ELSEVIER

CLINICAL INVESTIGATIONS

Histopathological Findings in Proliferative Membrane From a Patient With Sarcoid Uveitis

Akihiko Miyao,* Tsunehiko Ikeda,† Yasuhiro Matsumoto,†
Kuniko Uchida,‡ Teruyo Machida,‡ Miki Hongo† and Shigeru Kinoshita†

**Department of Ophthalmology, Nishijin Hospital, Kyoto, Japan;*
†Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan; ‡Department of Ophthalmology, Machida Hospital, Kochi, Japan

Background: Sarcoid uveitis is occasionally accompanied by proliferative changes, such as retinal neovascularization and vitreous hemorrhage. Steroid administration, retinal photocoagulation, and vitrectomy may be indicated in such proliferative cases.

Case: A 19-year-old woman presented with proliferative sarcoid uveitis accompanied by recurrent vitreous hemorrhage.

Observations: At the initial examination, bilateral vitreous opacity, retinal exudates, mild vitreous hemorrhage, retinal vasculitis, and neovascularization of the retina and optic disc were observed. Although prednisolone was administered and panretinal photocoagulation was performed several times, recurrent vitreous hemorrhage continued. Since the vitreous hemorrhage was not absorbed, pars plana vitrectomy and lensectomy were performed. After surgery, neovascularization and intraocular inflammation decreased, and the corrected visual acuity in the right eye improved to 20/50. Histopathologic analysis of the proliferative membrane removed during surgery revealed substantial neovascularization and numerous neutrophils in the vessels.

Conclusions: Based on these findings, an inflammatory reaction as well as retinal ischemia were thought to be involved in the proliferative changes in this patient. **Jpn J Ophthalmol 1999;43:209–212** © 1999 Japanese Ophthalmological Society

Key Words: Intraocular inflammation, neovascularization, pars plana vitrectomy, sarcoid uveitis, vitreous hemorrhage.

Introduction

To date, few studies have examined intraocular proliferative tissues histologically.[1] In the present case, pars plana vitrectomy was performed on a patient who presented with severe sarcoid uveitis accompanied by recurrent vitreous hemorrhage and subsequent proliferative membrane of the retina and optic disc. The fibrovascular membrane in the optic disc obtained during surgery was examined histopathologically. We report the histopathologic findings in this membrane and speculate on the mechanism of intraocular fibrovascular proliferation.

Case Report

A 19-year-old woman presented with the chief complaint of visual disturbance in both eyes. At the end of June 1994, she experienced general malaise, bilateral parotid enlargement, anthema in the arms and legs, and visual disturbance. The patient visited the Department of Ophthalmology, Machida Hospi-

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Correspondence and reprint requests to: Akihiko MIYAO, MD, Department of Ophthalmology, Nishijin Hospital, 1035 Mizomaecho, Kamigyo-ku, Kyoto 602, Japan

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tal, on July 26, 1994. At the initial examination, her corrected visual acuity was 20/50 in the right eye and 20/30 in the left; her intraocular pressure was 9 mm Hg in the right eye and 7 mm Hg in the left. In both eyes, inflammatory cells in the anterior chamber, mutton-fat keratic precipitates on the posterior surface of the cornea, nodules in the pupillary margin, iris peripheral anterior synechiae, and rubeosis iridis were observed. Severe vitreous opacity, subretinal exudation, sheathing of the retinal vessels, and retinal hemorrhage were also observed in both eyes. In the right eye, neovascularization was noted on the optic disc and throughout the upper temporal retina. Because of the vitreous opacity and incomplete mydriasis, fluorescein angiography could not be performed. Serum levels of angiotensin-converting enzyme (ACE) (61.5 IU/L) and lysozyme (44.7 μg/mL) were both high. The patient was positive for the C-reactive protein, but negative for tuberculin. A chest x-ray showed bilateral hilar lymphadenopathy. Conjunctival and skin biopsies were then performed for histopathologic analysis. The results of the conjunctival biopsy revealed granulomatous nodules consisting of epithelioid cells beneath the conjunctival epithelium with lymphocytes, plasmocyte infiltration, and fibrosis surrounding the nodules. The results of the skin biopsy similarly showed a noncaseating granuloma. Based on these findings, sarcoidosis was diagnosed.

