Long-term follow-up of ischaemic retinopathy in the antiphospholipid syndrome with lupus-like disease

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CLINICAL STUDY

Abstract

Purpose **Antiphospholipid syndrome (APS), as an acquired prothrombotic disorder, is increasingly being recognised as an important cause of systemic venous and arterial thrombosis. The defining feature of the condition is the presence of raised levels of antibodies to negatively charged phospholipids in the serum.**

Methods **We describe 2 cases of APS with ocular involvement and review the recent literature. Both patients experienced acute visual loss. It was the presenting symptom in one case – a finding that led to the diagnosis of the syndrome.**

Results **Management with anticoagulation therapy, in which the International Normalised Ratio (INR) has been maintained at or above 3, resulted in reperfusion of the ischaemic retina and stabilisation of the retinopathy in one patient, whilst in the other case, where the INR was less than 3, irreversible visual loss occurred.**

Conclusion **Anticoagulation with warfarin appears to result in reperfusion of ischaemic retina with stabilisation of the neovascular process when the INR is greater than 3.**

Key words Anticardiolipin antibody, Antiphospholipid syndrome, Lupus anticoagulant, Retinal ischaemia

Antiphospholipid syndrome (APS) is characterised by arterial and venous thrombosis, thrombocytopenia and fetal loss, occurring in the presence of antiphospholipid antibodies such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and others.[1] Although first described in patients with systemic lupus erythematosus (SLE), APS is now recognised as a distinct clinical entity, so-called primary APS, as most patients with the syndrome have no signs suggestive of SLE. However, in those patients in whom the criteria for a diagnosis of SLE are incomplete,[2] APS is said to exist in so-called lupus-like disease. Patients with APS may develop ocular manifestations.[3–13] We describe 2 cases of ischaemic retinopathy caused by APS occurring in the lupus-like state which were complicated by retinal neovascularisation.

Case reports

Case 1

A 41-year-old white woman presented in 1995 with sudden, painless loss of vision in her right eye. Previously she had been diagnosed with blepharospasm for which she received botulinum toxin injections when required. Her past medical history was unremarkable until 1987 when she developed epilepsy that was controlled with carbamazepine. Subsequently she developed photosensitivity[2] and was also diagnosed with hypertension that was controlled with lisinopril. She smoked 25 cigarettes a day and drank 28 units of alcohol a week. In her obstetric history her first pregnancy had been uneventful. Her second pregnancy, however, resulted in a stillbirth at 7 months gestation. Following this she developed a deep venous thrombosis in a lower limb. Her family history was also significant in that her mother had died at the age of 25 years, 7 weeks after birth of her second child, from a possible thrombotic-related event.

On examination best corrected visual acuity was 6/24 in her right eye and 6/6 in her left eye. Anterior segment assessment was normal. There was no relative afferent pupillary defect. Fundoscopy revealed the presence of both intravitreal and preretinal haemorrhage in the right eye with normal left fundus findings. B-scan ultrasonography showed no evidence of a retinal or posterior vitreous detachment. The vitreous haemorrhage resolved spontaneously within 3 weeks with a visual acuity of 6/5. Repeat fundus examination failed to reveal a source of haemorrhage.

Investigations at her initial presentation revealed a platelet count of 109×10^9/l (normal range (NR) 150–400) and an activated partial thromboplastin time (APTT) of 46.7 s (NR 27–37). Subsequently her aCLs were found to be

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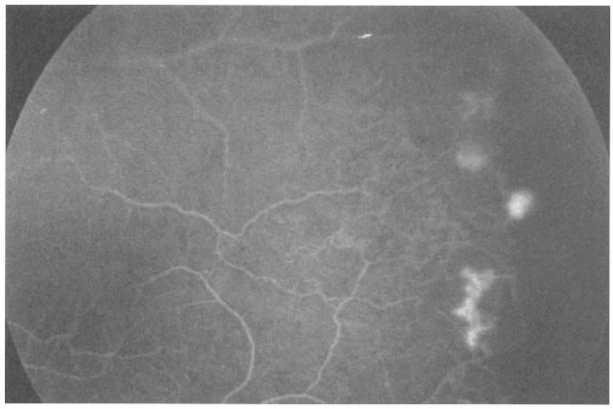


Fig. 1. *Case 1. Fluorescein angiogram, arteriovenous phase. Hyperfluorescence consistent with neovascularisation is seen adjacent to an area of peripheral ischaemia.*

grossly elevated at 142 GPL u/ml (NR 0–9). The rest of her autoantibody screen including LA, anti-nuclear antibody, anti-double-stranded DNA antibody and anti-mitochondrial antibody, was negative. A diagnosis of secondary APS was made on the basis of the above history, examination and investigations. Subsequently magnetic resonance imaging of the brain revealed abnormal areas of increased intensity in the deep white matter of both cerebral hemispheres as well as in the left cerebellar hemisphere, features deemed to be consistent with ischaemia.

