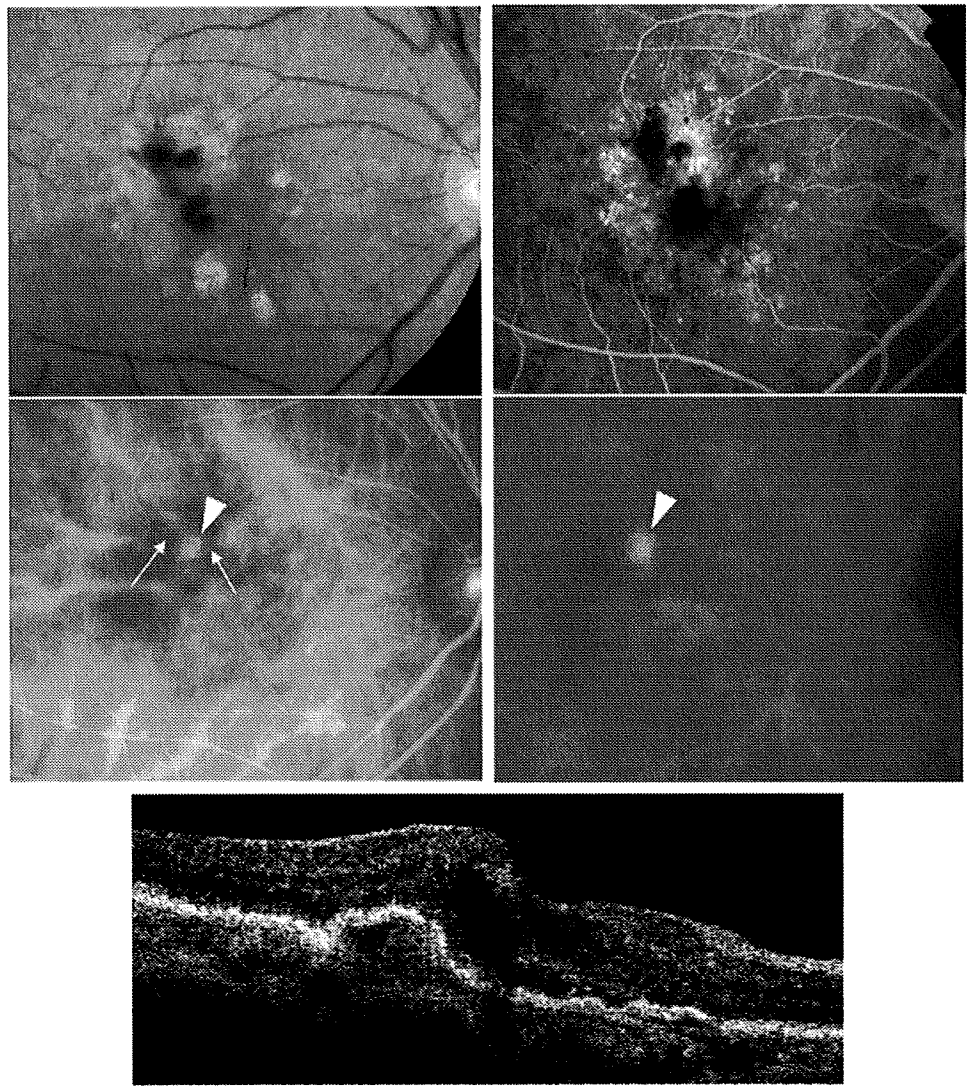


FIGURE 3. Case 7: an 84-year-old woman was treated with combined intravitreal triamcinolone acetonide with photodynamic therapy (IVTA plus PDT) for stage 2 retinal angiomatous proliferation (RAP) with a pigment epithelial detachment (PED). At baseline, the best-corrected visual acuity (BCVA) was 0.6 decimal VA in the right eye with stage 2 RAP. (Top left) Red-free photograph showing small intraretinal and preretinal hemorrhages, a PED, and drusen. (Top right) Fluorescein angiogram showing leakage and intraretinal edema. (Middle left) Early-phase indocyanine green angiogram (ICGA) showing retinal-retinal anastomosis (arrows) and a RAP lesion (arrowhead). (Middle right) Late-phase ICGA showing a focal area of intense hyperfluorescence (hot spot; arrowhead). (Bottom) Baseline horizontal optical coherence tomography image showing cystoid macular edema and a PED. Photodynamic therapy was applied (laser spot size, 3700 μm) 1 week after IVTA.

