Antiphospholipid Syndrome

by Erik Letko, M.D.

CC (6/97): Blurry vision, headaches.

HPI: A 55 year old woman complained of blurry vision in both eyes and headaches. The patient consulted her ophthalmologist who treated her Pred Forte and Atropine eye drops into both eyes without improvement.

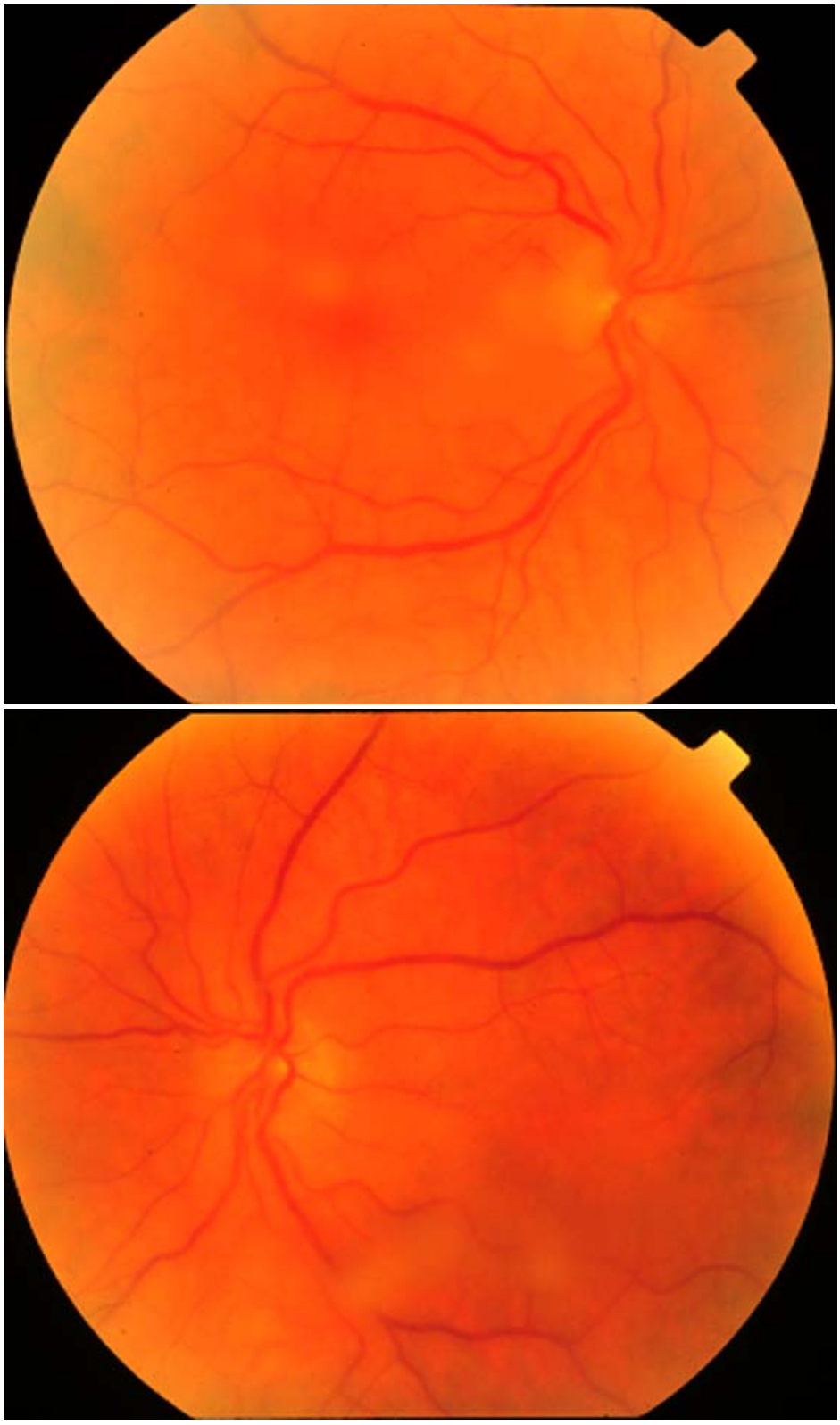
ROS: Hypertension, migraine, thyroid gland dysfunction, spastic colitis, colon polyps, anemia, recurrent UTIs, chlamydia, chills, fever, night sweat, fatigue, malaise, dizziness, paresthesia, alopecia, myalgia, arthralgia.

