

# White Thread-Like Retinal Arterioles Associated With Antiphospholipid Antibody Syndrome

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**Background:** Report of 2 patients with antiphospholipid antibody syndrome (APS) who had elevated anti- $\beta_2$ -glycoprotein I antibodies and showed white thread-like retinal arterioles.

**Cases:** A complete ophthalmological examination was conducted on 2 patients who presented with blurred or distorted vision. Fluorescein angiography was used to examine the integrity of the retinal circulatory system. Laboratory blood studies were conducted.

**Observations:** In both patients, some of the major retinal arterioles appeared white and had a thread-like appearance. Fluorescein angiography demonstrated progressive occlusion or stenosis of these major arterioles with extensive insufficiency of the regional capillary bed. Patient 2 had systemic lupus erythematosus and was treated with oral corticosteroid and aspirin. Recanalization occurred during a 3-year follow-up in one of the patients.

**Conclusions:** APS should be considered in cases of white thread-like retinal arterioles. Occlusion of the retinal arterioles in APS may be progressive and responsible for the chronic hypoxia of the retina. **Jpn J Ophthalmol 1999;43:553-558** © 1999 Japanese Ophthalmological Society

**Key Words:** Antiphospholipid antibody syndrome, anti- $\beta_2$ -glycoprotein I antibodies, occlusion of retinal arterioles, white thread-like retinal arterioles.

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## Introduction

Patients with antiphospholipid antibody syndrome (APS) were first characterized by Harris et al<sup>1</sup> as having thrombotic events associated with systemic lupus erythematosus (SLE). Elevated anticardiolipin (aCL) antibodies and lupus anticoagulant (LA) were considered to be closely related to the mechanism of thrombosis formation in this syndrome.<sup>2-5</sup> Recently, cases<sup>6-8</sup> have been reported that had thrombotic episodes without a history of SLE, but fulfilled the other criteria of APS. APS is classified as a primary antiphospholipid antibody syndrome (PAPS) and

secondary APS with or without a history of collagen disease.<sup>6-8</sup>

Obstruction of the retinal arteries and veins, ischemic optic neuropathy, amaurosis fugax, and vasculitis of the retinal arteries have been reported in the eyes of patients with APS. Fundus examination is a useful means of detecting thrombosis of vessels although patients with PAPS have less opportunity to be screened because they lack specific episodes.

We report two cases that showed white thread-like retinal arterioles and were diagnosed as having APS by additional investigation. We discuss the changes of the retinal arterioles associated with APS.

## Case Reports

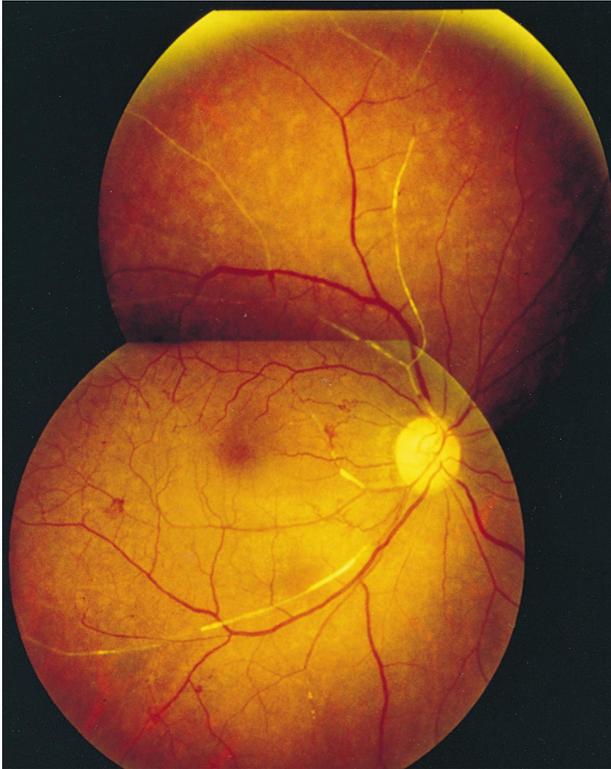
### Case 1

A 53-year-old woman was examined for blurred vision in January 1996. Laser photocoagulation had been performed on her left eye in 1993 and she had

