophthalmic manifestations in the antiphospholipid syndrome. In: *The Antiphospholipid Syndrome*. Asherson RA, Cervera R, Piette J-C, Shoenfeld Y (Eds). CRC Press, FL, USA. 213–218 (1996).

62 Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, Stevens MB: Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch. Ophthalmol.* 104, 558–563 (1986).

63 Asherson RA, Merry P, Acheson JF, Harris EN, Hughes GRV: Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome. *Ann. Rheum. Dis.* 48, 358–361 (1989).

64 Montehermoso A, Cervera R, Font J *et al.*: Association of antiphospholipid antibodies with retinal vascular disease in systemic lupus erythematosus. *Semin. Arthritis Rheum.* 28, 326–332 (1999).

65 Gerber SL, Cantor LB: Progressive optic atrophy and the antiphospholipid antibody syndrome. *Am. J. Ophthalmol.* 110, 443–444 (1990).

66 Watts MT, Greaves M, Rennie IG, Clearkin LB: Antiphospholipid antibodies in the aetiology of ischemic optic neuropathy. *Eye* 5, 75–79 (1991).

67 Reino S, Muñoz-Rodríguez FJ, Cervera R, Espinosa G, Font J, Ingelmo M: Optic neuropathy in the "primary" antiphospholipid syndrome: Report of a case and review of the literature. *Clin. Rheumatol.* 16, 629–631 (1997).

68 Morton KE, Gavaghan TP, Krilis SA *et al.*: Coronary artery bypass graft failure: an autoimmune phenomenon? *Lancet* 2, 1353–1356 (1986).

69 Eber B, Schumacher M, Auer-Grumbach P, Toplak H, Klein W: Increased IgM anticardiolipin antibodies in patients with restenosis after percutaneous transluminal coronary angioplasty. *Am. J. Cardiol.* 69, 1255–1258 (1992).

70 Murphy JJ, Leach IH: Findings of necropsy in the heart of a patient with anticardiolipin syndrome. *Br. Heart J.* 62, 61–64 (1989).

71 Brown JH, Doherty CC, Allen DC, Morton P: Fatal cardiac failure due to myocardial microthrombi in systemic lupus erythematosus. *Br. Med. J.* 296, 1505 (1988).

72 Nihoyannopoulos P, Gómez PM, Joshi J, Loizou S, Walport MJ: Cardiac abnormalities in systemic lupus erythematosus. Association with raised anticardiolipin antibodies. *Circulation* 82, 369–375 (1990).

73 Leung WH, Wong KL, Lau CP, Wong CK, Cheng CH: Association between antiphospholipid antibodies and cardiac abnormalities in patients with systemic lupus erythematosus. *Am. J. Med.* 89, 411–419 (1990).

74 Hasnie AM, Stoddard MF, Gleason CB *et al.*: Diastolic dysfunction is a feature of the antiphospholipid syndrome. *Am. Heart J.* 129, 1009–1113 (1995).

75 Bruce D, Bateman D, Thomas R: Left ventricular thrombi in a patient with the antiphospholipid syndrome. *Br. Heart J.* 74, 202–203 (1995).

76 Baum RA, Jundt JW: Intracardiac thrombosis and antiphospholipid antibodies: a case report and review of the literature. *South. Med. J.* 87, 928–932.

77 Coppock MA, Safford RE, Danielson GK: Intracardiac thrombosis, phospholipid antibodies and two-chambered right ventricle. *Br. Heart J.* 60, 455–458 (1988).

78 O'Neill D, Magaldi J, Dobkins D, Greco T: Dissolution of intracardiac mass lesions in the primary antiphospholipid antibody syndrome. *Arch. Intern. Med.* 155, 325–327 (1995).

79 O'Hickey S, Skinner C, Beattie J: Life threatening right ventricular thrombosis in association with phospholipid antibodies. *Br. Heart J.* 70, 279–281 (1993).

80 Gertner E, Leatherman JW: Intracardiac mural thrombus mimicking atrial myxoma in the antiphospholipid syndrome. *J. Rheumatol.* 19, 1293–1298.

81 Nickele GA, Foster DA, Kenny D: Primary antiphospholipid syndrome and mitral valve thrombosis. *Am. Heart J.* 128, 1245–1247 (1994).

