Eye (1991) **5**, 48–55

Vaso-occlusive Retinopathy in the Primary Anti-phospholipid Antibody Syndrome

J. F. ACHESON,[1] R. M. C. GREGSON,[2] P. MERRY,[3] W. E. SCHULENBURG[1]
London

Summary

We report two patients with contrasting patterns of retinal vascular occlusion associated with the primary anti-phospholipid antibody syndrome. The immuno-pathological features and clinical associations are discussed. This condition is of interest to ophthalmologists because of its association with thrombosis in the eye, brain and elsewhere and because it provides new insights into the pathogenesis of retinal vascular disease in young patients.

In recent years a strong association has become apparent between thrombosis and the presence of antibodies to negatively charged phospholipids. Anti-phospholipid antibodies may be found in patients who have systemic lupus erythematosis (SLE), syphilis and more rarely in other conditions. In addition, a distinct clinical entity has now been described in which arterial or venous thrombosis, thrombocytopaenia, and recurrent abortion occur in the presence of these antibodies without any associated medical disorder. This is known as the primary antiphospholipid antibody syndrome.[1–4]

We describe two patients with contrasting patterns of vaso-occlusive retinopathy in this condition. The first had a picture of peripheral retinal arteriolar obliteration and capillary closure complicated by neovascularisation, and the second had a branch retinal vein occlusion.

Case One

A 34 year old white female was referred to the in March 1989 for the assessment of a left unilocular supero-nasal visual field defect.

In 1975, age 21, hypertension and classical migraine were diagnosed but no specific medications were given. The oral contraceptive pill was stopped. In 1977 she became pregnant, developed pre-eclamptic toxaemia with a blood pressure of 200/120 mm Hg and at 34 weeks gestation had an induced delivery of a still-born macerated 24 week fetus. The cause of the intrauterine death was placental insuffiency. In the post-partum period hypertension persisted and she was given propranolol 40 mg and prazosin 2 mg both three times daily.

In the period between 1978 and 1980 the hypertension was well controlled but Raynaud's phenomenon developed and atenolol 100 mg daily was given instead of propranolol. Troublesome Raynaud's phenomenon persisted and from 1982 all beta-blockers were stopped and she remained on prazosin alone. In 1983 she had a spontaneous abortion at 12 weeks gestation and in 1984 a further pregnancy was lost due to intrauterine death attributed to placental failure at 30 weeks. Blood pressure was well controlled and the

From: [1]Department of Ophthalmology, Hammersmith Hospital, London W12 and Western Ophthalmic Hospital, London NW1. [2]Medical Retinal Clinic, Moorfields Eye Hospital, London EC1. [3]Department of Rheumatology, Charing Cross Hospital, London W6.

Correspondence to: J. F. Acheson FRCS FCOphth, Western Ophthalmic Hospital, Marylebone Road, London NW1 5YE.

prazosin was changed to Dyazide one tablet twice daily.

From May 1985 she took no anti-hypertensive medications and was admitted to hospital as an emergency in December 1985 with a blood pressure of 135/100 mmHg standing, 185/110 lying and a right spastic hemiparesis. There had been no migrainous episodes for a number of years. A CT head scan without administration of contrast showed a wedge shaped area of low-attenuation in the left parietal region consistent with a cerebral infarction. Extensive livedo reticularis and acrocyanosis was noted. An intra-arterial digital subtraction angiogram of the aortic arch, neck and intra-cranial vessels was normal. Doppler ultrasound studies of carotid blood flow, an echocardiogram and intravenous pyelogram were also normal. Full blood count, platelets, ESR, renal and hepatic function were all normal. A screen for anti-nuclear antibodies (ANA) was negative. The prothrombin time and the partial thromboplastin time were within normal limits and serological tests for syphilis were negative. IgG anti-cardiolipin antibodies were present in high titres (Table I).