Prednisolone was administered both locally and systemically because there was inflammation of the anterior segment. The initial systemic dose was 1,000 mg/day, which was later reduced. After 1 month of steroid administration the inflammation decreased and the fundus visibility improved. The visual acuity improved to 20/20 in both eyes. Fluorescein angiography performed 3 weeks after the initial examination revealed dye leakage from the optic disc and along the retinal veins, and a widespread capillary nonperfusion area in both eyes (Figure 1). Despite continued steroid treatment, neovascularization in the disc and retina of the right eye did not decrease, so additional retinal photocoagulation was performed 4 weeks later. However, because of incomplete mydriasis, a dense posterior subcapsular cataract, and vitreous opacity, photocoagulation could not be performed effectively on the capillary nonperfusion areas. The steroid dosage was reduced gradually to a maintenance dose of 10 mg/day. Four months after the initial examination, vitreous hemorrhage and recurrent anterior chamber inflammation occurred in the right eye. The prednisolone dose was increased to 40 mg/day. Despite a reduction in inflammation, the vitreous hemorrhage continued. In the meantime, neovascularization of the optic disc and retina progressed gradually, developing into a widespread fibrovascular membrane. Nine months after the initial examination, massive vitreous hemorrhage occurred in the right eye. Even 2 months later the vitreous hemorrhage had not been absorbed and the patient's visual acuity worsened to hand motion. Consequently, pars plana vitrectomy and lensectomy were performed on the right eye on July 15, 1995.

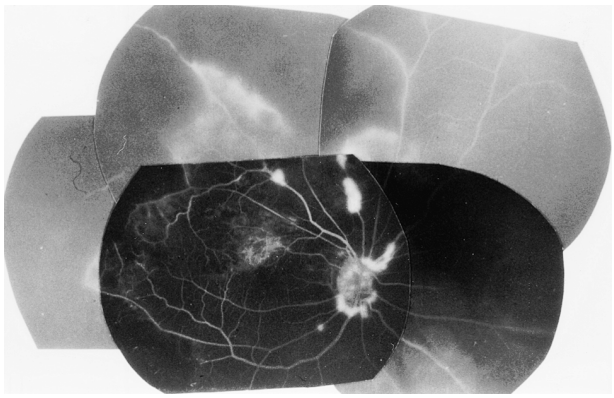

Figure 1. Fundus fluorescein angiograph of right eye taken 3 weeks after initial visit. Dye leakage from optic disc and retinal veins surrounded by wide area of capillary nonperfusion is evident.

During these procedures, the fibrovascular membranes in the retina and optic disc were removed, and end photocoagulation and an encircling buckling were performed. At 1 month postsurgery, the fundus fluorescein angiography of the right eye showed a decrease in the dye leakage from the retinal vascular walls (Figure 2). At 4 months postsurgery, although mild macular cystoid edema was detected, her corrected visual acuity improved to 20/100 in the right eye. The rubeosis iridis and iris nodules disappeared 5 months later. In the left eye, intraocular inflammation and neovascularization of the optic disc and temporal peripheral retina were observed, however, no vitreous hemorrhage had occurred and the visual acuity did not decrease. At present, the inflammation has clearly resolved and our patient's corrected visual acuity has improved to 20/50 in the right eye. However, she is still being closely monitored because of the potential for reproliferation and/or intraocular inflammation.

Materials and Methods

The fibrovascular membrane that was obtained surgically was divided into two pieces. One piece was

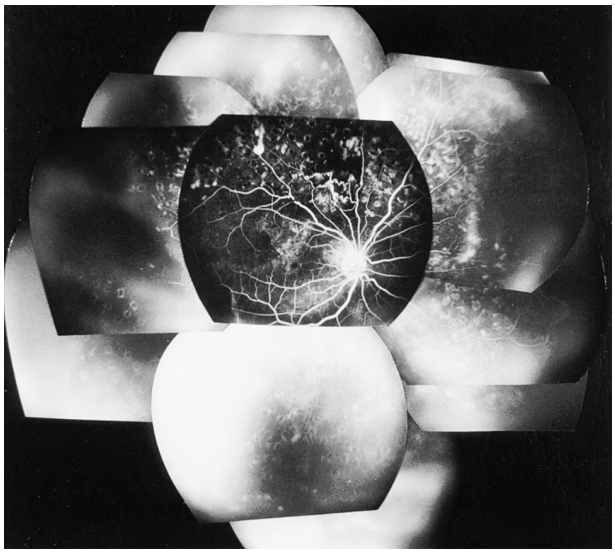

Figure 2. Fundus fluorescein angiograph of right eye taken 1 month after surgery. Neovascularization of optic disc and retina had disappeared, and dye leakage from retinal vessel had also decreased. Corrected visual acuity 20/70.

fixed with 4% paraformaldehyde in 0.1 mmol/L phosphate buffer (PB), dehydrated in graded alcohol series, and then embedded in methacrylate embedding mixture (JB-4 embedding kit; Polyscience, Warrington, PA, USA). One-micrometer sections of this specimen were stained with toluidine blue. The other piece was fixed with PB containing 2.5% glutaraldehyde and 1% OsO_4, dehydrated in graded acetone series, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate, and then examined by electron microscopy (JEM 100-S; Nihon Denshi, Tokyo).