Examination

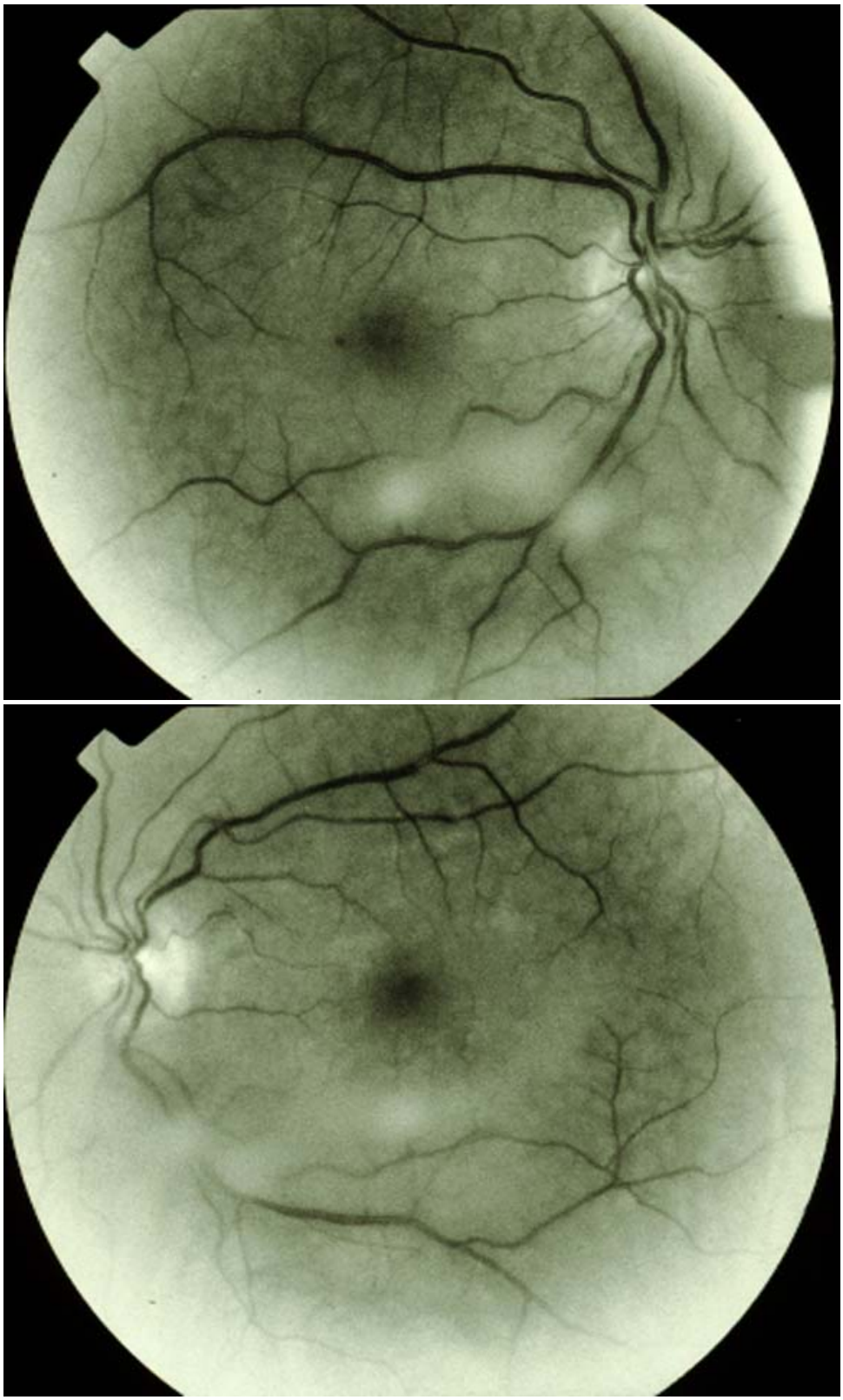
Visual acuity: 20/40 OD and 20/25 OS

IOP: normal

SLE: no conjunctival injection, one old keratic precipitate, 1/2+ flare and trace cells in the anterior chamber, 1+ posterior subcapsular cataract, 1/2+ vitreous cells, cell clumps adhered to the vitreous fibrils.