From February 1986 to May 1987 she was fully anti-coagulated with oral warfarin, and the hypertension was well controlled with hydrallazine 50 mg twice daily, pindolol 5 mg daily and Dyazide once daily. From May 1987 warfarin was stopped and aspirin 75 mg daily commenced. From July 1987 the pindolol was changed to nifedipine slow release 20 mg and pizotifen was given for fresh migrainous headaches. In November 1987 the platelet count was mildly reduced at 105×10^9/1 and the IgG titre of anti-cardioliin antibodies remained elevated.

Oral prednisolone 10 mg daily was given for eight months. In October 1988 ketanserin was given for continuing migraine attacks and the blood pressure was mildly elevated at 150/95 standing, 145/100 lying. In November 1988 she underwent detailed reassessment following recurrent transient ischaemic attacks, worsening migraines and left sided visual field disturbances. The blood pressure was 160/70. Neurological examination showed a new left homonymous hemianopia. A magnetic resonance brain scan showed multiple patchy lesions in the periventricular white matter consistent with small vessel cerebral vaso-occlusive disease and a dark region in the right occipito-parietal region consistent with an old cerebral infarction (Figs 1a and b).

Doppler ultrasound studies of carotid blood flow were again normal. The platelet count had fallen to 88×10^9/L and IgG anti-cardiolipin antibodies remained present (Table I). The erythrocyte sedimentation rate and C-reactive protein levels were normal. A repeat partial thromboplastin time was slightly prolonged at 43 seconds (normal 40). Repeat studies for antinuclear antibodies including anti-Ro, La, Sm, and RNP were again negative.

She underwent her first ophthalmic evaluation in March 1989. Corrected visual acuities were 6/5 on the right and 6/6 on the left. Visual fields to confrontation and on Goldman perimetry showed a left monocular supero-nasal defect which did not respect the vertical meridian. The intraocular pressures were normal and there were no cells in the anterior chamber or vitreous.

Fundoscopy showed normal optic discs and mild generalised vascular calibre attenuation with arterio-venous nipping. In the left infero-

Table I. *Summary of investigations for case one*

	Platelets (*normal 120 − 400 × 10^9/L*)	*Anti-cardiolipin antibody levels*	
		IgG (normal <9 units)	*IgM (normal <9 units)*
December 1985	140	60	7.4
March 1986		130	3.1
December 1986		18.5	
November 1987	146	16	
January 1988		54	
May 1988		60	1.2
September 1988	101	35	
October 1988	99	35	2.8
March 1989	88	58	4.2

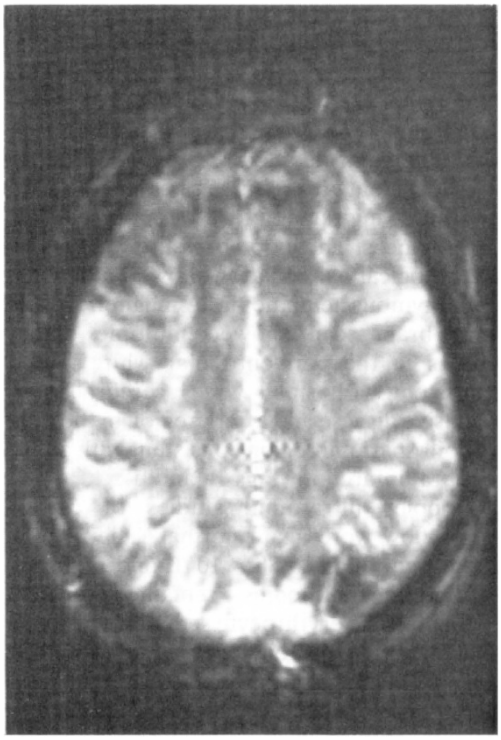

Fig. 1a.