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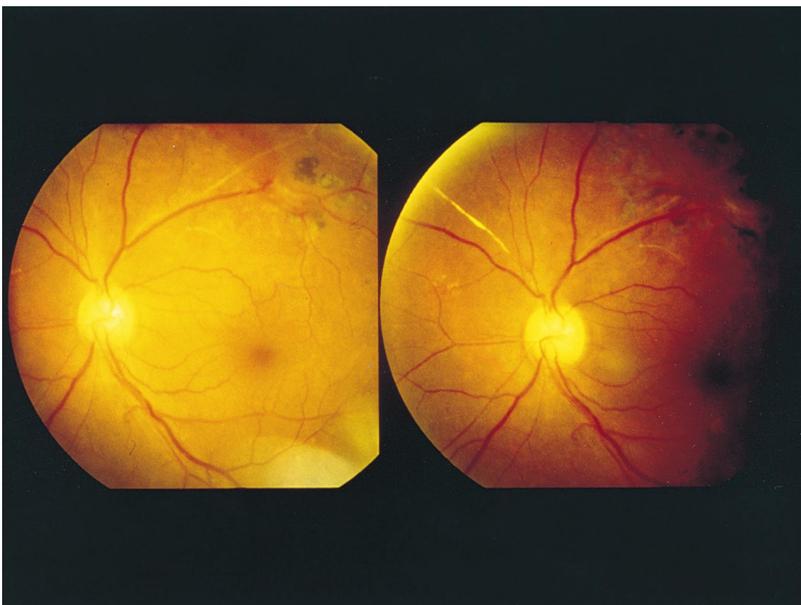
**Figure 1.** Right fundus at time of initial examination. Major retinal arterioles showed white thread-like appearance.

received treatment for retinal hemorrhage of undetermined origin at another clinic in 1995. She had a history of hypertension and multiple cerebral infarction. Her best corrected visual acuity was RE 20/25

and LE 20/22. Results of slit-lamp microscopy examination were normal except for mild bilateral cataracts. Goldmann perimetry revealed a homonymous inferotemporal scotoma.

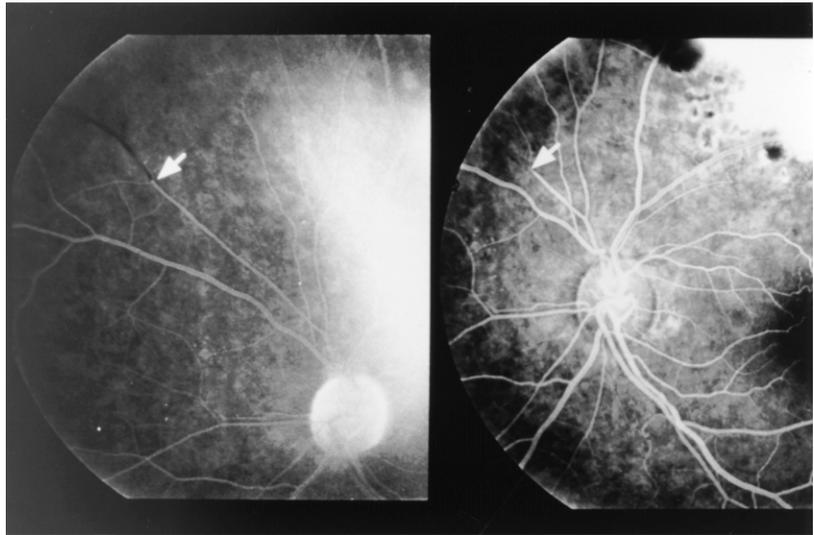
Fundus examination showed that the major retinal arterioles were white and thread-like. Retinal neovascularization was present in both eyes (Figures 1, 2). A fibrous membrane and mild vitreous hemorrhage were present in the left eye. Fluorescein angiography showed delayed filling, filling defects of the retinal arterioles, and leakage of dye from the neovascularization in the late phase. The capillary bed circulation was markedly insufficient in the area of the white thread-like arterioles.