or 2 days after IVB was injected. PDT with verteporfin was administered according to the protocol of the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy study.[30] A 689-nm laser system (Carl Zeiss Meditec) was used and 50 J/cm^2 energy was delivered with an 83-second exposure time. The greatest linear dimension (GLD) was measured based on FA findings. The laser spot size was determined by FA (FA-guided PDT) in 20 eyes and by ICGA (ICGA-guided PDT) in 5 eyes. FA-guided PDT was performed for the entire lesion seen on FA. ICGA-guided PDT was chosen if the lesion comprised a larger subretinal hemorrhage at least 1 disc diameter in size.

All patients were examined 3, 6, 9, and 12 months after the initial PDT was administered. Statistical analysis was performed using the Student *t* test to compare the VA and the central retinal thickness 3, 6, 9, and 12 months from baseline.

RESULTS

TABLES 1 AND 2 SHOW THE CHARACTERISTICS AND CLINICAL data of the 22 patients (25 eyes) at baseline and after treatment. All patients were Japanese and were observed

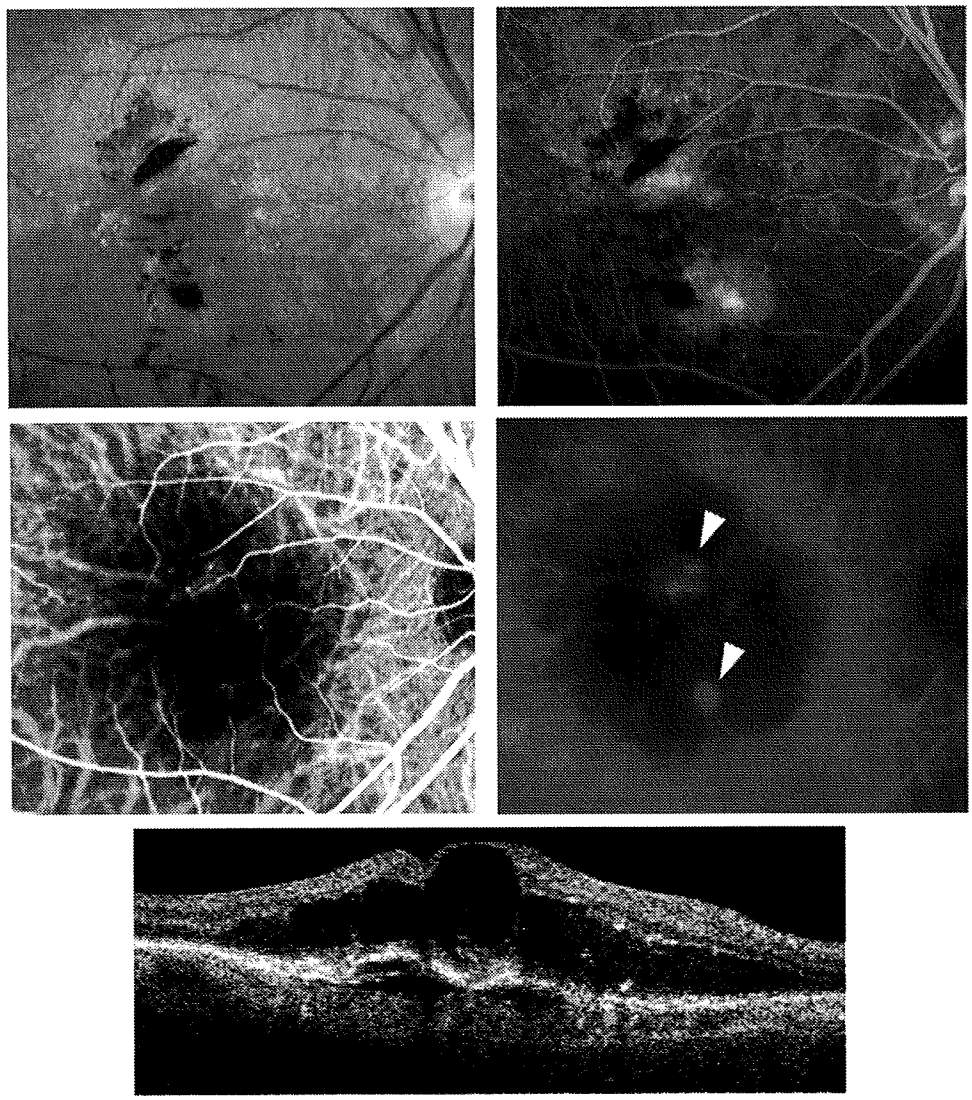


FIGURE 4. Case 7: 12 months after combined intravitreal triamcinolone acetonide with photodynamic therapy (IVTA plus PDT). Four treatments with combined therapy of IVTA plus PDT were administered over 12 months. The best-corrected visual acuity (VA) declined from 0.6 to 0.08 decimal VA. (Top left and right) Fluorescein angiograms showing that a hemorrhage, a shallow pigment epithelial detachment (PED), and leakage remain. (Middle left and right) Indocyanine green angiogram showing persistent and new retinal-retinal anastomosis and hot spots (arrowheads). (Bottom) Horizontal optical coherence tomography image showing persistent cystoid macular edema and a PED. A fifth treatment was administered.

for 12 months. There was no difference in the mean age between the 2 groups. In the 12 eyes treated with IVTA plus PDT, 7 eyes had stage 2 RAP without a retinal pigment epithelial detachment (PED) and 5 eyes had stage 2 RAP with a PED. In the 13 eyes treated with IVB plus PDT, 5 eyes had stage 2 RAP without a PED, 6 eyes had stage 2 RAP with a PED, and 2 eyes had stage 3 RAP. The mean GLD of the entire lesion was 2670 μm. There was no significant difference in the baseline patient characteristics between the 2 treatment groups.

In the 12 eyes treated with IVTA plus PDT, the mean BCVA levels at baseline and 3, 6, 9, and 12 months after treatment were 0.29, 0.25, 0.27, 0.22, and 0.13, respectively (Figure 1), indicating a significant ($P < .05$, paired t test) decline in the mean BCVA from baseline at 12 months. The mean changes in the BCVA at 6 and 12 months from baseline were a decline of 0.19 and 3.28 lines, respectively. One of the 12 eyes (8.3%) had an increase in the BCVA of 3 lines or more, 10 eyes (83.4%) had stable VA, and 1 eye (8.3%) had a decrease in the BCVA of 3 lines or more 6 months from baseline. At 12 months, 2 (16.7%) of 12 eyes had an increase in the BCVA of 3 lines or more, 7 eyes (58.3%) had stable VA, and 3 eyes (25%) had a decrease in the BCVA of 3 lines or more from baseline (Figure 2). The central retinal thickness significantly ($P < .05$, paired t test) decreased from baseline from 406 ± 125 μm (mean ± standard deviation) to 287 ± 124 μm at 3 months, 274 ± 174 μm at 6 months, 261 ± 208