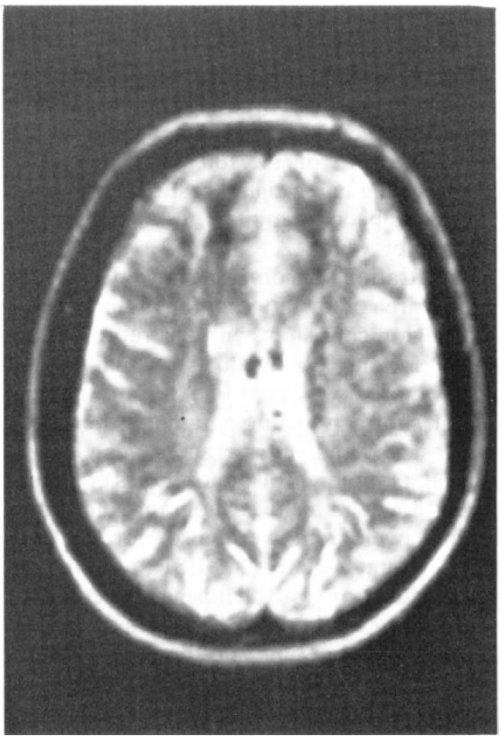

Fig. 1b.

Figs. 1a and 1b. *Case 1. Magnetic resonance imaging scans of brain showing periventricular changes in both hemispheres, more marked on the right consistent with but not diagnostic of vascular disease, and evidence of an old right occipito-parietal haemorrhage.*

temporal periphery there was collateral vessel formation and an elevated extraretinal fibrovascular complex with localised pre-retinal haemorrhage.

Fluorescein angiography demonstrated delayed arteriolar filling in the affected quadrant with several neovascular complexes and peripheral capillary non-perfusion. The remaining retinal periphery showed vascular attenuation and further areas of peripheral capillary closure. In addition there was patchy hypofluorescence of the pigment epithelium throughout both fundi (Figs 2a-f).

In view of the probable longstanding nature of the neovascularisation indicated by the fibrous component and the absence of any significant vitreous haemorrhage, laser photocoagulation was not performed and after twelve months follow-up the vision remains stable.

Case Two

A 30 year old white woman presented to the Eye Casualty Department in July 1988 with a one day history of floaters in the right eye. Full ophthalmic examination was normal apart from an incomplete posterior vitreous detachment and a small subhyaloid haemorrhage at the right optic disc margin. At age of 17 the lupus anticoagulant was first diagnosed after viral pneumonia complicated by deep venous thrombosis. She was given oral anticoagulants and corticosteroids for three years after which time all treatment was stopped as she remained well.

At routine review three months later the corrected right visual acuity was 6/6 and a localised area of intra-retinal haemorrhage and retinal swelling within the right temporal vascular arcade was first noted. The blood pressure was 160/95 and nifedipine 20 mg twice daily was started.

Fluorescein angiography (Figs 3a-c) showed an area of capillary non-perfusion with venous collaterals in the territory drained by one macular branch vein. No leak-

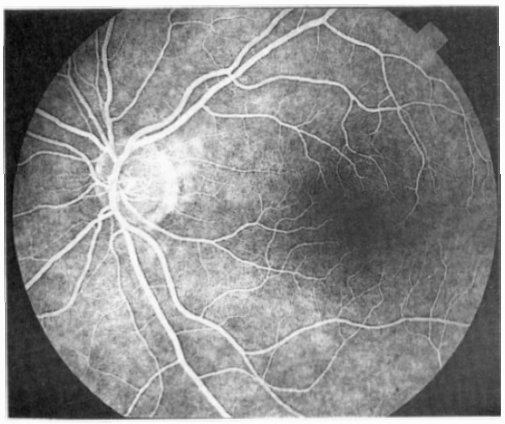

Fig. 2a.

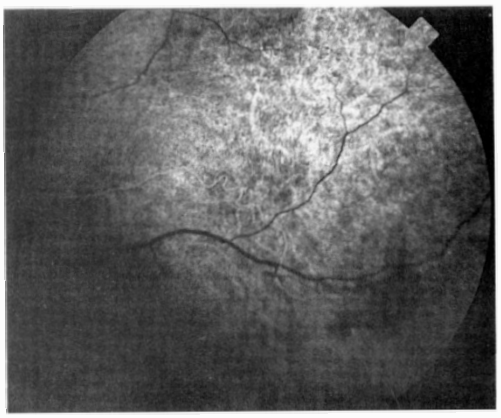

Fig. 2b.

