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Peripapillary Subretinal Neovascularization in Sarcoidosis: Remission and Exacerbation During Oral Corticosteroid Therapy

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Background: In sarcoidosis, peripapillary subretinal neovascularization is rare. The role of corticosteroid therapy for subretinal neovascularization is controversial.

Case: A 38-year-old female patient weighing 38 kg with histologically diagnosed sarcoidosis presented with peripapillary subretinal neovascularization, retinal phlebitis, a hyperemic disc, and snowball vitreous opacities in the left eye.

Observation: Oral betamethasone therapy at an initial dose of 3 mg/day reduced the size of subretinal neovascular membrane, and the membrane became fibrous. Despite the total initial 140 mg of betamethasone given over 2.5 months and the additional total 700 mg of prednisolone given over the next 2 months, the subretinal neovascularization recurred. Six months after the first recurrence, a second recurrence developed during the tapering-off period of oral corticosteroid therapy. At the second recurrence, the oral corticosteroid therapy was ineffective in reducing the size of the neovascular membrane.

Conclusion: In our patient, oral corticosteroids temporarily suppressed peripapillary subretinal neovascularization but failed to prevent extension of neovascular membrane to the fovea because of recurrent sarcoidosis. Over time, oral corticosteroids appear to lose their effectiveness for treating repeated recurrence of peripapillary subretinal neovascularization associated with sarcoidosis. **Jpn J Ophthalmol 2002;46:95–99** © 2002 Japanese Ophthalmological Society

Key Words: Corticosteroid therapy, sarcoidosis, subretinal neovascularization.

Introduction

Sarcoidosis is characterized by noncaseating epithelioid-cell granulomas with giant cells and can involve multiple organs, including the eye. In a patient with sarcoidosis, retinal periphlebitis can cause a large area of capillary nonperfusion resulting in retinal neovascularization. Subretinal neovascularization, however, is a rare finding and has been reported in the macular[1,2] and peripapillary regions.[3] We report a patient who showed temporary regression of peripapillary subretinal neovascularization after oral corticosteroid therapy but later suffered extension of the neovascular membrane to the fovea after repeated recurrence in the membrane.

Received: December 18, 2000

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Case Report

In June 1995, a 38-year-old woman presented with peripapillary subretinal hemorrhage. Elsewhere, she had been treated for 4 months for iritis in both eyes. Her family history was unremarkable, but her medical history included a hysterectomy done 6 months earlier because of uterus myoma. Histological examination showed nodular proliferation of mature smooth muscle cells and noncaseating epithelioid-cell granulomas with giant cells in the endometrium and myometrium of the uterus. Acid-fast staining was negative, and a histopathological diagnosis of sarcoidosis was made.

Her best visual acuity was 0.5 in the right eye because of anisometropic amblyopia due to high astigmatism, and 0.9 in the left eye. Intraocular pressure and the anterior segment were normal bilaterally except for a small grayish white nodule on the iris of

Jpn J Ophthalmol 46, 95–99 (2002)

Published by Elsevier Science Inc.

0021-5155/02/$–see front matter
PII S0021-5155(01)00457-9

Jpn J Ophthalmol
Vol 46: 95–99, 2002

her left eye. Neither peripheral anterior synechia nor a trabecular nodule was observed bilaterally. Both eyes showed a hyperemic optic disc with a blurred margin. The right eye showed two snowball vitreous opacities at the inferior fundus. The left eye showed an elevated, subretinal, grayish peripapillary region bordered by hemorrhage (Figure 1A), vascular sheathing of an inferior retinal vein, snowball vitreous opacities at the inferior and the superior fundus, and inflammatory cells in the vitreous. Laboratory tests showed normal or negative values. However, chest x-ray and computed tomography detected enlargement of the hilar lymph nodes, and gallium-67 imaging depicted increased uptake in the right lung. These findings supported the diagnosis of histologically proven sarcoidosis with ocular manifestations.

Fluorescein angiography (FAG) of the left eye revealed subretinal neovascular membrane in the temporal peripapillary region, wall staining of major retinal veins, dilated, small vessels on the disc (Figure 1B), and dye leakage of inferior retinal veins (Figure 1C). Late FAGs showed staining of both optic discs. Late indocyanine green (ICG) angiograms showed a hyperfluorescent region of the neovascular membrane in the left eye and hyperfluorescent optic discs (Figure 1D). The patient, whose body weight was 38 kg, was treated with subtenular injection of 2 mg/day betamethasone sodium phosphate for 4 days and, at the same time, with 3 mg/day oral betamethasone (0.79 mg/kg per day) for the first 2 weeks, 2.5 mg/day for the next 2 weeks, and 1.5 mg/day for 4 more weeks. During this course of therapy, snowball vitreous opacities, retinal vascular sheathing, and subretinal hemorrhage disappeared. FAGs showed a decrease in size of the neovascular membrane. However, because leakage persisted at both optic discs, corticosteroid therapy was continued with prednisolone sodium phosphate at 15 mg/day for 4 weeks until the borders of both optic discs became clear. The prednisolone was tapered and continued at a maintenance dose of 10 mg/day. Two weeks after this final change to the 10 mg/day dose, the subretinal neovascularization recurred.

