Abstract
The antiphospholipid syndrome is an autoimmune disease characterised by recurrent arterial or venous thrombosis, pregnancy morbidity and the persistence of positive antiphospholipid antibodies. Many other clinical manifestations may occur including heart valve disease, livedo reticularis, thrombocytopenia and neurological manifestations such as migraine and seizures. We review a number of other manifestations including stenotic lesions, coronary artery disease and accelerated atherosclerosis, skeletal disorders and the concept of seronegative antiphospholipid syndrome.

Introduction
The antiphospholipid (Hughes) syndrome (APS), first described in 1983, is an autoimmune disease characterised by recurrent arterial or venous thrombosis, pregnancy morbidity and the persistence of positive antiphospholipid antibodies (aPL) [1]. Although only thrombosis and pregnancy loss are included in the revised classification criteria for APS [2], other features are also described [3]. These include heart valve disease, livedo reticularis, thrombocytopenia and neurological manifestations such as migraine and seizures. Recently a number of other features have been described in APS, which we discuss in this review.

Stenotic lesions and vasculopathy
Vascular occlusions are increasingly being recognized in patients with APS, although the exact etiology remains unclear [4]. We found a high prevalence of renal artery stenosis (RAS) in APS patients with uncontrolled hypertension compared to two control groups [5]. Other stenotic lesions such as coeliac [6] and intracerebral arterial stenosis [7] have also been reported. These stenotic lesions are smooth and well defined and are different from those seen in atherosclerotic RAS or fibromuscular dysplasia [5]. Interestingly histological examination in SLE patients with APS [8] and a case report of a resected superior mesenteric artery showed fibro-elastic thickening of the intima and thrombosis [9]. These findings suggest that thrombosis and intimal and smooth muscle hyperplasia may be responsible for the vasculopathy in APS. Preliminary reports suggest that anticoagulation with a high intensity international normalized ratio (INR) helps to control blood pressure and prevents re-stenosis in APS patients with RAS [10]. Similarly, other case reports emphasize the importance of high intensity INR in various stenotic lesions in APS patients [7,11,12].

Coronary artery disease
Since the description of the APS syndrome, a number of cardiac manifestations have been described including cardiac valvular abnormalities (Libman-Sacks endocarditis) [13,14]. Coronary artery disease in young adults and cor-
Skeletal manifestations of the APS
APS may involve multiple organs such as kidney, brain, eye, ear and liver and it may also affect the skeleton. A prospective cohort study [29] together with several case reports of osteonecrosis in primary APS in the absence of osteoporosis [30,31], have strengthened the possible association between aPL and osteonecrosis. Our own experience is that non-traumatic metatarsal fractures are more prevalent in APS/aPL positive patients [32,33]. Interestingly most had normal DEXA scans, none had any preceding trauma and none had received high doses of steroids. To assess the true prevalence of these fractures and their relation to aPL, a prospective study is needed in both symptomatic and asymptomatic patients.

Cerebral manifestations
Although stroke is the only accepted neurological criterion for the diagnosis of APS, a number of other manifestations are observed in the APS. The spectrum of non-thrombotic cerebral manifestations may range from focal neurological lesions to diffuse global dysfunction. It includes severe headaches, often migranous, hemiplegic migraine, cognitive dysfunction and memory deficits, dysphasia (mixing or inappropriate words), behavioural changes and seizure disorders [25]. Extrapyramidal symptoms such as chorea have also been described in association with sub-cortical dementia in patients with APS [26]. Tektonidou et al noted a significant association between cognitive dysfunction and white matter lesions in the brain in patients with APS [27]. It is not uncommon to see white matter changes in the brain mimicking multiple sclerosis. Although a double blind cross-over trial comparing low molecular weight heparin with placebo failed to show positive results [28], clinical experience suggests that severe cognitive dysfunction and intractable headaches often respond to anticoagulation therapy in these patients [25].

Complications following renal biopsy in patients with APS/aPL
Although APS is by definition a hypercoaguable state, a surprising recent preliminary report by Chaib et al found an increased risk of bleeding complications following renal biopsy in patients with lupus nephritis (LN) and APS/aPL as compared to LN alone [42]. This single centre study examined > 200 patients of which 86 were APS/aPL positive. The study identified a positive lupus anticoagulant and elevated serum creatinine levels as significant risk factors for post biopsy bleeding complications.

Livedo reticularis and "Seronegative APS"
"Sero-negative" APS has remained an enigma and the concept is controversial. According to classification criteria for APS, aPL (lupus anticoagulant and anticardiolipin antibodies) and Beta 2 Glycoprotein I (B2GPI) antibodies are...
essential for the classification of patients with APS. Although aPL and anti-B2GPI are sensitive tests, they are not sensitive enough to pick up all patients with APS. A small group of APS patients remain persistently negative for routine assays of aPL [43,44]. Livedo reticularis was included in the original clinical description of the APS. Frances et al reported significant associations between pathological livedo reticularis (racemosa) and cerebral or ocular ischemic arterial events, seizures, heart valve abnormalities, hypertension and Raynaud’s phenomenon in patients with APS [45]. As with APS, livedo reticularis in the absence of aPL has been associated with pregnancy morbidity and abnormal ABI [46]. Livedo reticularis shares a number of features with APS such as pregnancy loss, arterial thrombosis, heart valve abnormalities and seizures [47] and indeed it is the most common cutaneous manifestation of APS [48,49]. There is therefore increasing evidence that “seronegative” APS does exist and it may be that serological markers other than aPL and anti-B2GPI are important in these patients. Pathological livedo reticularis may therefore be a clinical marker of the “seronegative APS” [46,50].

Conclusion
The spectrum of APS is not limited to thrombosis or pregnancy morbidity and clinicians should be aware of the broad range of manifestations with multi-system involvement.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
MM has written the manuscript, SRS has conceived and compiled the material and helped to write the manuscript and DPD has supervised the drafting of the manuscript. All authors have read and approved the final manuscript.

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