Laboratory examination disclosed reduction of platelet count to  $3000/\text{mm}^3$ , and the total plasma cholesterol was slightly elevated to 262 mg/dL. Activated partial thromboplastin time (APTT) was prolonged to 55.3 seconds (control, 32.4 seconds). Serum aCL antibody level of immunoglobulin G (IgG) determined by the ELISA method (IgGaCL) and LA were negative, but the titer of anti- $\beta_2$ -glycoprotein I antibodies (aCL $\beta_2$ GPI) was elevated to 14.0 U/mL (normal level:  $<3.5$  U/mL). The complete blood count, fasting blood glucose, complement level, and antinuclear antibody data were normal. B-mode ultrasonography and magnetic resonance angiography (MRA) showed a mild and clinically insignificant atherosclerosis of the internal carotid artery. Color Doppler imaging (CDI) showed normal velocity in the ophthalmic and central retinal arteries. Brain MRI revealed degeneration of the brain



**Figure 2.** Fundus of left eye. Left: Initial examination. White thread-like appearance is severe in branch of superotemporal retinal artery. Fibrous membrane and mild vitreous hemorrhage are present. Focal photocoagulation has already been applied. Right: One year after first visit. White thread-like appearance of superonasal retinal artery has extended toward optic disc.

**Figure 3.** Fluorescein angiogram corresponding to Figure 2. Left: There is leakage of dye from neovascularization at 470 seconds after dye injection. Right: Reduction in caliber of lumen of superotemporal retinal artery is seen at 82 seconds after dye injection. Filling defect in superonasal artery extends proximally toward optic disc as indicated by arrow.



resulting from multiple cerebral infarction. The electrocardiogram showed minor changes but was still within normal range.

With increasing time, the white thread-like appearance of the superonasal retinal artery in the left eye gradually extended toward the optic disk (Figure 2). Fluorescein angiography demonstrated the progress of the filling defect toward the optic disk (Figure 3). In the right eye, neovascularization on the optic disk as well as elsewhere developed, and preretinal hemorrhage was present. Panretinal photocoagulation was applied to the right eye and focal photocoagulation to the left eye. The neovascularization in the right eye tended to regress, and a fibrous membrane developed in the left eye. The visual acuity deteriorated to counting fingers as a result of dense vitreous hemorrhage in March 1997. Pars plana vitrectomy, lensectomy, and intraocular lens implantation were performed in the left eye, and visual acuity improved to 20/25 in September 1998.

Throughout the follow-up period, no oral steroids or agents that affect coagulation and platelet function were given.

### Case 2

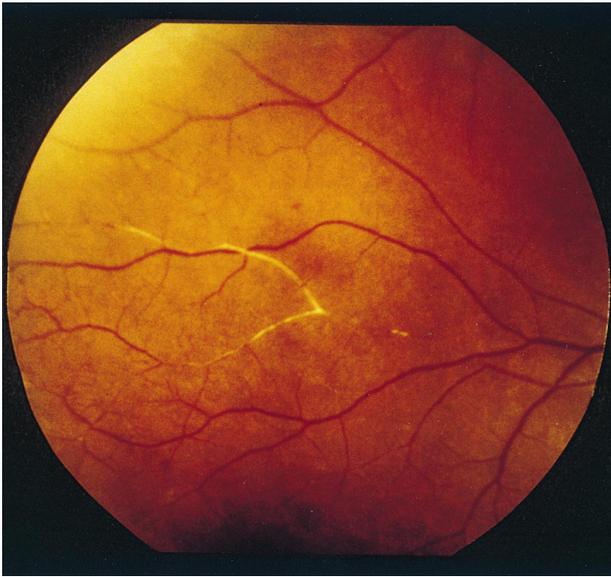
A 39-year-old woman was started on prednisone 30 mg/day and aspirin 81 mg/day orally after being diagnosed with SLE. In June 1995, she visited our clinic complaining of distorted vision, indicative of metamorphopsia, for the past several months.