Figures 1 & 2: Fundus photos of OD and OS respectively, before treatment. Note bilateral vitreous opacities.



Figures 3 & 4. Fluorescein angiogram / red free photographs, before treatment. Vitreous opacities are more easily seen in these red free photos compared to fundus photographs.

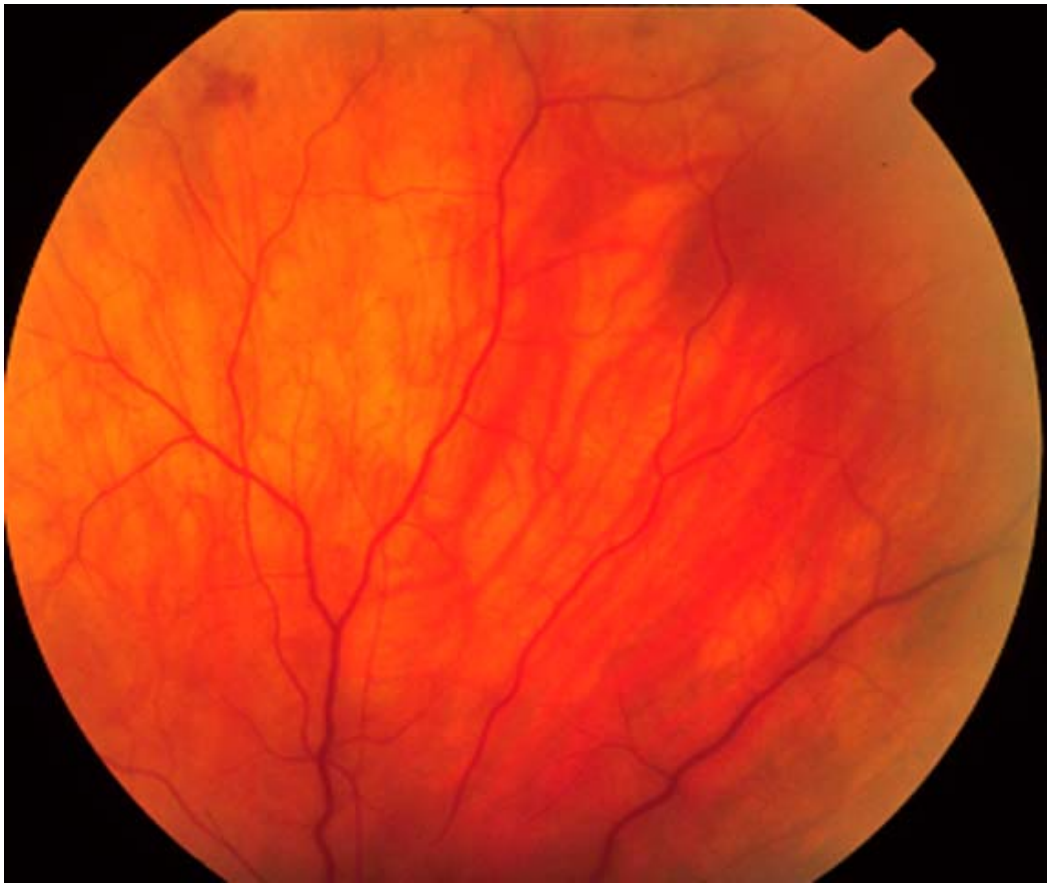


Figure 5. Fundus photograph of retinal periphery showing dot/blot hemorrhages.