Her progress was unremarkable until 9 months following her initial presentation when ophthalmic examination revealed the presence of neovascularisation in the right eye involving the temporal retina associated with peripheral ischaemia. The left fundus remained normal. Fundus fluorescein angiography confirmed these findings (Fig. 1). Her ophthalmic status remained unchanged but on further follow-up she developed extensive pinpoint erythematous lesions with nail-bed infarcts affecting both upper and lower limbs. Meanwhile her aCL levels remained markedly elevated. On the basis of her ocular and skin findings we commenced anticoagulation aiming for an International Normalised Ratio (INR) of 3–3.5. Within a month of beginning anticoagulation, resolution of the skin lesions had begun and ophthalmoscopy revealed early regression of the new vessels. However, when her INR dropped to 2.6 she developed two episodes of amaurosis fugax in the right eye.[10] With stabilisation of her INR she has not developed any further episodes of thrombosis in the 4 years since her presentation.

Case 2

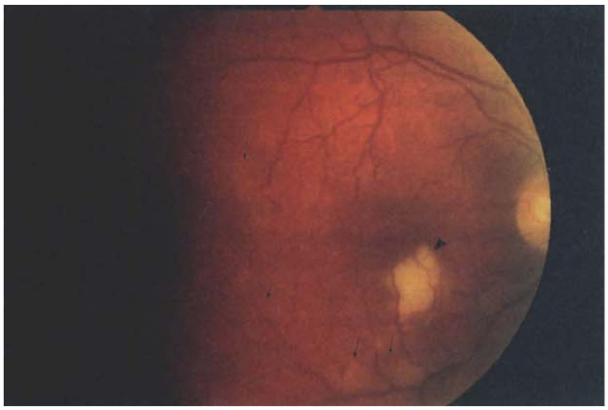
A 42-year-old white woman presented with sudden painless loss of vision in her right eye. Previously she had been diagnosed with lupus-like disease and secondary APS on the basis of a history that included 9 previous miscarriages, epilepsy, hypertension and a cerebrovascular accident occurring in a setting of LA, anti-double-stranded DNA antibodies and thrombocytopenia. Best corrected visual acuity on the right was counting fingers with normal vision in the left eye. There was a relative afferent pupillary defect and branch arterial occlusions in addition to widespread retinal oedema and vasculitis involving the right eye (Fig. 2a,b). Left ocular findings were normal except for the presence of mild arteriolar attenuation with arteriovenous nipping. Investigations at this time demonstrated the presence of both LA and anti-double-stranded DNA in the presence of thrombocytopenia.

On the basis of these ocular and serological abnormalities the patient was anticoagulated and 40 mg/day of oral prednisolone was commenced. Attainment of INR in the therapeutic range was difficult from the outset, with stabilisation in the desired therapeutic range taking 9 months to achieve. Although the steroids had been initially tapered and discontinued because of side effects, they were recommenced within 6 weeks because of persistent vasculitis and as prophylaxis for the fellow eye. Over the ensuing months, in the presence of a widely fluctuating INR and a maintenance dosage of 20 mg/day oral prednisolone, she experienced episodes of visual obscurations of her left eye. Fundus examination at that time revealed small peripheral haemorrhages. The ocular findings on the right remained unchanged except for the expected resolution of the original thromboses.