82 Donaldson MC, Weinberg D, Belkin M *et al.*: Screening for hypercoagulable states in vascular surgical practice: a preliminary study. *J. Vasc. Surg.* 11, 825–831 (1990).

83 Shortell CK, Ouriel K, Green RM *et al.*: Vascular disease in the antiphospholipid syndrome: a comparison with the patient population with atherosclerosis. *J. Vasc. Surg.* 15, 158–166 (1992).

84 Taylor IM, Chitwood RW, Dalman RL *et al.*: Antiphospholipid antibodies in vascular surgery patients: a cross-sectional study. *Ann. Surg.* 226, 545–551 (1994).

85 Ciocca RG, Choi J, Graham AM: Antiphospholipid antibodies lead to increased risk in cardiovascular surgery. *Am. J. Surg.* 170, 198–200 (1995).

86 Luchi ME, Asherson RA, Lahita RG: Primary idiopathic pulmonary hypertension complicated by pulmonary arterial thrombosis: association with antiphospholipid antibodies. *Arthritis Rheum.* 35, 700–705 (1992).

87 Asherson RA, Oakley CN: Pulmonary hypertension and systemic lupus erythematosus. *J. Rheumatol.* 13, 1–5 (1986).

88 Gertner E, Lie JT: Pulmonary capillaritis, alveolar haemorrhage and recurrent microvascular thrombosis in primary antiphospholipid syndrome. *J. Rheumatol.* 20, 1224–1228 (1993).

89 Brucato A, Baudo F, Barberis M *et al.*: Pulmonary hypertension secondary to thrombosis of the pulmonary vessels in a patient with the primary antiphospholipid syndrome. *J. Rheumatol.* 21, 942–944 (1994).

90 Ghosh S, Walters HD, Joist JH, Osborn TG, Moore TL: Adult respiratory distress syndrome associated with antiphospholipid antibody syndrome. *J. Rheumatol.* 20, 1406–1408 (1993).

91 Kerr JE, Poe R, Kramer Z: Antiphospholipid antibody syndrome presenting as a refractory non-inflammatory pulmonary vasculopathy. *Chest* 112, 1707–1710 (1997).

92 Howe HS, Boey ML, Fong KY, Feng PH: Pulmonary haemorrhage, pulmonary infarction and the lupus anticoagulant. *Ann. Rheum. Dis.* 47, 869–872 (1988).

93 Hillerdal G, Hagg A, Licke G, Wegenius G, Scheibenflug L: Intraalveolar haemorrhage in the anticardiolipin antibody syndrome. *Scand. J. Rheumatol.* 20, 58–62 (1991).

94 Crausman RS, Achenbach GA, Pluss WT *et al.*: Pulmonary capillaritis and alveolar haemorrhage associated with the antiphospholipid syndrome. *J. Rheumatol.* 22, 554–556 (1995).

95 Schwab EP, Schumacher HR, Freundlich B, Callegari PE: Pulmonary alveolar haemorrhage in systemic lupus erythematosus. *Semin. Arthritis Rheum.* 23, 8–15 (1993).

96 Asherson RA, Greenblatt M: Recurrent alveolar hemorrhage and pulmonary capillaritis in the 'primary' antiphospholipid syndrome. *J. Clin. Rheumatol.* 7, 30–33 (2001).

97 Branch DW, Kochenour NP, Rote NS *et al.*: New post-partum syndrome associated with antiphospholipid antibodies. *Obstet. Gynacol.* 69, 460–468 (1987).

98 Kupferminc MJ, Lee MJ, Green D, Pieceman AM: Severe post-partum pulmonary, cardiac and renal syndrome associated with antiphospholipid antibodies. *Obstet. Gynacol.* 83, 806–807 (1994).

99 Bhathena DB, Sobel BJ, Mydal SD: Non-inflammatory renal microangiopathy of systemic lupus erythematosus ("lupus vasculitis"). *Am. J. Nephrol.* 1, 144–159 (1981).