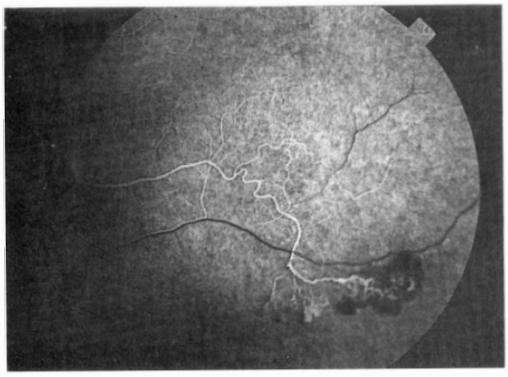

Fig. 2c.

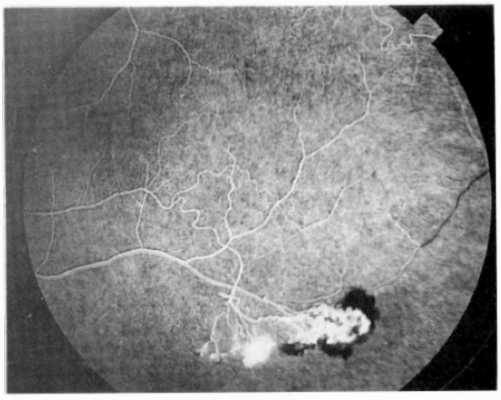

Fig. 2d.

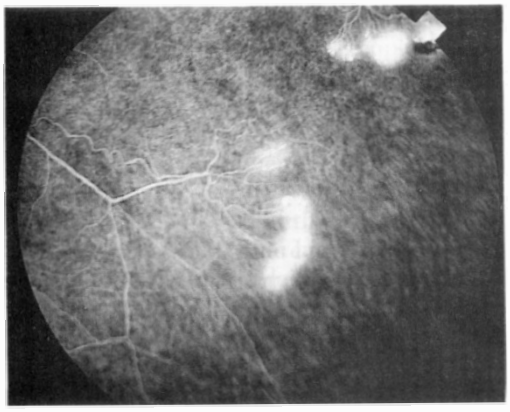

Fig. 2e.

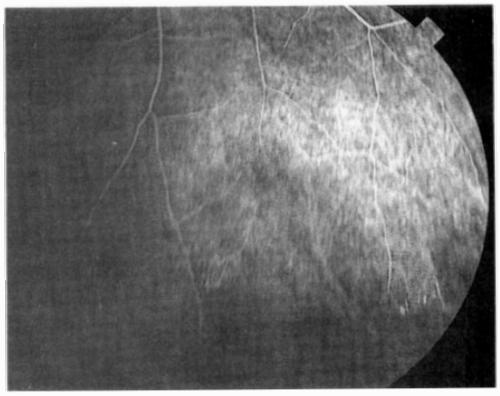

Fig. 2f.

Figs. 2a-f. *Fluorescein angiograms from one run showing peripheral arteriolar attenuation, capillary non-perfusion and neovascularisation. See text for details.*

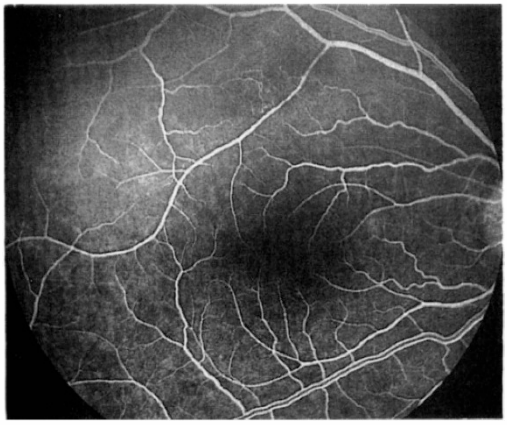

Fig. 3a.