At the recurrence in November 1995, we observed new subretinal grayish regions with hemorrhage. FAGs showed new regions of dye leakage at the border of the previous neovascular membrane (Figure 2A). A late ICG angiogram showed a hyperfluorescent region of recurrent neovascularization (Figure 2B). The patient initially rejected an increase of corticosteroids because of her cushingoid appearance. However, we persuaded her to increase her corticosteroid therapy to 3 mg/day betamethasone for 1 week. The dose was then tapered to 2.5 mg/day for the next week, 2 mg/day for 2 weeks, 1.5 mg/day for 2 weeks, and 1.0 mg/day for 1 week. During the tapering-off period, only subretinal fibrous tissue remained. The corticosteroid therapy was continued with prednisolone at 10 mg/day for 2 weeks, alternating doses of 10 and 5 mg/day for 6 weeks, 5 mg/day for 4 weeks, and finally 5 mg/day every other day for 2 weeks, at which time the second recurrence occurred. During the tapering off period, the patient's left vision had remained between 0.7 and 0.9. At the second recurrence in May 1996, we noted subretinal hemorrhage again in the left eye. The patient's vision had deteriorated to 0.4 because of retinal serous detachment. FAGs showed dye leakage just nasal to the hemorrhage near the macula and wall staining of major retinal veins at the optic disc (Figure 2C). Late ICG angiograms revealed again a hyperfluorescent area (Figure 2D). Since the posterior edge of the neovascular membrane was covered by hemorrhage, the region was considered as an ill-defined choroidal neovascularization. The neovascular membrane seemed to be juxtafoveal, and so photocoagulation was avoided. Betamethasone was administered again at 3 mg/day for 1 week and was tapered to 2.5 mg/day for 2 weeks and then to 2.0 mg/day for 2 more weeks. Despite the increased dose of corticosteroids, the hemorrhage enlarged, and by the end of July the neovascular membrane involved the macula. By October 1996, the patient's left vision had decreased to 0.1.

Discussion

In the ocular fundus, neovascularization can be caused by ischemia or inflammation. Because in our patient no circulatory defect was detected in the retina or choroid on FAGs or ICG angiograms, we think that inflammation was likely the cause. As an immunosuppressive drug, oral corticosteroid therapy is started ordinarily at 1 to 1.5 mg/kg per day prednisolone,[4] and in a previous report 60 mg/day prednisone was used.[1,2] Our patient took 3 mg/day betamethasone, which is equivalent to 30 mg/day prednisolone and means a dose of 0.79 mg/kg per day. Our initial dose was smaller than the 1.0 mg/kg per day for an immunosuppressive agent, but we did daily subtenular injection of 2 mg prednisolone. Thus, the initial dose of betamethasone of 3 mg/day was considered sufficient in our patient. In fact, during the first and second courses of corticosteroid therapy, the subretinal neovascular membrane became fibrous. Hoogstede and Copper[2] reported successful treatment with corticosteroids. However, be-