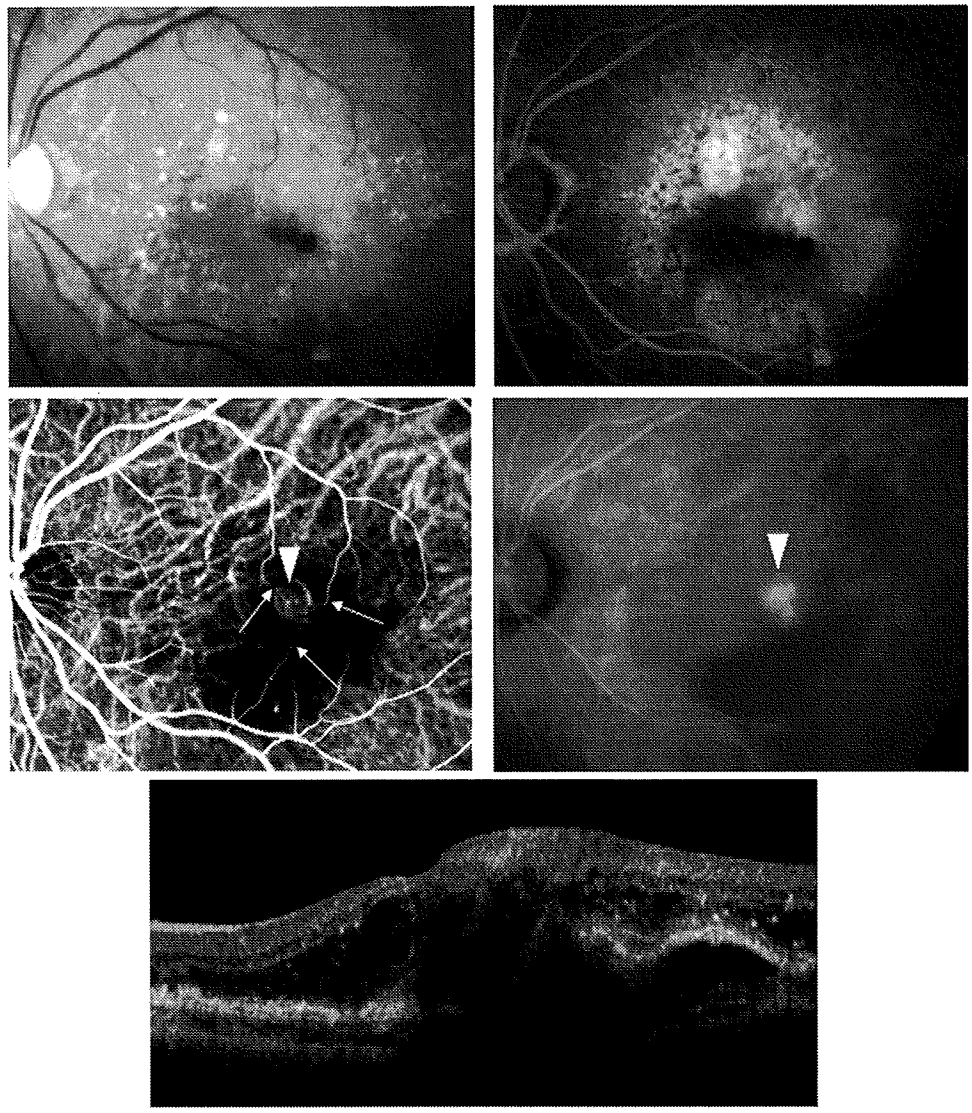


FIGURE 5. Case 22: an 83-year-old woman was treated with combined therapy of intravitreal bevacizumab and photodynamic therapy (IVB plus PDT) for stage 2 retinal angiomatous proliferation (RAP) with a pigment epithelial detachment (PED). At baseline, the best-corrected visual acuity (VA) was 0.3 decimal VA in the left eye with stage 2 RAP with a PED. (Top left) Red-free photograph showing small intraretinal and preretinal hemorrhages, a PED, and drusen. (Top right) Fluorescein angiogram showing leakage and intraretinal edema. (Middle left) Early-phase indocyanine green angiogram (ICGA) showing retinal-retinal anastomosis (arrows) and a RAP lesion (arrowhead). (Middle right) Late-phase ICGA showing a focal area of intense hyperfluorescence (hot spot; arrowhead). (Bottom) Baseline vertical optical coherence tomography image showing cystoid macular edema and a PED. Photodynamic therapy was applied (laser spot size, 5600 μm) 2 days after IVB.