100 Churg J, Goldstein MH, Bernstein J: Thrombotic angiopathy including haemolytic-uremic syndrome, thrombotic thrombocytopenic purpura and postpartum renal failure. In: *Renal Pathology With Clinical And Functional Correlates* (Volume 2). Tister CC, Brenner BM (Eds). JB Lippincott, PA, USA 1081–1113 (1989).

101 Hughson MD, Madasdy T, McCarty GA, Stoler C, Min K-W, Silva T: Renal thrombotic microangiopathy in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am. J. Kidney Dis.* 20, 150–158 (1992).

102 Kinkaid-Smith P, Fairley KF, Kross M: Lupus anticoagulation associated with renal thrombotic microangiopathy and pregnancy related renal failure. *Q. J. Ped.* 69, 795–815 (1988).

103 Asherson RA: The catastrophic antiphospholipid syndrome syndrome. *J. Rheumatol.* 19, 508–512 (1992).

▪▪ **Original description of the catastrophic APS.**

104 Asherson RA, Nobel GE, Hughes GRV: Hypertension, renal artery stenosis and the 'primary" antiphospholipid syndrome. *J. Rheumatol.* 18, 1413–1415 (1991).

105 Asherson RA, Hughes GRV, Derksen RHWM: Renal infarction associated with antiphospholipid antibodies in systemic lupus erythematosus and 'lupus-like' disease. *J. Urol.* 140, 1028 (1988).

106 Poux JM, Boudet R, Lacroix P *et al.*: Renal infarction and thrombosis of the infra-renal aorta in a 35-year old man with primary antiphospholipid syndrome. *Am. J. Kidney Dis.* 27, 721–725 (1996).

107 Asherson RA, Lanham JG, Hull RG, Boey ML, Gharavi AE, Hughes GRV: Renal vein thrombosis in systemic lupus erythematosus : association with the lupus anticoagulant. *Clin. Exp. Rheumatol.* 2, 75–79 (1984).

108 Asherson RA, Buchanan M, Baguley E, Hughes GRV: Postpartum bilateral renal vein thrombosis in the primary antiphospholipid syndrome. *J. Rheumatol.* 20, 874–876 (1993).

109 Hage ML, Liv R, Harcheschi DG, Bowie JD, Allen NB, Macik BG: Fetal renal vein thrombosis, hydrops fetalis and maternal lupus anticoagulant: a case report. *Prenat. Diagn.* 14, 873–877 (1994).

110 Liaño F, Mampaso F, Barcia-Martín F: Allograft membranous glomerulonephritis and renal vein thrombosis in a patient with lupus anticoagulation factor. *Nephrol. Dial. Transplant.* 3, 684–689 (1988).

111 Gronhagen-Riska C, Teppo AM, Helentera A, Honkanen E, Julkunen H: Raised concentration of antibodies to cardiolipin in patients receiving haemodialysis. *Br. Med. J.* 300, 1696–1697 (1990).

112 Prakash R, Miller CC, Suki WM: Anticardiolipin antibody in patients on maintenance haemodialysis and its association with recurrent arteriovenous graft thrombosis. *Am. J. Kidney Dis.* 26, 347–352 (1995).

113 Kirschbaum B, Mullinax F, Curry N, Mallory J: Association between anticardiolipin antibody and frequent clotting problems in haemodialysis patients. *J. Am. Soc. Nephrol.* 2, 332 (1991).

114 Brunet P, Aillava MF, San Marco M *et al.*: Antiphospholipids in haemodialysis patients: relationship between lupus anticoagulant and thrombosis. *Kidney Int.* 48, 794–800 (1995).

115 Radhakrishnan J, Williams GS, Appel GB, Cohen DJ: Renal transplantation in anticardiolipin antibody-positive lupus erythematosus patients. *Am. J. Kidney Dis.* 23, 286–289 (1994).

116 Mondragón-Ramírez G, Bochicchio T, García-Torres R *et al.*: Recurrent renal thrombotic angiopathy after kidney transplantation in two patients with end-stage renal disease. *Thromb. Res.* 72, 109–117 (1993).

117 Huang JJ, Chen MW, Sung JM, Lan RR, Wang MC, Chen FF: Postpartum haemolytic-uremic syndrome associated with antiphospholipid antibody. *Nephrol. Dial. Transplant.* 13, 182–186 (1988).