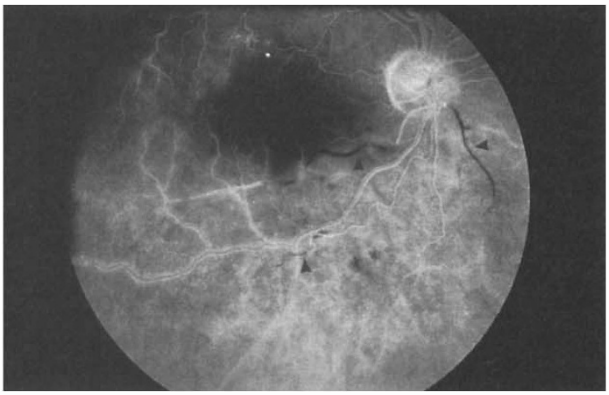
Six months following her presentation examination of the right fundus revealed retinal neovascularisation affecting both the optic disc and elsewhere and occurring in the presence of widespread ischaemia (Fig. 2c). Systematically her condition had also deteriorated. Her haemoglobin had dropped to 8 mg/dl secondary to menorrhagia, a situation made worse by anticoagulation. She received blood transfusions and was commenced on danazol for downregulation of her endometrium prior to a hysterectomy. This further destabilised her already fragile INR.[14] Her neovascularisation was treated with photocoagulation. However, despite a complete treatment and maintenance immunosuppressive therapy, the new vessels did not regress and she developed both preretinal and vitreous haemorrhage. This has not resolved and, because of her limited visual prognosis in her right eye, no further intervention has been undertaken. For the past 4 years she has been well and remains fully anticoagulated without any immunosuppression.

Discussion

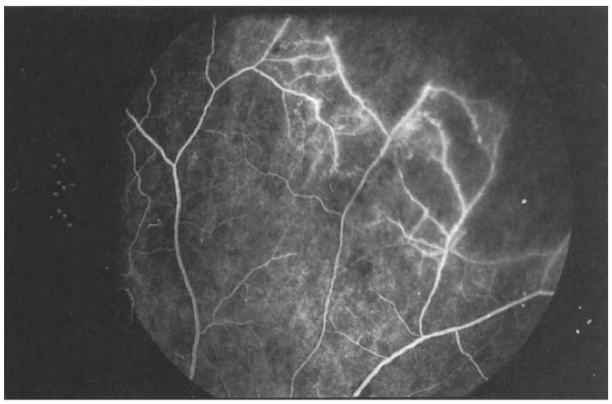
In 1983 Hughes first described antiphospholipid syndrome.[1] The major clinical manifestations of the syndrome are arterial and venous thrombosis, fetal loss and thrombocytopenia associated with the presence of antiphospholipid antibodies. These antibodies are a heterogeneous group of autoantibodies detected by either clotting or immunological assays. They include LA and aCLs and require the presence of co-factors, such as beta 2 glycoprotein I, for their effects.[15,16] Although first described in patients with SLE,[16] APS can be a primary condition unassociated with any other disease process or



(a)



(b)



(c)

Fig. 2. *Case 2. (a) Right eye showing well-defined (arrowhead) and diffuse areas of retinal oedema (arrows). Note the sheathing of the vessels and the presence of small haemorrhages throughout the macular area. (b) Fluorescein angiogram of the same area of the right eye. Late phase demonstrates non-perfusion of retinal arteries (arrowheads) with widespread ischaemia, vessel wall staining and leakage. (c) Fluorescein angiogram of the peripheral area of the right eye with vessel wall staining and leakage adjacent to area of peripheral non-perfusion. Note the sharp demarcation between perfused and non-perfused retina with abrupt cessation of intravascular dye columns.*

it can exist in so-called lupus-like disease where the criteria for a diagnosis of SLE are incomplete.[2,17] Additionally these antibodies may be found without any evidence of autoimmune disease[18] and in other non-connective tissue diseases.[19] Deep venous thrombosis of the lower limb is the most common thrombotic event. It can be recurrent and cause pulmonary embolism. Arterial thrombosis most commonly involves the intracranial arteries causing focal cerebral infarction.[20] Fetal loss usually occurs in the second trimester and the risk of fetal loss seems to be directly related to antibody titre.[21] The thrombocytopenia is usually mild and rarely requires treatment.

We describe 2 cases of APS occurring in association with lupus-like disease. Both cases were complicated by ischaemic retinopathy with secondary neovascularisation. In the first case ischaemia was due to thrombosis alone while in the second it was secondary to a combination of thrombosis and vasculitis. This combination of a vasculitis and a pre-existing systemic prothrombotic state significantly increased the risk of underlying retinal ischaemia. Neither patient had any evidence to suggest an associated endocarditis so it is unlikely that the retinal thrombosis was embolic in nature.