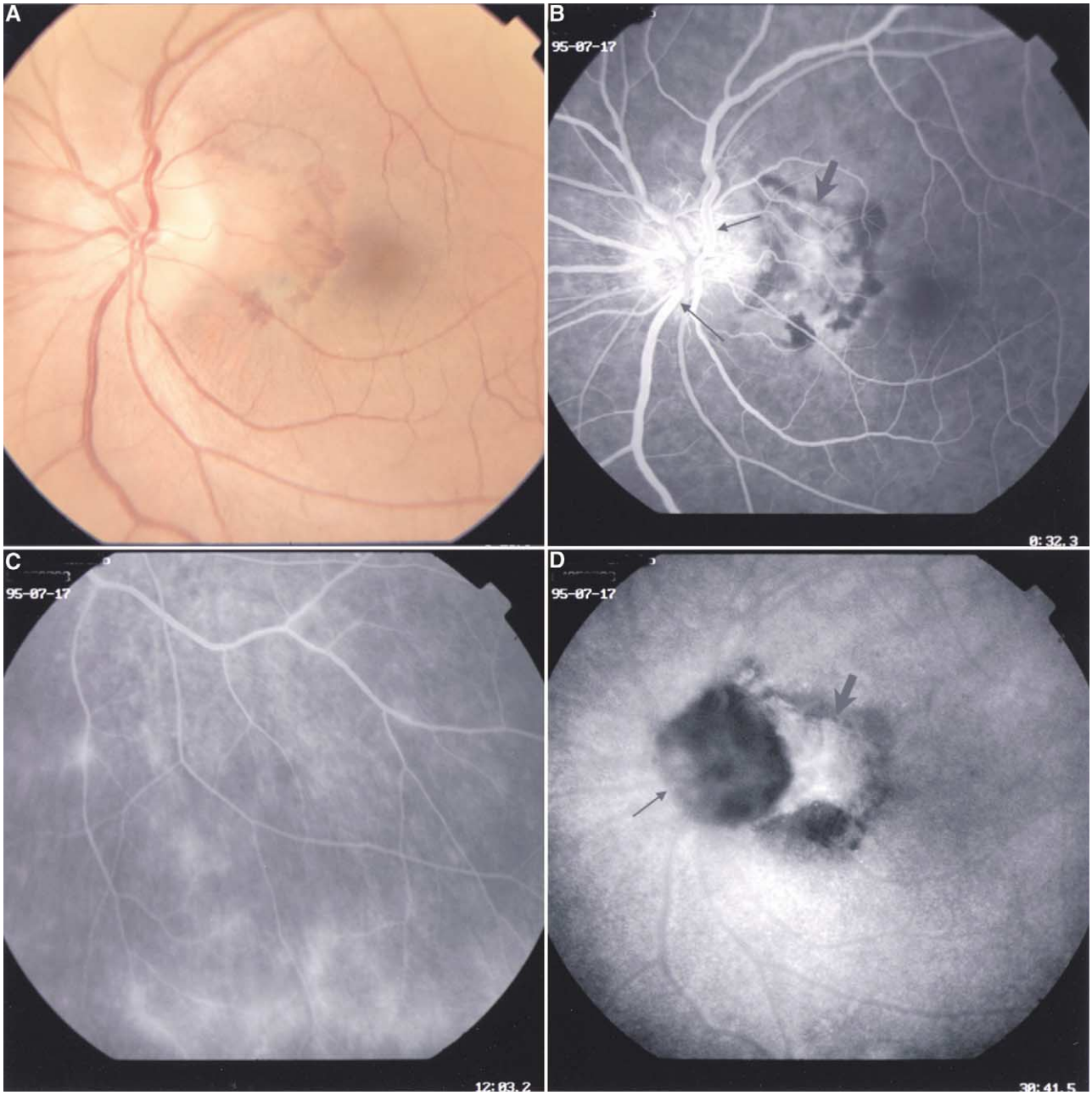

Figure 1. Fundus picture and angiograms of left eye of 38-year-old female sarcoidosis patient taken on 17 July before oral cortiocosteroid therapy. Subretinal, grayish peripapillary region bordered by hemorrhage and hyperemic disc with blurred margin are seen (**A**). Fluorescein angiograms taken 32 seconds (**B**) postinjection show hyperfluorescent region of subretinal neovascularization (thick arrow) at temporal peripapillary region. Staining of major retinal veins (thin arrows) and unusually exaggerated appearance of small vessels are noted on disc. Fluorescein angiogram taken 12 minutes (**C**) postinjection shows dye leakage of peripheral retinal veins at inferior fundus. Indocyanine green angiogram (**D**) taken 31 minutes postinjection shows hyperfluorescent region (thick arrow) of subretinal neovascular membrane. Disc shows staining (thin arrow)

cause our corticosteroid therapy failed to completely suppress recurrence of the membrane, we consider the effectiveness of oral corticosteroid therapy to be controversial. As a different therapeutic option, intravenous pulse megadose corticosteroid therapy at recurrence, or a large maintenance dose of corticosteroids could have been a better choice. However, it is difficult to decide when and how to taper corticosteroids. In patients requiring long-term corticosteroid treatment, Spalton and Sanders[5] reported that sarcoid-