118 Kniaz D, Eisenberg GH, Elrad H, Johnson CA, Valaitis J, Bregman H: Postpartum haemolytic-uremic syndrome associated with antiphospholipid antibodies. *Am. J. Nephrol.* 12, 126–133 (1992).

119 Ornstein MH, Rand JH: An association between refractory HELLP syndrome and antiphospholipid antibodies during pregnancy: a report of two cases. *J. Rheumatol.* 21, 1360–1364 (1994).

120 Asherson RA, Hughes GRV: Hypoadrenalism, Addison's disease and antiphospholipid antibodies. *J. Rheumatol.* 18, 1–3 (1991).

121 Asherson RA: Hypoadrenalism and the antiphospholipid antibodies. A new cause of idiopathic "Addison's disease". In: *Advances in Thomas Addison's Diseases* (Volume 1). Bhatt, James, Besser, Botazzo, Keen (Eds). J. Endocrinol. Ltd. Bristol, UK 87–101 (1994).

122 Arnason JA, Graziano FM: Adrenal insufficiency in the antiphospholipid antibody syndrome. *Semin. Arthritis Rheum.* 25, 109–116 (1995).

123 Pelkonen P, Simell O, Rasi V *et al.*: Venous thrombosis associated with the lupus anticoagulant. *Ann. Intern. Med.* 92, 156–159 (1980).

124 Grottolo A, Ferrari V, Mariarosa M *et al.*: Primary adrenal insufficiency, circulating lupus anticoagulant and anticardiolipin antibodies in a patient with multiple abortions and recurrent thrombotic episodes. *Haematologia* 73, 517–519 (1988).

125 Asherson RA, Hughes GRV: Recurrent deep vein thrombosis in Addison's disease in "primary" antiphospholipid syndrome. *J. Rheumatol.* 16, 378–380 (1989).

126 Carette S, Jobin F: Acute adrenal insufficiency as a manifestation of the anticardiolipin syndrome. *Ann. Rheum. Dis.* 48, 430–431 (1989).

127 Rao R, Vagnucci A, Amico, J: Bilateral massive adrenal haemorrhage: early recognition and treatment. *Ann. Intern. Med.* 110, 227–235 (1989).

128 Marie I, Levesque H, Heron F, Kailleux N, Borg JY, Courtois H: Acute adrenal failure secondary to bilateral infarction of the adrenal glands as the first manifestation of primary antiphospholipid antibody syndrome. *Ann. Rheum. Dis.* 567–568 (1997).

129 Argento A, Di Benedetto RJ: ARDS and adrenal insufficiency associated with the antiphospholipid antibody syndrome. *Chest* 113, 1136–1138 (1998).

130 Guibal F, Rybojad M, Cordoliani F *et al.*: Melanoderma revealing primary antiphospholipid syndrome. *Dermatology* 192, 75–77 (1996).

131 Provenzale JM, Ortel TL, Nelson RC: Adrenal haemorrhages in patients with primary antiphospholipid syndrome: imaging findings. *AJR Am. J. Roentgenol.* 165, 361–364 (1995).

132 Oelkers W: Adrenal insufficiency IV. *N. Engl. J. Med.* 335, 1206–1212 (1996).

133 Pessayre D, Larrey D: Drug induced liver injury. In : *Oxford Textbook of Clinical Hepatology*. McIntyre N, Benhamou J-P, Bircher J, Rizetto M, Rodés J (Eds). Oxford University Press, Oxford, UK 876–902 (1991).

134 Valla D, Benhamou J-P: Disorders of the hepatic veins and venules. In: *Oxford Textbook of Clinical Hepatology.* McIntyre N, Benhamou J-P, Bircher J, Rizetto M, Rodés J (Eds). Oxford University Press, Oxford, UK 1004–1011 (1991).

135 Pomeroy C, Knodell RG, Swain WR, Arneson P, Mahowald ML: Budd-Chiari syndrome in a patient with the lupus anticoagulant. *Gastroenterology* 86, 158–161 (1984).

136 Shimizu S, Miyata M, Kamiike W *et al.*: Budd-Chiari syndrome combined with antiphospholipid syndrome: case report and literature review. *Vasc. Surg.* 501–509 (1993).