Assessment

1. Uveitis OU
2. Dot/blot hemorrhages OU
3. Cataract OU

Plan

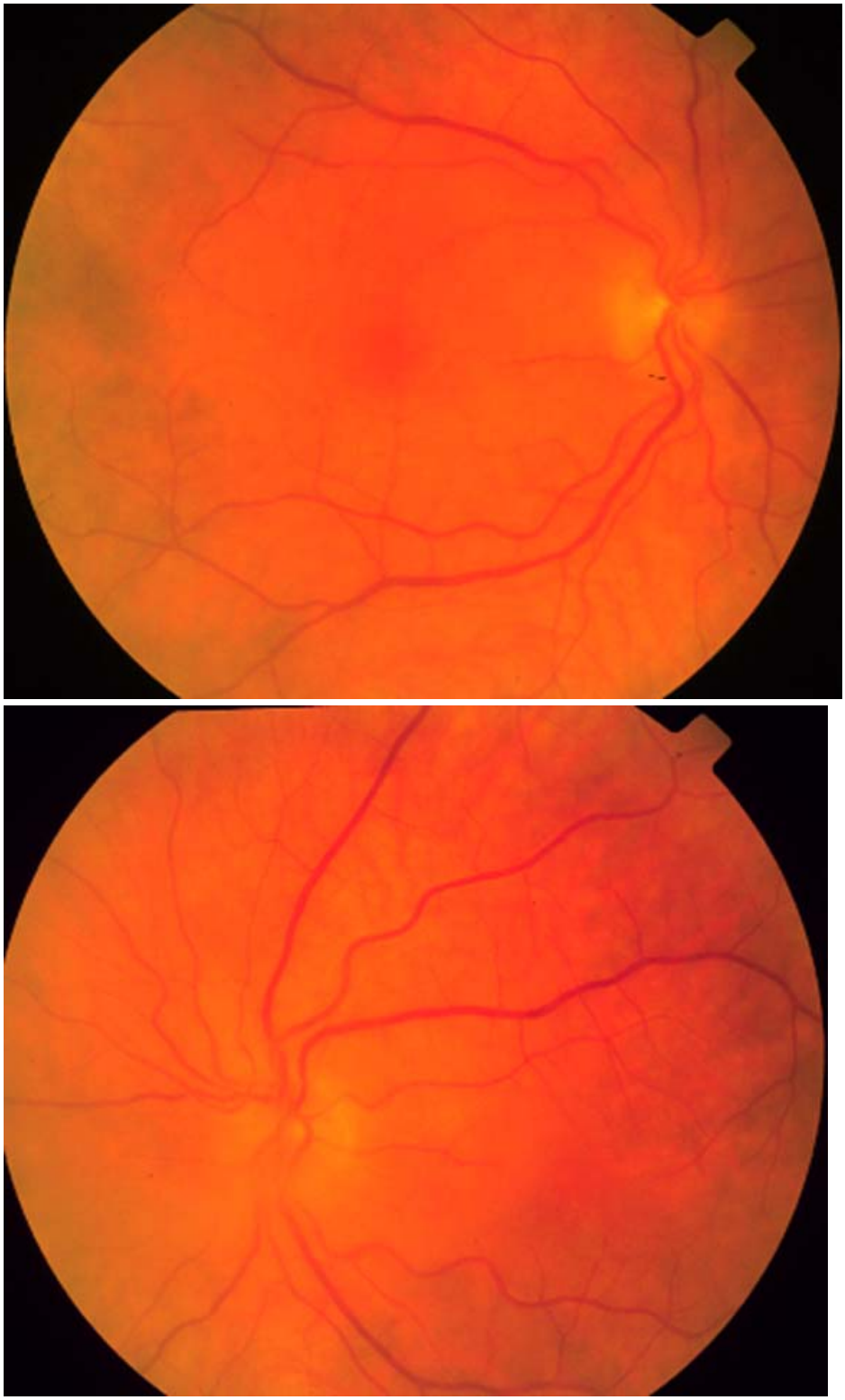
1. Work up of uveitis
2. Fluorescein angiography OU
3. Rule out underlying systemic disease
4. Consider treatment