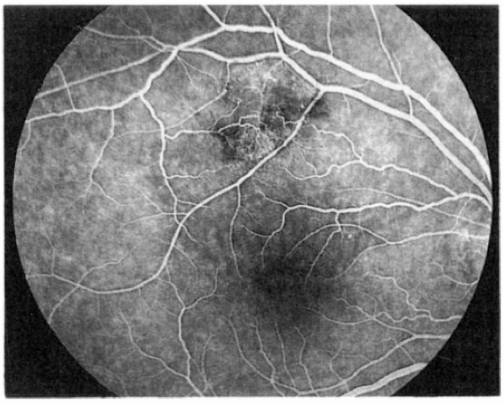

Fig. 3b.

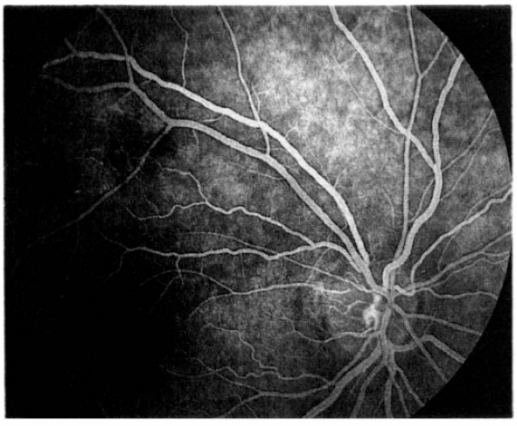

Fig. 3c.

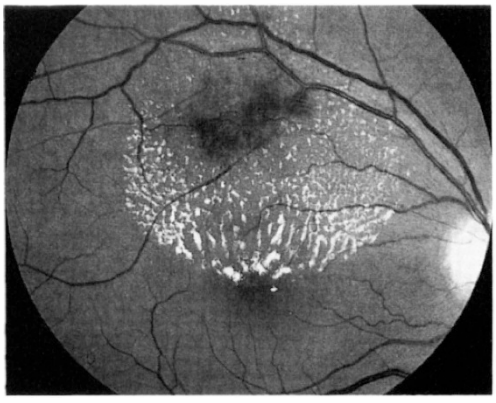

Fig. 3d.

Figs. 3a-c. *Fluorescein angiograms showing normal arteriolar filling (a), vein occlusion (b), and normal optic disc (c).*

Fig. 3d. *Red free fundus photograph three months later showing exudate formation.*

age was shown at this stage and there was no evidence of neovascularisation. Investigations showed an abnormal clotting screen, mild thrombocytopaenia, a false-positive VDRL, negative antinuclear activity and strongly positive anti-cardiolipin antibody levels (Table II).

Three months later the lesion was surrounded by hard exudates suggesting capillary decompensation (Fig 3d), but she declined further fluorescein angiography. No specific ophthalmic treatment was given and over the next six months the exudates resolved and the visual acuity remained 6/6.

In May 1989 she became pregnant and was treated with sub-cutaneous heparin 10,000 u twice daily from eight weeks gestation. The pregnancy was lost following a spontaneous abortion at 13 weeks.

Discussion

Anti-phospholipid antibodies are a group of autoantibodies which are detected by precipitation or complement fixation tests currently used in standard tests for syphilis, the lupus anticoagulant test, or by solid phase radioimmunoassay for anti-cardiolipin antibodies.