Results

The extracted tissue was flat and membranous. The cells with oval or spindle-shaped nuclei were arranged in mono- or stratified layers on the surface. Many large and small cavities were observed in the tissues (Figure 3). Many neutrophils, which were characterized by the presence of a segmented and heterochromatin-rich nucleus, were identified in the cavities; whereas red blood cells were rarely seen (Figures 3, 4A). Amorphous substances surrounded the cavities. Several long and slender cells were arranged in parallel within the deep layer of the membrane.

These cavities were formed by a few cells, as seen in cross section using a transmission electron microscope. Each cell had a few processes projecting into the lumen and incomplete basement membrane (Figure 4A). Junctions between these cells formed

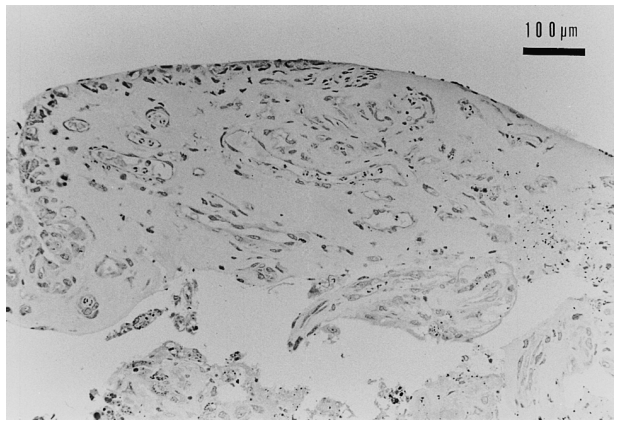

Figure 3. Light micrograph of proliferative membrane obtained during surgery from optic disc. Highly vascularized tissues are seen in proliferative membrane (toluidine blue stain).

interdigitating folds. Collagenous microfibrils were randomly arranged in the space surrounding the cavities. The long and slender cells in the deep layer of the membrane had a large nucleus, flat cytoplasm, and many processes (Figure 4B).

Discussion

In intraocular proliferative diseases, such as diabetic retinopathy, retinal vein occlusion, and premature retinopathy, the process of neovascularization is thought to be induced by a variety of angiogenic factors, such as vascular endothelial growth factor (VEGF), from the ischemic retina.[2] Two hypotheses have been proposed to explain the cause of the proliferative changes that develop in sarcoid uveitis. One is that the development of neovascularization is accelerated by severe inflammation in the eye. Another is that the inflammatory cells or sarcoid granuloma infiltrates the retinal vascular walls causing vascular occlusion and retinal ischemia, which facilitates the occurrence of retinal neovascularization.[3–5]

In the present case, a large capillary nonperfusion area was detected by fundus fluorescein angiography. Steroid administration did not lead to any retinal neovascularization, suggesting that the ischemic retina plays an important role in inducing angiogenesis. Nonetheless, this case differed from those cases with other vitreoretinal proliferative diseases, such as proliferative diabetic retinopathy, because histopathologic analysis revealed numerous neutrophils in the blood vessels of the excised proliferative membrane. This suggested the involvement of other factors, such as infection or suppurative inflammation