137 Farrant JM, Judge M, Thompson RDH: Thrombotic cutaneous nodules and hepatic vein thrombosis in the anticardiolipin syndrome. *Clin. Exp. Dermatol.* 14, 306–308 (1989).

138 Ouwendijk RJT, Koster JC, Wilson JHP *et al.*: Budd-Chiari syndrome in a young patient with anticardiolipin antibodies: need for prolonged anticoagulant treatment. *Gut* 35, 1004–1006 (1994).

139 Mackworth-Young CG, Gharavi AE, Boey ML, Hughes GRV: Portal and pulmonary hypertension in a case of systemic lupus erythematosus: possible relationship with a clotting abnormality. *Eur. J. Rheumatol. Inflamm.* 7, 71–74 (1984).

140 Ordi J, Vargas V, Vilardell M *et al.*: Lupus anticoagulant and portal hypertension. *Am. J. Med.* 84, 566–568 (1988).

141 De Clerck L, Michielsen PP, Ramael MR *et al.*: Portal and pulmonary vessel thrombosis associated with systemic lupus erythematosus and anticardiolipin antibodies. *J. Rheumatol.* 18, 1919–1921 (1991).

142 Takahaski C, Kumagai S, Tsubata R *et al.*: Portal hypertension associated with anticardiolipin antibodies in a case of systemic lupus erythematosus. *Lupus* 4, 232–235 (1995).

143 Mantz FA, Craige E: Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. *Arch. Pathol.* 52, 91–97 (1951).

144 Nakamura H, Uehara H, Okada T *et al.*: Occlusion of small hepatic veins associated with systemic lupus erythematosus with the lupus anticoagulant. *Hepatogastroenterology* 36, 393–397 (1989).

145 Morio S, Oh H, Hirasawa A *et al.*: Hepatic veno-occlusive disease in a patient with lupus anticoagulant after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 8, 147–149 (1991).

146 Rio B, Andreu G, Nicod A *et al.*: Thrombocytopenia in veno-occlusive disease after bone marrow transplantation or chemotherapy. *Blood* 67, 1773–1776 (1986).

147 Pérez-Ruiz F, Orte-Martínez FJ, Zea-Mendoza AC, Ruiz del Arbol L, Moreno-Caparrós A: Nodular regenerative hyperplasia of the liver in rheumatic diseases: report of seven cases and review of the literature. *Semin. Arthritis Rheum.* 21, 47–54 (1991).

148 Morlà RM, Ramos-Casals M, García-Carrasco M *et al.*: Nodular regenerative hyperplasia of the liver and antiphospholipid antibodies: report of two cases and review of the literature. *Lupus* 8, 160–163 (1999).

149 Mor T, Beigel Y, Inbal A, Goren M, Wysenbeek AG: Hepatic infarction in a patient with the lupus anticoagulant. *Arthritis Rheum.* 32, 491–495 (1989).

150 Kinoshita K: Hepatic infarction during pregnancy complicated by antiphospholipid syndrome. *Am. J. Obstet. Gynecol.* 169, 199–202 (1993).

151 Young N, Wong KP: Antibody to cardiolipin causing hepatic infarction in a postpartum patient with systemic lupus erythematosus. *Ausralas. Radiol.* 35, 83–85 (1991).

152 Cappell M: Oesophageal necrosis and perforation associated with the anticardiolipin antibody syndrome. *Am. J. Gastroenterol.* 89, 1241–1245 (1994).

153 Kalman DR, Khan A, Romain PL, Nompleggi DJ: Giant gastric ulceration associated with antiphospholipid antibody syndrome. *Am. J. Gastroenterol.* 91, 1244–1247 (1996).

154 Asherson RA, Morgan S, Harris EN *et al.*: Arterial occlusion causing large bowel infarction: a reflection of clotting diathesis in SLE. *Clin. Rheumatol.* 5, 102–106 (1986).

155 Asherson RA, Mackworth-Young C, Harris EN *et al.*: Multiple venous and arterial thromboses associated with the lupus anticoagulant and antibodies to cardiolipin in the absence of SLE. *Rheumatol. Int.* 5, 90–93 (1985).