The terms cardiolipin and phospholipid were first linked when it was demonstrated that the antigen bound by reagin in patients

Table II. *Summary of investigations for case two*

Clotting screen:	Hb 16 gms
	Platelet 98 × 10^9/ml (normal 120 – 400)
	Prothrombin time 15 secs (control 14)
	PTT 40 secs (control 35)
Autoantibody screen:	VDRL Positive
	FTA & TPHA Negative
	ANA Negative
	Antibodies to Double Stranded DNA Negative
Anti-Cardiolipin Antibodies:	IgG 212 Units (normal <5)
	IgM 100 Units (normal <3)

with syphilis, as detected by techniques such as the Wasserman Reaction (WR) and the Venereal Disease Reference Laboratory flocculation test (VDRL), was an acidic phospholipid obtained by alcohol extraction of ox heart muscle.[3]

With widespread screening for syphilis among military personnel during the Second World War it became apparent that some people had a positive test for syphilis without any other evidence of the disease. This was known as the biological false positive test for syphilis (BFP-STS) and had a high prevalence in connective tissue and autoimmune diseases, and a strong association with other autoantibodies, particularly antinuclear antibodies (ANA).[3]

Later it was shown that patients with the BFP-STS might have a circulating anticoagulant which because of its association with ANA became known as the Lupus Anticoagulant.[5] The lupus anticoagulant has been shown to be an antibody from the IgG or IgM class and reacts with the phospholipid portion of the prothrombin converter complex in the coagulation cascade to cause prolongation of the activated partial thromboplastin time (APTT), the Russell viper venom time (RVVT) and, less frequently, prolongation of the Prothrombin time (PT).[3]

It is now apparent that the lupus anticoagulant and the BFP-STS are anti-phospholipid antibodies with similar specificity to anti-cardiolipin antibodies, and collectively they are all referred to as anti-phospholipid antibodies. New solid phase radioimmunoassay techniques for detecting anti-cardiolipin antibodies are the most sensitive test for all members of this family.

In vitro, anti-phospholipid antibodies are anti-coagulant, but *in vivo* their effect is paradoxically to promote a thrombotic tendency, probably because of further actions on phospholipid components of platelet membranes and vascular endothelium, as well as on thrombolytic factors such as local prostacyclin, antithrombin III and Protein C activation .[6]

A thrombotic tendency is a feature of a subpopulation of patients with SLE[7] in whom a vaso-occlusive retinopathy may occasionally be seen rather than the commoner and milder picture of haemorrhages and cotton wool spots.[8] Asherson *et al.* have reported the presence of lupus anticoagulant and anti-cardiolipin antibodies in this subgroup and showed an important association with cerebrovascular disease.[9] The ophthalmic features were not however discussed in any detail. Retinal artery and vein occlusions associated with antiphospholipid antibodies have also been reported in Sneddon's syndrome (livedo reticularis, variable cerebrovascular events and labile hypertension) and "lupus-like disease" (resembling SLE but not including four or more of the 1982 revised American Rheumatism Association criteria for the classification of SLE).[10–14]

The association between retinal vascular occlusions and cerebrovascular disease in these patients is of interest in view of pathological evidence suggesting that not all vascular occlusions in SLE are due to vasculitis. Graham *et al.*[15] have reported post mortem details of a patient in whom cerebral and retinal vessels were occluded by amorphous hyaline material without arteritis. It has been suggested that in patients who have SLE, thrombosis in the brain, the retina and other sites is due to direct interference with the

coagulation system mediated by anti-phospholipid antibodies rather than by circulating immune complexes.[3] Antibodies to neuronal membrane antigens may also be important in some cases.[16]

It is now apparent that these phenomena are seen in ophthalmic clinical practice in patients with anti-phospholipid antibodies and a history of thrombosis and who do not have SLE or any other disease. Three out of five cases reported by Levine *et al.*[5] presenting to the ophthalmologist with a variety of cerebral and retinal ischaemic events did not have SLE and did have the lupus anticoagulant. They did not report details of specific sensitive anti-cardiolipin antibody levels. Three patients described by Kleiner *et al.*[17] had lupus anticoagulant without SLE or other disease. One was negative for anti-cardiolipin antibody. These three patients all had severe visual loss secondary to diffuse bilateral retinal vascular obstructions with rubeosis iridis and vitreous haemorrhage. Garcia Vicente *et al.*[18] have reported one similar patient with proliferative retinopathy and lupus anticoagulant without details of anti-cardiolipin antibody levels.