Her best corrected visual acuity was 20/20 OU. Fundus examination showed that many peripheral retinal arterioles of the right eye appeared white and thread-like and were surrounded by blot hemor-

rhages. A peripheral branch of the superotemporal retinal artery had a white thread-like appearance with uneven and irregular narrowing. There was also blockage of blood flow in certain regions. In the left eye, the white thread-like appearance was observed in some parts of the retinal arterial structure. Mild SLE retinopathy and its ensuing incomplete macular star were visible in the macula. Fluorescein angiography revealed a filling defect of the right peripheral retinal arterioles with a white thread-like appearance, retrograde filling from the periphery, and a filling delay in the veins (Figure 4). The arterioles with



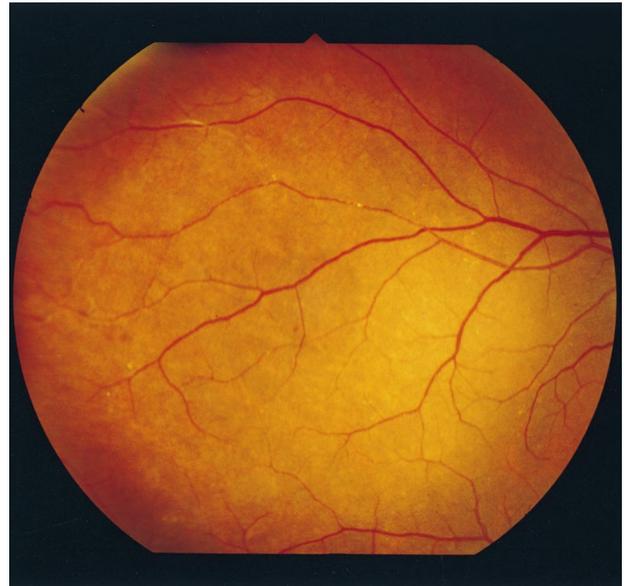
**Figure 4.** Fluorescein angiographic photograph of case 2 at initial visit. Filling defect in retinal arterioles can be seen (\*) (50 seconds after dye injection).



**Figure 5.** Changes in peripheral branch of superotemporal retinal artery 6 months after initial visit. White thread-like appearance has progressed in some regions.

the white thread-like appearance in the left eye showed no filling abnormalities.

Laboratory studies disclosed the following values: white blood cell count  $6900/\text{mm}^3$ , red blood cell count  $370 \times 10000/\text{mm}^3$ , platelet count  $15.3 \times 10000/\text{mm}^3$ , hemoglobin level 11.0 g/dL, and hematocrit 33.3%. The total cholesterol was 242 mg/dL and triglycerides were 133 mg/dL, indicating a mild elevation of cholesterol levels. Other values in the laboratory tests included erythrocyte sedimentation rate (60 minutes) 25 mm (normal level: 2 to 10 mm), CRP  $< 0.2$  mg/dL (normal level:  $< 0.5$  mg/dL), IgG 2170 mg/dL (normal level: 1000-1960 mg/dL), IgM 155 mg/dL (normal level: 35-310 mg/dL), IgA 657 mg/dL (normal level: 100-330 mg/dL), serum complement level (CH50) 23.3 U/mL (normal level: 30.0-40.4 U/mL), C3 value 27 mg/dL (normal level: 45-90 mg/dL), C4 value 3 mg/dL (normal level: 12-40 mg/dL), antinuclear antibody (+), and anti-DNA antibody (RIA) 16.9 IU/mL (normal level:  $\leq 7$  IU/mL). These findings are indicative of SLE. The findings on the parameters associated with hemagglutination were APTT 40.0 seconds (reference: 36.0 seconds), prothrombin time (PT) 98%, suggesting a mild APTT prolongation. In addition to these findings, (LA)(-),  $\text{aCL}_{\beta_2\text{GPI}} \geq 125.0$  U/mL and  $\text{IgGaCL}(+) 3.0$  (normal level:  $< 1.0$ ) were observed leading to a diagnosis of secondary APS with SLE as the underlying disease in this patient.