156 Sánchez-Guerrero J, Reyes E, Alarcón-Segovia D: Primary antiphospholipid syndrome as a cause of intestinal infarction. *J. Rheumatol.* 19, 623–625 (1992).

157 Hamilton ME: Superior mesenteric artery thrombosis associated with antiphospholipid syndrome. *West. J. Med.* 155, 174–176 (1991).

158 Blanc P, Barki J, Fabre JM *et al.*: Superior mesenteric vein thrombosis associated with anticardiolipin antibody without autoimmune disease. *J. Lab. Invest.* 72, 137 (1995).

159 England RJA, Woodcock B, Zeiderman MR: Superior mesenteric artery thrombosis in a patient with the antiphospholipid syndrome. *Eur. J. Vasc. Endovasc. Surg.* 10, 372–373 (1995).

160 Vahl AC, Gans ROB, Mackaay AJC, Van Der Waal C, Mauwerda JA: Superior mesenteric artery occlusion and peripheral emboli caused by an aortic ulcer in a young patient with antiphospholipid syndrome. *Surgery* 121, 588–590 (1997).

161 Cappell MS, Mikhail N, Gujral N: Gastrointestinal haemorrhage and intestinal ischaemia associated with anticardiolipin antibodies. *Dig. Dis. Sci.* 39, 1359–1364 (1994).

162 Gül A, Inanc M, Öcal L, Konice M, Aral O, Lie JT: Primary antiphospholipid syndrome associated with mesenteric inflammatory veno-occlusive disease. *Clin. Rheumatol.* 15, 207–210 (1996).

163 North JP, Wollenman OJ Jr: Venous mesenteric occlusion in the course of migratory thrombophlebitis. *Surg. Gynecol. Obstet.* 95, 665–667 (1952).

164 Hudson M, Hutton RA, Wakefield AJ, Sawyer AM, Pounder RE: Evidence for activation of coagulation in Crohn′s disease. *Blood Coagul. Fibrinolysis* 3, 773–778 (1992).

165 Webberly MJ, Hart MT, Melikian V: Thromboembolism in inflammatory bowel disease. Role of platelets. *Gut* 34, 247–251 (1993).

166 Vianna JL, D′Cruz D, Khamashta MA, Asherson RA, Hughes GRV: Anticardiolipin antibodies in a patient with Crohn′s disease and thrombosis. *Clin. Exp. Rheumatol.* 10, 165–168 (1992).

167 Chamouard P, Grunebaum L, Wiesel ML *et al.*: Prevalence and significance of anticardiolipin antibodies in Crohn′s disease. *Dig. Dis. Sci.* 39, 1501–1504 (1994).

168 Chamouard P, Duclos B, Baumann R *et al.*: Antiphospholipid antibodies in inflammatory bowel disease. *Dig. Dis. Sci.* 40, 1525 (1995).

169 Souto JC, Borrell M, Fontcuberta J, Roca M: Antiphospholipid antibodies in inflammatory bowel disease. *Dig. Dis. Sci.* 40, 1524–1525 (1995).

170 Papi C, Ciaco A, Acierno G *et al.*: Severe ulcerative colitis, dural sinus thrombosis and the lupus anticoagulant. *Am. J. Gastroenterol.* 80, 1514–1517 (1995).

171 Arnold MH, Schreiber L: Splenic and renal infarction in systemic lupus eythematosus: association with anticardiolipin antibodies. *Clin. Rheumatol.* 7, 406–410 (1988).

172 Pettersson T, Julkunen H: Asplenia in a patient with systemic lupus erythematosus and antiphospholipid antibodies. *J. Rheumatol.* 19, 115 (1992).

173 Lê Thi Huong D, Weschler B, Edelman P *et al.*: Postpartum cerebral infarction associated with aspirin withdrawal in the antiphospholipid antibody syndrome. *J. Rheumatol.* 20, 1229–1232 (1993).

174 Hochfeld M, Druzin ML, Maia D *et al.*: Pregnancy complicated by primary antiphospholipid antibody syndrome. *Obstet. Gynecol.* 83, 804–805 (1994).

175 Ornstein MH, Rand JH: An association between refractory HELLP syndrome and antiphospholipid antibodies during pregnancy: a report of 2 cases. *J. Rheumatol.* 21, 1360–1364 (1994).