Both patients also suffered with epilepsy, the mechanism of which may be due to thrombosis and secondary ischaemia. There is a strong association between epilepsy in SLE, central nervous system (CNS) involvement and an underlying secondary APS.[22–25] Although the pathological hallmark of SLE is vasculitis, SLE affecting the CNS is notable by the absence of any vasculitis and this is supported by the finding of thrombosis without vasculitis at post-mortem.[25,26] Bland thrombus is also the pathological hallmark of APS.[27] Such an assocation, as suggested by others,[28] would probably indirectly support the assertion that epilepsy in SLE or lupus-like disease in the presence of a secondary APS may have a thrombotic aetiology. The findings in SLE occlusive retinopathy are also notable for the paucity of vasculitic changes. They too are characterised by thrombus formation,[26] findings which may be at variance with the apparent clinical signs.[3] If there is an association between SLE and a secondary APS in CNS involvement,[28] there is perhaps a similar association between central involvement and retinal disease. Our observations and that of others[9] would support this association. It has also been suggested that the presence of antiphospholipid antibodies is an independent risk factor for retinal vascular occlusion in both SLE and primary APS.[29] We would suggest a similar association in lupus-like disease.

The risk of recurrent thrombosis in patients with APS is high and long-term anticoagulation is probably necessary.[30–33] It has been proposed that one should maintain an INR of 3–3.5 and that lifelong treatment may be necessary as discontinuation of warfarin may lead to further thrombosis.[31,32] On this basis we commenced anticoagulation with warfarin for our first patient rather than resorting to conventional laser treatment for retinal

neovascularisation. Anticoagulation caused regression of the new vessels, and while maintaining an INR of between 3 and 3.5 she has not developed any further ocular or systemic problems. The patient described by Palimar and Cota[8] underwent panretinal photocoagulation but was simultaneously commenced on warfarin. Neovascular regression occurred but whether this was secondary to laser, anticoagulation or both it was not possible to deduce. The case reported by McKibbin *et al*.[7] involved recurrent retinal arterial occlusion and was treated with aspirin and prednisolone. They concluded by recommending anticoagulation with warfarin for all patients with the syndrome who experience a retinal vascular event. Their case is also interesting in that repeated testing failed to demonstrate LA after its initial detection. LA may by abolished by steroid administration whereas aCL levels remain unaffected.[34]

In the second patient adequate anticoagulation was difficult to achieve for several reasons. The patient had been commenced on danazol, which can increase sensitivity to warfarin, prior to her hysterectomy.[14] (Paradoxically danazol has been used as a steroid sparing agent in the treatment of thrombocytopenia associated with APS.[35]) It was only after discontinuation of the danazol that her INR stabilised within the therapeutic range. On the other hand, and just like the first patient, she was also on carbamazepine, which is known to reduce the anticoagulant ability of warfarin. Warfarin resistance has also been reported in APS[29] and explains why larger doses may be necessary in achieving an INR in the correct therapeutic range. In case 1 up to 15 mg of warfarin were required and up to 29 mg in case 2, and it was only after the danazol was discontinued in case 2 that her warfarin requirement dramatically increased.

Despite the probable irreversible visual loss in the right eye, the continuation of both warfarin and systemic steroids was necessary as prophylaxis for the fellow eye. The patient eventually developed vitreous haemorrhage secondary to new vessels on the disc and elsewhere in the right eye. The failure to achieve adequate anticoagulation, in addition to the persistent vasculitis, may have contributed to an unavoidable prolongation of her retinal ischaemia and the subsequent development of neovascularisation, despite attempts to counteract this ischaemia with laser and steroids.

In conclusion, ischaemic retinopathy in APS can be due to either thrombosis alone or a combination of thrombosis and vasculitis if it occurs in SLE or lupus-like disease. Adequate anticoagulation maintaining the INR above 3 at all times is essential to prevent recurrent thrombosis. If there is concomitant vasculitis adequate immunosuppression should be commenced. With these measures we feel there is probably little role for photocoagulation if retinal neovascularisation is present in this syndrome. Finally APS should always be suspected, and therefore appropriate investigations undertaken, in any patient with unexplained vitreous haemorrhage or retinal vascular disease.

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