Our cases can be added to these first reports of vaso-occlusive retinopathy occurring in the presence of the primary anti-phospholipid antibody syndrome. The interpretation of both cases is complicated by the fact that both patients were hypertensive.

The first patient presented after a long history of cerebro-vascular events with peripheral retinal neovascularisation straddling perfused and non-perfused retina. This pattern has been observed in several conditions including sickle cell disease, peripheral retinal vasculitis and carotid insufficiency.[19] This patient did not have a haemoglobinopathy and the angiogram does not suggest vessel wall inflammation. Carotid insufficiency was explicitly excluded. Peripheral retinal arteriolar attenuation with capillary non-perfusion with and without peripheral and disc new vessels has been well described in a small number of patients with SLE[8,20] and this patient shows a similar pattern. Variable hypertension is frequently seen in both SLE and in Sneddon's syndrome but is not a prerequisite for the development of vaso-occlusive retinopathy[2,8]. As discussed above, anti-phospholipid antibodies have been implicated in the pathogenesis of vaso-occlusive disease in SLE. This patient has a hypercoagulable state and thrombotic tendency associated with anti-phospholipid antibodies but without SLE or any evidence of embolisation. We believe that the retinopathy is best explained on this basis although possibly aggravated by hypertension induced arteriolar sclerosis and attenuation.

In the second case, the subhyaloid haemorrhage was due to either an acute partial posterior vitreous detachment or to breakthrough blood from an acute venous occlusion. There was no evidence of neo-vascularisation or of peripheral retinal pathology. On review, the haemodynamic disturbance had the appearances of a macular branch retinal vein occlusion with capillary decompensation and leakage explaining the pattern of hard exudate formation. Mild hypertension was diagnosed at this time. Macular branch retinal vein occlusion in a 30 year old patient is a sufficiently uncommon condition to merit further investigation and it is clear that in this patient a combination of a thrombotic tendency and raised blood pressure produced the clinical picture. This case is of particular interest as, to our knowledge, branch retinal vein occlusion has not been reported in SLE.

The anti-phospholipid antibody syndrome is of great interest to ophthalmologists firstly because of reports of a poor visual prognosis and secondly because of its association with thrombosis in the brain and elsewhere. Treatment with anticoagulation and immunosuppression and by control of any associated hypertension may improve the prognosis in cases where stroke or recurrent abortion are prominent features.

Ophthalmologists will want to know when it might be worth looking for this condition in patients presenting with retinal vascular occlusions. There is no evidence to support a general screening in all such patients,[21] but in younger patients it may be very valuable to look for clotting screen abnormalities particularly if there is a history of thrombosis at other sites or recurrent abortion. In the presence of any of these features, a search for specific anti-phospholipid antibodies is justified.

We are grateful to Dr. M. J. Walport PhD MRCP, Department of Rheumatology, Hammersmith Hospital (case 1), Dr. Makin MRCP, Department of Haematology, Middlesex Hospital and Mr. A. M. P. Hamilton FRCS, FCOphth, Medical Retinal Clinic, Moorfields Eye Hospital (case 2), for permission to report these cases and for advice on the preparation of this report.

We are also grateful to the Departments of Medical Photography, Western Ophthalmic Hospital and Moorfields Eye Hospital for preparing the illustrations.

Key words: Anti-Cardiolipin antibodies/Lupus Anticoagulant/Primary Anti-Phospholipid Antibody syndrome/Retinal vein occulusion/Vaso-occlusive retinopathy.

References

[1] Mackworth-Young CG, Loizou S, Walport MJ. Primary antiphospholipid antibody syndrome; features of patients with raised anticardiolipin antibodies and no other disorder. *Ann Rheumatic Dis* 1989, **48:** 362–7.