176 Lioté F, Meyer O: Osteoarticular manifestations in the antiphospholipid syndrome. In: *The Antiphospholipid Syndrome.* Asherson RA, Cervera R, Piette J-C, Shoenfeld Y (Eds). CRC Press, PA, USA 195–200 (1996).

177 Klippel TM, Stevens MB, Zizic TM, Hungerford DS: Ischemic necrosis of bone in systemic lupus erythematosus. *Medicine (Baltimore)* 55, 251–257 (1976).

178 Zizic TM, Marcor K, Hungerford DS, Dansereau JV, Stevens MB: Corticosteroid therapy associated with ischemic necrosis of bone in systematic lupus erythematosus. *Lancet* 1, 902–906 (1987).

179 Massando L, Jacobelli S, Leissner M, Gonzalez M, Villaroel L, Rivero S: High dose intravenous methylprednisone therapy associated with osteonecrosis in patients with systemic lupus erythematosus. *Lupus* 2, 401–405 (1992).

180 Zizic TM, Hungerford DS, Stevens MB: Ischemic bone necrosis in systemic lupus erythematosus. II. The early diagnosis of ischemic necrosis of bone. *Medicine (Baltimore)* 59, 134–142 (1980).

181 Asherson RA, Jungers P, Lioté F *et al.*: Ischaemic necrosis of bone associated with the "lupus anticoagulant" and antibodies to cardiolipin. *Proceedings of the XVIth International Congress of Rheumatology.* Sydney, Australia 373 (1983).

182 Asherson RA, Lioté F, Page B *et al.*: Avascular necrosis of bone and antiphospholipid antibodies in systemic lupus erythematosus. *J. Rheumatol.* 20, 284–288 (1993).

183 Asherson RA, Khamashta MA, Ordi-Ros J *et al.*: The 'primary' antiphospholipid

syndrome: major clinical and serological features. *Medicine (Baltimore)* 68, 366–374 (1989).

184 Seleznick MJ, Silveira LH, Espinoza LR: Avascular necrosis associated with anticardiolipin antibodies. *J. Rheumatol.* 18, 1416–1417 (1991).

185 Alijotas J, Argemí M, Barquinero J: Kienbock's disease and antiphospholipid antibodies. *Clin. Exp. Rheumatol.* 8, 297–298 (1990).

186 Alarcón-Segovia D, Delezé M, Oria CV *et al.*: Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 patients. *Medicine (Baltimore)* 68, 353–365 (1989).

187 Picillo U, Migliaresi S, Marciolis MR, Longobardo A, La Palombara F, Tirri G: Longitudinal survey of anticardiolipin antibodies in systemic lupus erythematosus. Relationship with clinical manifestations and disease activity in an Italian series. *Scand. J. Rheumatol.* 21, 271–276 (1992).

188 Petri M: Musculoskeletal complication of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. *Arthritis Care Res.* 18, 137–145 (1995).

189 Houissau FA, N'Zeusseu-Toukap A, Depresseu XG *et al.*: Magnetic resonance imaging-detected, avascular necrosis in systemic lupus erythematosus: lack of correlation with antiphospholipid antibodies. *Br. J. Rheumatol.* 37, 448–453 (1998).

190 Nagasawa K, Ishii Y, Mayumi T *et al.*: Avascular necrosis of bone in systemic lupus erythematosus: possible role of haemostatic abnormalities. *Ann. Rheum. Dis.* 48, 672–676 (1989).

191 Mont MA, Glueck CJ, Pacheco IH, Wang P, Hungerford DS, Petri M: Risk factors for osteonecrosis in systemic lupus erythematosus. *J. Rheumatol.* 24, 654–662 (1997).

192 Kleiner RC, Najarian IV, Schatten S *et al.*: Vaso-occlusive retinopathy associated with antiphospholipid antibodies (lupus anticoagulant retinopathy). *Ophthalmology* 96, 896–904 (1989).

193 Francès C, Tribout B, Boisnic S *et al.*: Cutaneous necrosis associated with the lupus anticoagulant. *Dermatologica* 178, 194–201 (1989).