μm at 9 months, and 276 ± 166 μm at 12 months. At baseline, cystoid macular edema (CME) was observed in 11 of the 12 eyes; there was a serous retinal detachment (SRD) in 7 of the 12 eyes, and a PED in 5 of the 12 eyes. The CME resolved in 5 (45.5%) eyes a mean of 5.4 weeks after baseline and decreased in 6 eyes. The SRD resolved completely in 5 (71.4%) eyes a mean of 3.1 weeks after baseline and decreased in 2 eyes. The PED resolved completely in 2 (40%) eyes a mean of 6.5 weeks after baseline and remained in 3 eyes. The mean GLD of the entire lesion was 2885 μm at baseline and 936 μm at 12 months ($P = .06$ compared with baseline). Six eyes were phakic and 6 eyes were pseudophakia. The mean intraocular pressure (IOP) was 13.7 mm Hg at baseline and 13.3 mm Hg at 12 months. Figures 3 and 4 show ocular images obtained from a patient treated with IVTA plus PDT.

In the 13 eyes treated with IVB plus PDT, the mean BCVA levels at baseline and 3, 6, 9, and 12 months after treatment were 0.25, 0.35, 0.35, 0.34, and 0.37, respectively (Figure 1). A significant improvement in the mean BCVA from baseline was seen at 3, 6, and 12 months ($P < .01$, $P < .05$, $P < .05$, respectively, paired t test; Figure 1).