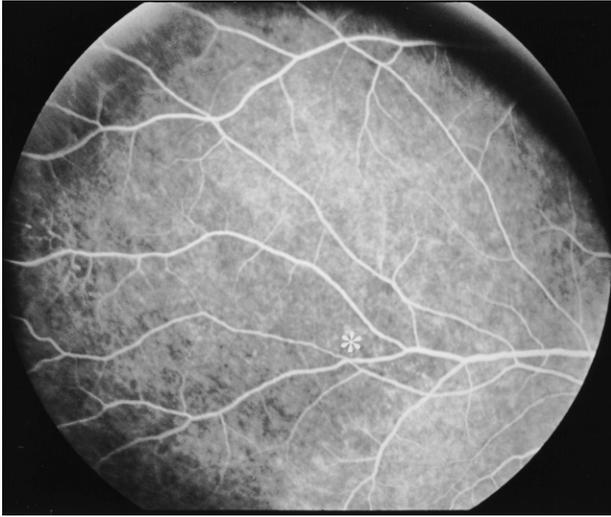
**Figure 6.** Three years after initial visit, white thread-like appearance has improved in some areas.

B-mode ultrasonography of the carotid artery disclosed no stenosis of the internal carotid artery. Color Doppler imaging detected no abnormality in the velocity in the ophthalmic and central retinal arteries.

In July 1995, hematological tests revealed normalization of serum complement and anti-DNA antibody levels, which permitted a tapering of the oral prednisone to 15 mg/day by the Department of Internal Medicine. This dose was maintained until September 1995, followed by a gradual decrease without recurrence of SLE. In December 1995, 6 months after her initial visit, the white thread-like appearance in the right peripheral branch of the superotemporal retinal artery was found to have progressed (Figure 5); no other new angiographic findings were observed. In April 1996, fluorescein angiography verified a recanalization of the previously occluded arterial branch, and an alleviation of white thread-like appearance in some regions. During the subsequent 2-year monitoring period, no notable alterations in fundusoscopic and angiographic findings were found (Figures 6, 7). Three years after her initial presentation, she is on prednisone 5 mg/day and aspirin 81 mg/day orally.

## Discussion

In both patients, the white thread-like retinal arterioles led to the suspicion of APS. Patients with APS



**Figure 7.** Three years after initial visit, some previously occluded arterioles have recanalized (\*) (67 seconds after injection).

often have fatal complications, such as ischemic heart disease and cerebrovascular disease.<sup>9,10</sup> It has also been reported that the recurrent rate of stroke is higher in APS-positive than APS-negative groups.<sup>11</sup> It is, therefore, stressed that early diagnosis is important. Physicians with knowledge of APS often suspect secondary APS and conduct further tests when patients with SLE have thrombotic events. On the other hand, patients with PAPS have less opportunity to be detected because the clinical events are not so specific. The fundus appearance in the present two cases suggested APS; blood circulation tests confirmed the presence of APS. We propose that the white thread-like appearance of retinal arterioles be used to screen patients suspected of having APS. Further observations are required on the findings of the retinal arterioles in APS.

The mechanism of thrombosis in APS is still controversial. Carreras et al<sup>12</sup> demonstrated that LA might prevent the release of arachidonic acid by cross-reacting with phospholipid in the endothelial cell membrane and thereby inhibiting the production of prostacyclin, an inhibitor of platelet aggregation. Another mechanism to be considered is the inhibition of the release of plasminogen activator leading to a reduction of the conversion of plasminogen to plasma. This would then result in a decrease of fibrin breakdown.<sup>12</sup> Recently, a hypothesis was put forth that  $\beta_2$  GPI, a plasma protein cofactor, is associated with the mechanism of thrombosis in APS.<sup>13</sup> One of the physiological functions of  $\beta_2$  GPI is to inhibit the

activation of the contact phase system of the intrinsic pathway of blood coagulation.<sup>14</sup> Anticardiolipin antibodies are directed not to cardiolipin, but to an immune complex of cardiolipin and  $\beta_2$  GPI.<sup>15</sup> Anticardiolipin antibodies may inhibit the biological function of  $\beta_2$  GPI by binding to  $\beta_2$  GPI, leading to thrombosis.<sup>16</sup>