194 Dessein PH, Lamparelli RD, Phillips SA, Rubenchik IA, Zwi S: Severe immune thrombocytopenia and the development of skin infarctions in a patient with an overlap syndrome. *J. Rheumatol.* 16, 1494–1496 (1989).

195 Dodd HJ, Sarkany I, O'Shaughnessy D: Widespread cutaneous necrosis associated with the lupus anticoagulant. *Clin. Exp. Dermatol.* 10, 581–586 (1985).

196 Aronoff DM, Callen JP: Necrosing livedo reticularis in a patient with recurrent pulmonary haemorrhage. *J. Am. Acad. Dermatol.* 37, 300–302 (1997).

197 Soweid M, Hajjar RR, Hewan-Low KO, Gonzalez EB: Skin necrosis indicating antiphospholipid syndrome in a patient with AIDS. *South. Med. J.* 88, 786–788 (1995).

198 Del Castillo LF, Soria C, Schoendorff C *et al.*: Widespread cutaneous necrosis and antiphospholipid antibodies: two episodes related to surgical manipulation and urinary tract infection. *J. Am. Acad. Dermatol.* 36, 872–875 (1997).

199 Amster MS, Conway J, Zeid M *et al.*: Cutaneous necrosis resulting in protein S deficiency and increased antiphospholipid antibody in a patient with systemic lupus erythematosus. *J. Am. Acad. Dermatol.* 29, 853–857 (1993).

200 Wolf P, Soyer P, Auer-Grumbach P *et al.*: Widespread cutaneous necrosis in a patient with rheumatoid arthritis associated with anticardiolipin antibodies. *Arch. Dermatol.* 127, 1739–1740 (1991).

201 Hill VA, Whittaker SJ, Hunt BJ *et al.*: Cutaneous necrosis associated with the antiphospholipid syndrome and mycosis fungoides. *Br. J. Dermatol.* 130, 92–96 (1994).

202 Doff HJ, Sarkany I, O'Shaughnessy D: Widespread cutaneous necrosis associated with the lupus anticoagulant. *Clin. Exp. Dermatol.* 10, 581–586 (1985).

203 Wattiaux MJ, Hervé R, Robert A, Cabane J, Housset B, Imbert JC: Coumarin-induced skin necrosis associated with acquired protein S deficiency and antiphospholipid antibody syndrome. *Arthritis Rheum.* 37, 1096–1100 (1994).

204 Grobb JJ, Bonerandi JJ: Cutaneous manifestations associated with the presence of the lupus anticoagulant: a report of two cases and review of the literature. *J. Am. Acad. Dermatol.* 15, 211–219 (1986).

205 Asherson RA, Jacobelli S, Rosenberg H *et al.*: Skin nodules and macules resembling vasculitis in the antiphospholipid syndrome. *Clin. Exp. Dermatol.* 17, 166–169 (1992).

206 Renfro L, Franks AG, Grudberg M, Kamino H: Painful nodules in a young female – antiphospholipid syndrome. *Arch. Dermatol.* 128, 847 (1992).

207 Asherson RA: Subungual splinter haemorrhages: a new sign of the antiphospholipid coagulopathy? *Ann. Rheum. Dis.* 49, 268 (1990).

208 Font J, Cervera R, López-Soto A *et al.*: Non-infective verrucous endocarditis in a patient with 'primary' antiphospholipid syndrome. *Br. J. Rheumatol.* 30, 305–307 (1991).

209 Bucciarelli S, Espinosa G, Cervera R *et al.*; European Forum on Antiphospholipid Antibodies: Mortality in the catastrophic antiphospholipid syndrome. Causes of death and prognostic factors in a series of 250 patients. *Arthritis Rheum.* 54, 2568–2576 (2006).

▪▪ **Largest series of patients with catastrophic APS.**

210 Digre KB, Durcan FJ, Branch DW, Jacobson DM, Varner MW, Baringer JR: Amaurosis fugax associated with antiphospholipid antibodies. *Ann. Neurol.* 25, 228–232 (1989).

211 Francès C, Piette J, Saada V *et al.*: Multiple subungual splinter haemorrhages in the antiphospholipid syndrome. A report of 5 cases and review of the literature. *Lupus* 30, 123–128 (1994).