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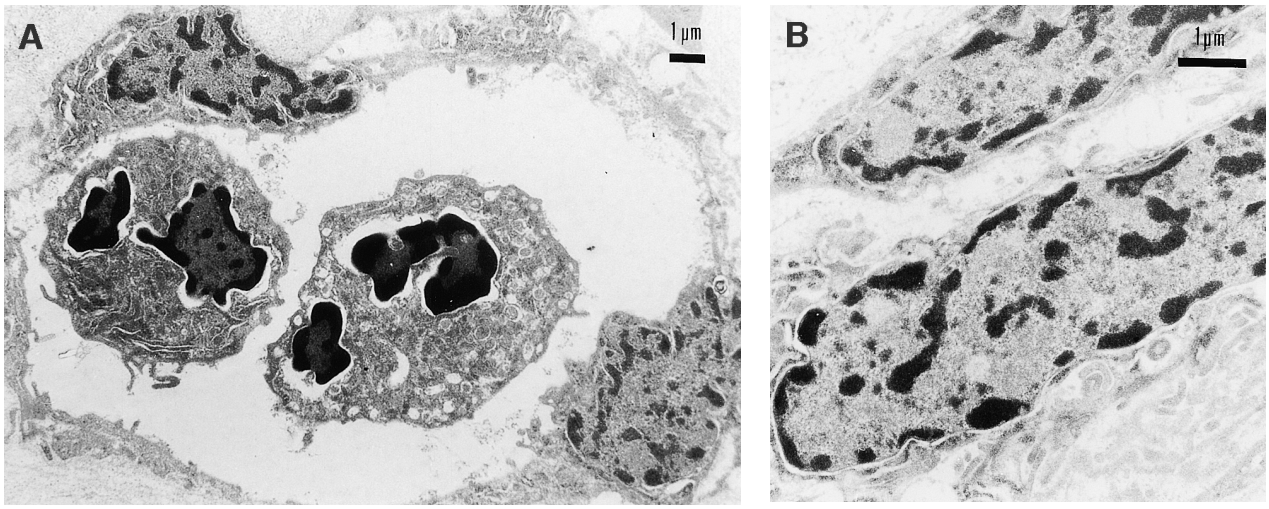

Figure 4. Electron micrograph of proliferative membrane collected during surgery. (**A**) Many neutrophils are seen in newly formed blood vessels. (**B**) Long and slender cells in deep layer of membrane had large nucleus, flat cytoplasm, and many processes.

in our case. Although the role of inflammation in the process of angiogenesis remains unclear, it is believed that factors facilitating the migration of white blood cells are released from the inflammatory tissue, which accelerates intraocular angiogenesis. Several inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), and interleukin 8 (IL-8) are reportedly induced in uveitis. In particular, IL-1 and IL-8 are cytokines with neutrophil chemotactic and activating properties.[6] Thus, accumulation of neutrophils in proliferative tissues may be the result of the release of IL-1 and IL-8 in the area of inflammation. On the other hand, recent reports have suggested that infection of *Borrelia burgdorferi* and *Propionibacterium acnes* are associated with sarcoidosis.[7,8] These infections may be related to the accumulation of neutrophils in proliferative tissues.[9]

When patients with sarcoid uveitis develop retinal neovascularization, it is generally treated by combined corticosteroid and retinal photocoagulation, based on the well-documented effectiveness of these medications.[10] Vitrectomy is generally performed on patients with vitreous hemorrhage or tractional retinal detachment. Okinami and associates[5] performed vitrectomy on cases with unabsorbable vitreous hemorrhage or retinal detachment. In the present patient, the neovascularization did not decrease, despite long-term administration of steroids, and photocoagulation could not be effectively performed as a result of vitreous hemorrhage. Based on the disappearance of inflammatory cells and chemical mediators in the vitreous cavity, which led to a reduction in intraocular inflammation, vitrectomy was considered to be effective.

References

1. Frank KW, Weiss H. Unusual clinical and histopathological findings in ocular sarcoidosis. Br J Ophthalmol 1983;67:8–16.
2. Wiedemann P. Growth factors in retinal diseases: proliferative vitreoretinopathy, proliferative diabetic retinopathy, and retinal degeneration. Surv Ophthalmol 1992;36:373–84.
3. Duker JS, Brown GC, McNamara JA. Proliferative sarcoid retinopathy. Ophthalmology 1988;95:1680–6.
4. Archer DB. Retinal neovascularization. Trans Ophthalmol Soc UK 1983;103:2–27.
5. Okinami S, Iwaki M, Ogino N. Sarcoid uveitis with vitreous hemorrhage. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1992;43:1319–22.
6. De Vos AF, Hoekzema R, Kijlstra A. Cytokines and uveitis. Curr Eye Res 1992;11:581–97.
7. Ishihara M, Ohno S, Ono H, et al. Seroprevalence of anti-Borrelia antibodies among patients with confirmed sarcoidosis in a region of Japan where Lyme borreliosis is endemic. Graefes Arch Clin Exp Ophthalmol 1998;236:280–4.
8. Nakata Y, Kataoka M, Kimura I. Sarcoidosis and *Propionibacterium acnes*. Nippon Rinsho 1994;52:1492–7.
9. Puhvel SM, Sakamoto M. The chemoattractant properties of comedonal components. J Invest Dermatol 1978;71:324–9.
10. Hirose S, Ohno S. Argon laser treatment of retinal neovascularization associated with sarcoidosis. Jpn J Ophthalmol 1984;28:356–61.