Jpn J Ophthalmol
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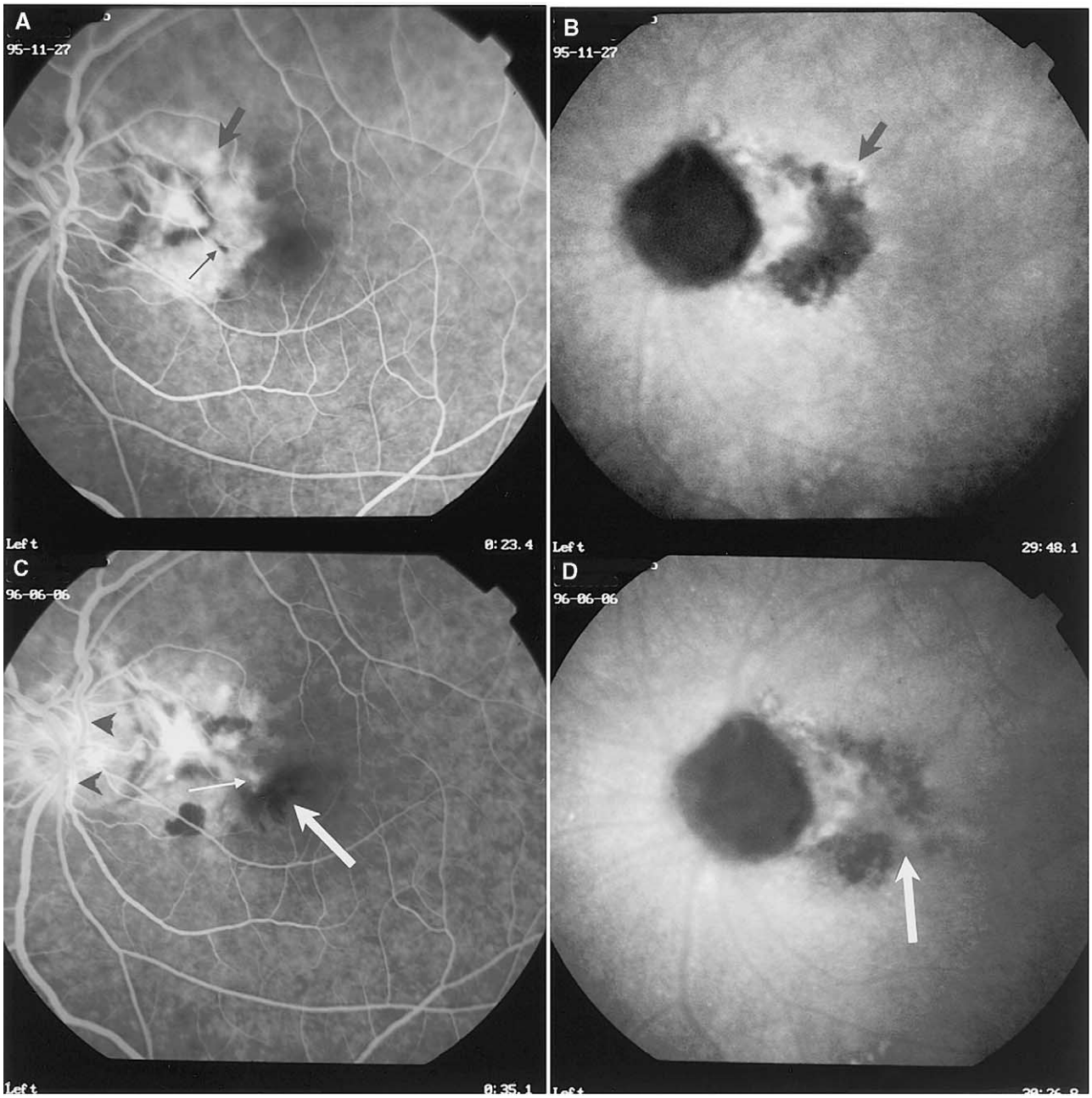

Figure 2. Angiograms at first and second recurrence of subretinal neovascularization. (**A**,**B**) Angiograms taken on 27 November 1995 at first recurrence. (**C**,**D**) Angiograms taken on 6 June 1996 at second recurrence. Small vessels are no longer visible at disc on fluorescein angiogram (**A**) taken 23 seconds postinjection. However, hyperfluorescent regions of a recurrent subretinal neovascular membrane extends circumferentially (thick arrow). Thin arrow points to hypofluorescent area of new subretinal hemorrhage. Late indocyanine green (ICG) angiogram (**B**) taken 29 minutes postinjection shows hyperfluorescent region (arrow) corresponding to extended neovascular membrane. At second recurrence, new dye leakage site (white thin arrow) is seen at previous border of subretinal neovascular membrane on fluorescein angiogram (**C**) taken 35 seconds postinjection. Hypofluorescent region (white thick arrow) of subretinal hemorrhage is seen at macular side of fluorescein leakage. Black arrowheads indicate staining of vessel walls at disc. Late ICG angiogram (**D**) taken 21 minutes postinjection shows that part of hypofluorescence observed in November 1995 is now fluorescent (white arrow). This fluorescent region is just nasal to and may include site of fluorescein dye leakage.

osis can flare up after long periods of quiescence. Gragoudas and Regan[3] reported two successful treatments with laser photocoagulation, and Frank and Weiss[1] performed laser photocoagulation after oral corticosteroid therapy. However, intense photocoagulation at the papillomacular bundle area could have damaged nerve fiber bundles in our patient.

In conclusion, peripapillary subretinal neovascularization can be seen rarely in a sarcoidosis patient without inflamed anterior segments. The neovascular vessels regress temporarily with oral betamethasone therapy (0.79 mg/kg per day), but its longer-term effectiveness is controversial.

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