Work-up

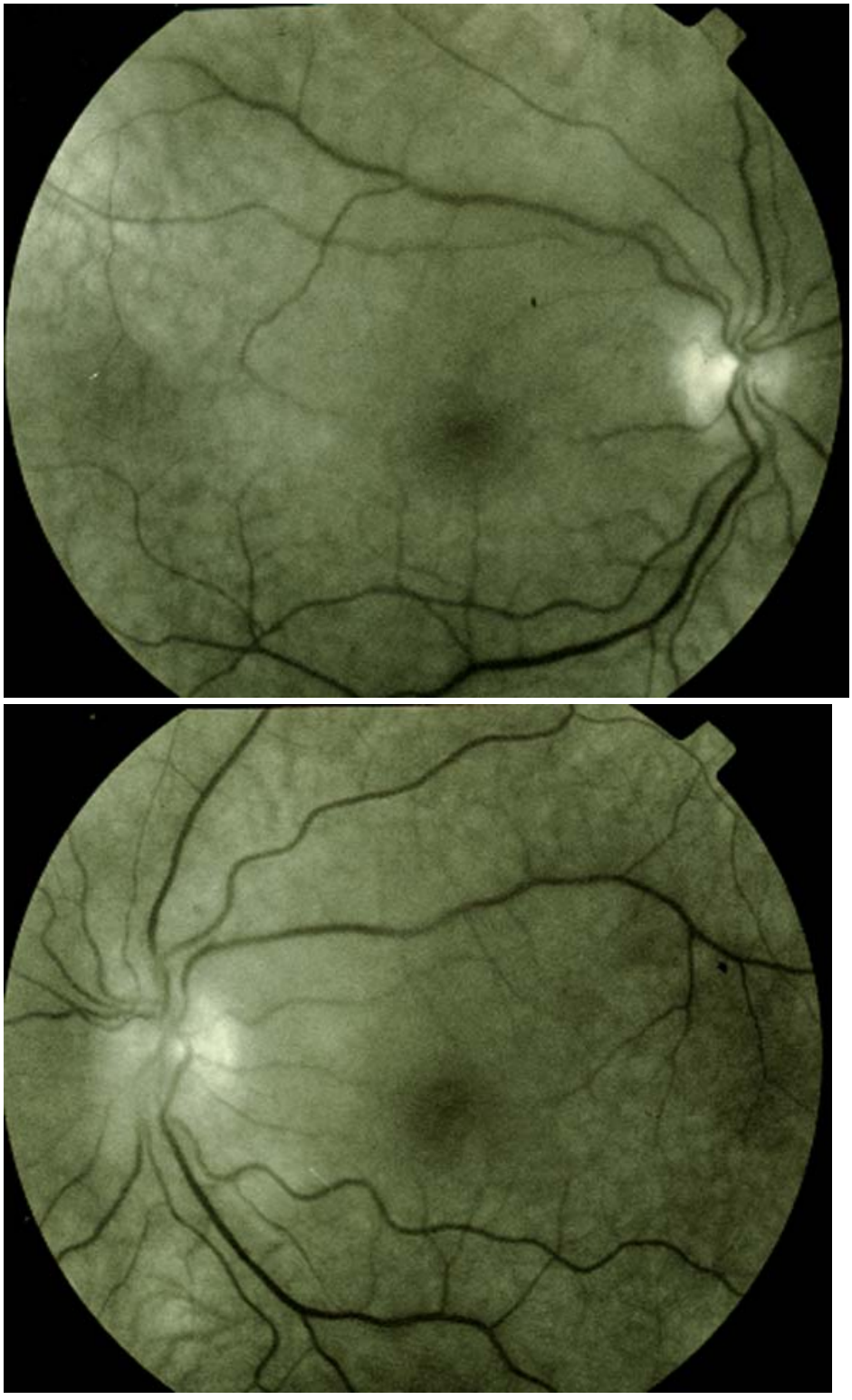
Her work-up was significant for elevated levels of cholesterol, light density lipoproteins, triglycerides, erythrocyte sedimentation rate, C reactive protein, and anticardiolipin antibodies IgG and IgA. Urine analysis showed 4+ proteinuria, positive leukocyte esterase, bacteria, and presence of white blood cells. Fluorescein angiography showed vitreous opacity in both eyes and intraretinal dot/blot hemorrhage in OD.

Clinical Course

Based on the clinical findings and work-up that did not confirm any other systemic disease, a diagnosis of probable primary antiphospholipid syndrome was proposed. Since July 1997 the patient has been on systemic therapy - Aspirin QD, MTX 10 mg/week, and Folic acid 5 times a week together with her previous hypertension and thyroid gland medication. The complete blood count, liver function tests, anticardiolipin antibodies and INR (international normalized ratio) have been monitored on the regular basis. Renal biopsy was performed in October 1997 due to the proteinuria. The results showed thrombotic microangiopathy that was consistent with the diagnosis of antiphospholipid syndrome. The treatment with Aspirin was discontinued, and Coumadin was begun, 2.5 and 5 mg once a day alternatively. In April 1998 the level of her IgG anticardiolipin antibodies was 260 and she had increased number of dot/blot hemorrhages in both eyes. Therefore we recommended that she increase the dose of Methotrexate to 12.5 mg per week. On the last exam in August her vision was 20/25 bilaterally. The number of dot/blot hemorrhages in the right eye was significantly decreased and there were no hemorrhages in the left eye. However, the level of her IgG anticardiolipin antibodies was still elevated. We discovered that the patient did not increase her Methotrexate dose to 12.5 mg.