[2] Hughes GRV, Asherson RA, Khamashita MA. Antiphospholipid syndrome: linking many specialities. *Ann Rheumat Dis* 1989, **48:** 355–6.

[3] Harris EN, Gharavi AE, Hughes GRV. Anit-Phospholipid Antibodies. *Clin Rheum Dis* 1985, **11**(3): 591–609.

[4] Asherson RA, Khamashata MA, Ordi-Ros J, *et al.* The Primary Anti-Phospholipid Antibody Syndrome—Major clinical and serological features.. *Medicine* (Baltimore) 1989, **68:** 366–74.

[5] Feinstein DI and Rapaport SI. Acquired inhibitors of blood coagulation. *Prog Haemost. Thromb* 1972, **1:** 75–95.

[6] Cariou R, Tobelem G, Soria C, Caen J. Inhibition of protein C activation by endothelial cells in the presence of Lupus Anticoagulant. *New Eng J Med* 1986, **314**(18): 1193–4.

[7] Boey ML, Colaco, Gharavi AE, Elkon KB, Loizou S, Hughes GRV. Thrombosis in systemic lupus erythematosis: striking association with the presence of circulating lupus anticoagulant. *Br Med J* 1983, **287,** 1021–3.

[8] Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, Stevens MB. Severe retinal vaso-occlusive disease in systemic lupus erythematosis. *Arch Ophthalmol* 1986, **104:** 558–63.

[9] Asherson RA, Merry P, Acheson JF, Harris EN, Hughes GRV. Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus eythematosis and the 'primary' antiphospholipid antibody syndrome. *Ann Rheumat Dis* 1989, **48:** 358–61.

[10] Jonas J, Kolble K, Volcker HE, Kaiden JR. Central retinal artery occlusion in Sneddon's disease associated with anti-phospholipid antibodies. *Am J Ophthalmol* 1986, **102:** 37–40.

[11] Elias M and Eldor A. Thromboembolism in patients with 'lupus'-type circulating anticoagulant. *Arch Intern Med* 1984, **144:** 510–5.

[12] Pulido JS, Ward LM, Fishman GA. Anti-phospholipid antibodies associated with retinal vascular disease. *Retina* 1987, **7:** 215–18.

[13] Levine SR, Crofts JW, Lesser R, Floberg J, Welch KMA. Visual symptoms associated with the presence of a lupus anticoagulant. *Ophthalmol* 1988, **95**(5), 686–92.

[14] Levine SR and Welch KM. The spectrum of neurologic disease associated with anti-phospholipid antibodies, lupus anticoagulant and anti-cardiolipin antibodies *Arch Neurol* 1987, **44:** 876–83.

[15] Graham EM, Spalton DJ, Barnard RO, Garner A, Ross Russell RW. Cerebral and retinal vascular changes in systemic lupus erythematosis. *Ophthalmol* 1985, **92**(3), 444–8.

[16] Bonfa E, Golembek SJ, Kaufmal D, *et al.* Association between lupus psychosis and anti-ribosomal P protein antibodies. *New Eng J Med* 1987, **317:** 265–71.

[17] Kleiner RC, Najarian LV, Schatten S, Jabs DA, Patz A, Kaplan HJ. Vaso-occlusive Retinopathy associated with anti-phospholipid antibodies (lupus anticoagulant retinopathy). *Ophthalmol* 1989, **96**(6): 896–904.

[18] Vicente DCG, Martinez JB, Lopez JR, Castellano J. Retinopathia proliferante y anticoagulante lupico. *Arch Soc Esp Oftal* 1988, **55:** 387–92.

[19] Gass JDM. Stereoscopic atlas of macular disease: diagnosis and treatment. CV Mosby, St Louis, 1987, vol 1, p 340–53.

[20] Sanders MD. Retinal arteritis, retinal vasculitis and autoimmune vasculitis. *Eye* 1987, **1:** 441–65.

[21] Merry P, Acheson JF, Asherson RA, Hughes GRV. Management of retinal vein occlusion. *Br Med J* 1988, **296:** 294.