Thrombosis or obstruction of a large artery such as the cerebral artery, coronary artery, and femoral artery is reported to be present in patients with APS.<sup>9-12</sup> On the other hand, changes in small arteries, such as the retinal artery, have not been thoroughly investigated. Graham et al<sup>17</sup> reported that immunoglobulin is deposited in the retinal vessel walls in SLE patients. In our cases, fundus examination revealed the white thread-like appearance of the retinal arterioles, and fluorescein angiography showed a reduction in the caliber of the lumen and occlusion of arterioles. These findings suggest that the antiphospholipid antibody promotes the deposition of material on the walls of the retinal arterioles. Some cases may show narrowing of the lumen with eventual complete obstruction of the arterioles. Others may show increased permeability of the arterioles and extensive sheathing of the arterioles as in retinal vasculitis.<sup>18</sup> The pathogenesis of the material that deposits on the wall of the retinal arterioles is uncertain, and the presence of cases of APS that do not show any change in the retinal arterioles suggests a more complex and unidentified mechanism.

The occlusion of retinal arterioles in our cases differs from central retinal artery obstruction (CRAO) or branch retinal artery obstruction (BRAO) in some respects. In most cases of acute retinal artery occlusion with cotton wool spots and whitening of the retina, the occlusion is spontaneously relieved. Our two cases did not show any sign that indicated an episode of acute retinal artery occlusion. Moreover, in case 1, we could follow the progress of the white thread-like appearance and occlusion of the superonasal retinal artery toward the optic disk for about 2 years. In case 2, the white thread-like appearance became gradually more severe and recanalization occurred during a 3-year follow-up. These findings suggest that chronic and progressive changes, as well as the acute changes of the arterioles, may play important roles in the occlusion of retinal arteries in APS.

A second interesting point is that the insufficiency of retinal circulation was variable in these cases, possibly because of the variation in the degree of reduction in the caliber of the lumen. Even in the same fundus, some arterioles maintained normal circula-

tion and others showed mild to severe insufficiency. This indicates that occlusion need not occur at only one point, but can occur multifocally along the wall of the retinal arterioles. The more severe the narrowing of the arterioles, the more impaired the retinal circulation.

Neovascularization in CRAO or BRAO is rare in the absence of diabetes mellitus or ocular ischemic syndrome.<sup>19-22</sup> Neovascularization is believed to occur after stimulation by angiogenic factors produced by the ischemic retina.<sup>23</sup> In most cases of CRAO or BRAO, there is a relatively rapid tissue death of the hypoxic inner retina and vascular cells, and retinal circulation is reestablished when the obstruction is spontaneously relieved.<sup>23</sup> These events may stop the production of the angiogenic factors and are responsible for the rarity of neovascularization after CRAO or BRAO.<sup>23</sup> In case 1, the neovascularization persisted. Case 1 had no definable stenosis of the internal carotid artery or ophthalmic artery to cause the ocular ischemic syndrome shown by MRA and CDI results. Kleiner et al<sup>6</sup> have also reported cases with PAPS that showed neovascularization, although it is uncertain whether it accompanied ocular ischemic syndrome. Neovascularization after occlusion of the retinal arterioles in APS may not be so rare as in CRAO or BRAO. Chronic and other types of insufficiencies of the retinal arterioles may lead to chronic hypoxia of the retina and stimulate neovascularization, although this is still speculative.

Many aspects associated with APS remain unclear, such as choroidal circulation and the treatment of retinal vascular occlusion, and further investigation is needed. In the presence of retinal arteriole events as reported in this study, the search for antiphospholipid antibodies might be useful.

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