Figures 6 & 7. Fundus photographs 5 months after initiation of therapy.



Figures 8 & 9. Fluorescein angiogram red free photos, 5 months after treatment. Note that there are no longer any vitreous opacities.

Discussion: Antiphospholipid Syndrome

Antiphospholipid syndrome is defined as the presence of antiphospholipid antibodies, arterial or venous thrombosis, recurrent spontaneous abortions, and thrombocytopenia. However, not all patients develop such complications. The risk of thrombotic event in patients with antiphospholipid syndrome is 0.5 to 30%. The syndrome can occur within the context of several diseases, mainly autoimmune, or it may be present without any recognizable disease, the so-called primary antiphospholipid syndrome.

History

The history of this disorder dates from the 1950s when an *in vitro* anticoagulant phenomenon without deficiency of any clotting factor was first described in patients with systemic lupus erythematosus (SLE). In 1963 a paradoxical thrombotic event occurring *in vivo* was observed in these patients. In 1972 the term "lupus anticoagulant" was first used for the *in vitro* phenomenon caused by an inhibitor directed against phospholipid in the clotting cascade, at the stage of conversion from prothrombin to thrombin. The development of specific radioimmunoassay in 1983 and subsequently ELISA technique helped to prevent false positive results of VDRL.

Systemic manifestations

Systemic manifestations of antiphospholipid syndrome are multisymptomatic and can affect most of the systems (Table 1). The symptoms are secondary to the thrombosis that can be located in the vessels of each caliber. Most commonly antiphospholipid syndrome is associated with systemic lupus erythematosus. Approximately 35% of SLE patients have elevated levels of antiphospholipid antibodies. Migraine can be the first symptom of antiphospholipid syndrome long before the diagnosis is considered. Other neurological symptoms include cerebral ischemia, stroke, epilepsy, chorea, and myelopathy. Twenty two percent of patients with multiple sclerosis were reported to have elevated levels of antiphospholipid antibodies.

Table 1. Systemic manifestations of antiphospholipid syndrome.

Rheumatology	SLE, discoid LE, subacute cutaneous LE, Sjogren's syndrome, RA, vasculitis, scleroderma, polymyosistis, dermatomyoisistis
Neurology	cerebral ischemia, stroke, migraine, epilepsy, chorea, myelopathy, multiple sclerosis
Cardiology	myocardial infarction, pulmonary hypertension, valvular disease
Nephrology	renal vein thrombosis, glomerular thrombosis, thrombotic microangiopathy, vasculitis, malignant hypertension
Endocrinology	Addison's disease from adrenal thrombosis
Gastroenterology	gut ischemia, hematemesis, liver vein thrombosis, Budd-Chiari syndrome
Dermatology	livedo reticularis, Sneddon's syndrome, skin ulcers, skin nodules
Hematology	thrombocytopenia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia

Obstetrics	recurrent spontaneous abortion
Intensive care	thromboembolism, adult respiratory distress syndrome
Surgery	bone necrosis, postoperative thrombosis

Ocular manifestations

Ocular manifestations can also be multisymptomatic (Table 2). Patients can complain on blurry vision, transient diplopia, transient field loss, amaurosis fugax and photopsia. Almost 90% of patients with primary antiphospholipid syndrome have ocular involvement. However, 30% of them can be asymptomatic. Visual acuity is markedly decreased in about 15% of the eyes.

The most serious changes might be seen in the retina, optic nerve, and vitreous. Anticardiolipin antibodies were found in 85% of patients with systemic lupus erythomatosus and retinal vasculitis, and in 42% of patients with idiopathic retinal vasculitis. Interestingly, IgG anticardiolipin antibodies are a highly specific (91%) marker, a useful diagnostic tool for anterior ischemic optic neuropathy associated with giant cell arteritis. Furthermore, the IgA anticardiolipin antibodies were found in 29% of the patients with acute retinal necrosis, particularly in those with negative PCR results of HSV from anterior chamber fluid.

Table 2. Ocular manifestation of APS.

Symptoms	blurry vision, transient diplopia, transient field loss, amaurosis fugax, photopsia, asymptomatic
Conjunctiva	telangiectasias, aneurysms, episcleritis
Cornea	keratoprecipitates, limbal keratitis
Anterior chamber	flare, cells
Vitreous	hemorrhage, cells
Optic nerve	disc edema, anterior ischemic optic neuropathy
Retina	arterial or venous occlusion, venous tortuosity, aneurysms, cotton-wool spots, vasculitis, vascular sheathing, macular serous detachment, acute retinal necrosis

Diagnosis

The diagnosis of antiphospholipid syndrome is based on the presence of antiphospholipid antibodies - anticardiolipin antibodies and lupus anticoagulant. A potential presence of systemic disease must be excluded. Detailed examination of the conjunctival and retinal vessels including fluorescein angiography is helpful not only for the eye evaluation, but also for the evaluation of the systemic microcirculation, the picture of which is mirrored in the eye. Vitreous opacity,

pigment epithelial window defects, early hyperfluorescence of atrophic areas, occlusive retinopathy with fluorescein leakage, areas of retinal hypoperfusion, neovascularization, and unsuspected occlusion can be presented on fluorescein angiography.

PATHOGENESIS

The mechanism of action of antiphospholipid antibodies is not known. It has been shown, that the antibodies bind to the anionic phospholipids of platelet membranes, endothelial cells, and clotting components such as prothrombin, protein C and protein S. There is a discrepancy between prolongation of clotting time *in vitro* and thrombosis *in vivo*. No satisfactory explanation of this phenomenon has yet been established, but several theories are proposed. *In vitro* lupus anticoagulant is thought to prolong clotting times by binding to phospholipids and thereby limiting the phospholipid surface necessary for binding of the prothrombinase complex. The mechanism of paradoxical thrombosis observed *in vivo* is not known. The simplest theory is that there is an antibody directed against the patient's own platelet and endothelial cell phospholipids that cause platelet aggregation and subsequent vascular occlusion. This also accounts for thrombocytopenia seen in these patients. However, the mechanism of action seems to be more complex and probably not all participating components are known yet.

Lupus anticoagulant and anticardiolipin antibodies can both cause a false-positive result of VDRL assay, although it is another phospholipid responsible for true-positive result of this assay in syphilis. Anticardiolipin antibodies are also directed against plasma proteins such as beta-2-glycoprotein I and prothrombin, co-factors, the absence of which can decrease the binding of antibodies to phospholipids. The recently proven cross reaction between beta-2-glycoprotein I and lipoproteins could explain the pathogenesis of both thrombosis and atherosclerosis in patients with primary antiphospholipid syndrome.

Familial occurrence of elevated levels of antiphospholipid antibodies as well as an association with certain HLA DR4, DR7, DQw7, and DQw53 types were reported. Approximately 4 % of normal population has elevated levels anticardiolipin antibodies.

Treatment and monitoring

Anticoagulation and immunosuppression seem to be the most effective treatment. Long-term therapy with aspirin, warfarin or heparin was suggested, but duration of the treatment and the point at which it should be discontinued are not clear. The level of INR is recommended to be more than 3. Life-long anticoagulation is necessary in some patients. Laser photocoagulation is an additional treatment of non-perfused retinal areas.

Treatment can be modulated based on the levels of INR and antiphospholipid antibodies. Patients with IgG anticardiolipin antibodies are at higher risk than those with IgM or IgA antibodies. The probability of thrombosis is higher if both anticardiolipin antibodies and lupus anticoagulant are present simultaneously. Significantly higher incidence of thrombosis was also described in patients who had elevated levels of IgG anti beta-2-glycoprotein I antibodies.

Summary

Antiphospholipid syndrome is a life threatening and vision threatening multisymptomatic disorder. Laboratory tests are essential for the diagnosis and should be considered in patients with unexplained vascular occlusion. Long-term anticoagulation and immunosuppression seem to be the most effective treatment. The patients have to be monitored on the regular basis particularly for INR and antiphospholipid antibodies. It is noteworthy, that relatively decreased titers of antiphospholipid antibodies were also observed in patients with an ongoing thrombotic event. This could be explained by the consumption of antibodies during the event.

Reading list

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