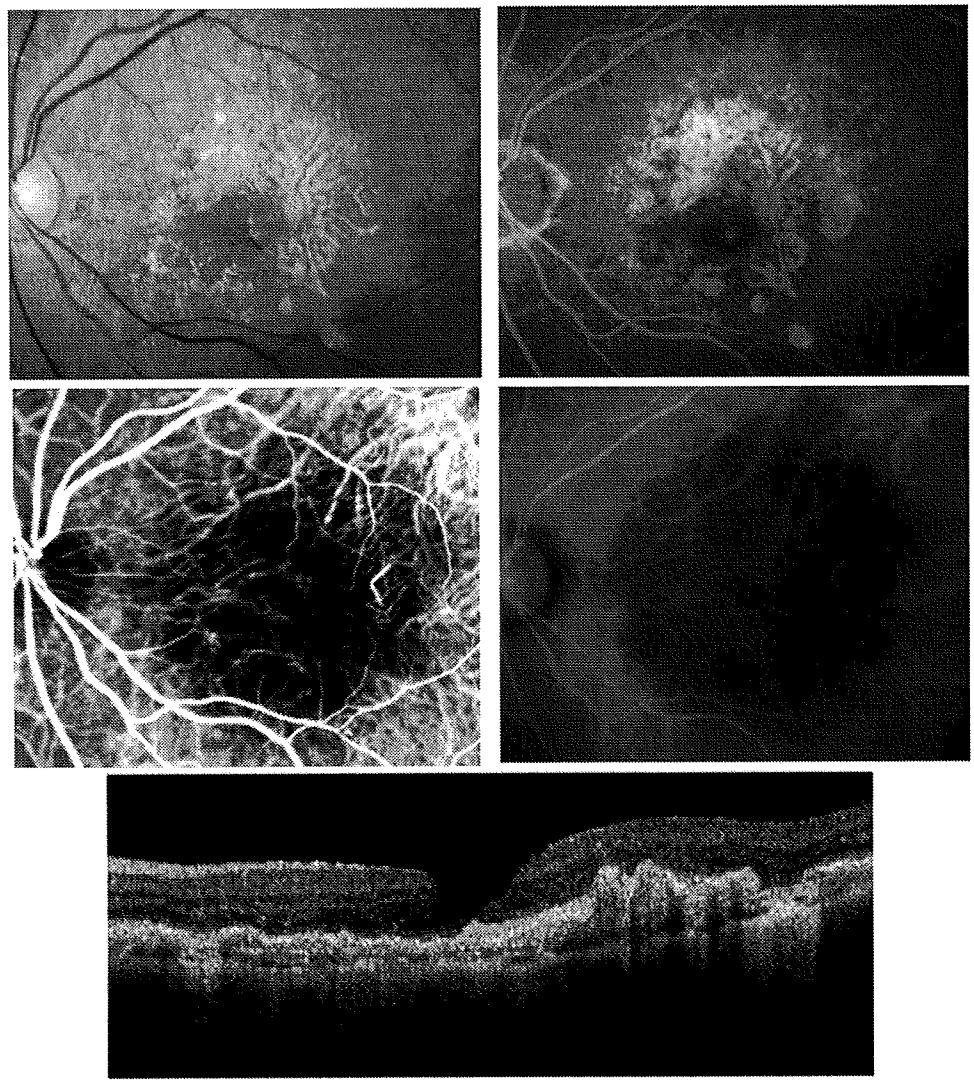


FIGURE 6. Case 22: 12 months after combined therapy of intravitreal bevacizumab and photodynamic therapy (IVB plus PDT). Three treatments were administered over 12 months. The best-corrected visual acuity (VA) improved from 0.3 to 0.6 decimal VA. (Top left and right) Fluorescein angiogram showing no hemorrhages, pigment epithelial detachment (PED), or leakage. (Middle left and right) Indocyanine green angiogram showing clear resolution of the retinal-retinal anastomosis and a hot spot. (Bottom) Vertical optical coherence tomography image showing absorption of the cystoid macular edema and a PED.

Although there was no significant difference in the mean BCVA at baseline between the 2 treatment groups ($P = .74$), there was a significant difference in the mean BCVA at 12 months ($P < .05$, nonpaired t test; Figure 1). The mean changes in BCVA at 6 and 12 months from baseline were improvements of 1.46 and 1.73 lines, respectively. The mean changes in BCVA at 3, 6, and 12 months were significantly better in the IVB plus PDT group than in the IVTA plus PDT group ($P < .05$, $P < .05$, $P < .01$, respectively, using the nonpaired t test). Four (30.8%) of the 13 eyes had an increase in the BCVA of 3 lines or more, and 9 eyes (69.2%) had stable VA at 6 months. At 12 months, 6 (46%) of 13 eyes had an increase in the BCVA of 3 lines or more, and 7 eyes (54%) had stable VA from baseline (Figure 2). No patient had decreased BCVA of 3 lines or more after treatment during any 12 months. The central retinal thickness decreased significantly from 456 ± 171 μm at baseline to 229 ± 213 μm at 3 months ($P < .01 \times 10^{-3}$), 233 ± 162 μm at 6 months ($P < .01 \times 10^{-5}$), 164 ± 120 μm at 9 months ($P < .01 \times 10^{-3}$), and 135 ± 94 μm at 12 months ($P < .01 \times 10^{-4}$). At baseline, all 13 eyes had CME, 8 of the 13 eyes had an SRD, and 8 of the 13 eyes had a PED. The CME resolved in 11 (84.6%) eyes a mean of 2.4 weeks after baseline and decreased in 2 eyes. The SRD resolved in 7 (87.5%) eyes 3.9 weeks after baseline and decreased in 1 eye. The PED resolved in 4 (50%) eyes a mean of 4.4 weeks after baseline and decreased in 3 eyes. The mean GLD of the entire lesion was 3108 μm at baseline and 0 μm at 12 months ($P < .01 \times 10^{-3}$, compared with baseline). Eight eyes

were phakic and 5 eyes were pseudophakia. The mean IOP was 14.1 mm Hg at baseline and 12.1 mm Hg at 12 months. Figures 5 and 6 show ocular images obtained from a patient treated with IVB plus PDT. The mean numbers of treatments at 12 months in the IVTA plus PDT and IVB plus PDT groups were 2.7 and 1.6, respectively, a difference that reached significance ($P < .05$, nonpaired t test). At the 12-month follow-up, FA showed resolution of leakage in all eyes treated with IVB plus PDT and resolution of leakage in 8 of the 12 eyes treated with IVTA plus PDT; the remaining 4 eyes underwent retreatments for persistent leakage.

At baseline, early-phase ICGA identified retinal–retinal anastomosis in 11 of 12 eyes treated with IVTA plus PDT and in 10 of 13 eyes treated with IVB plus PDT. Three months after treatment, complete occlusion of the retinal–retinal anastomosis was achieved in 1 (9.1%) of the 11 eyes treated with IVTA plus PDT and in 6 (60%) of the 10 eyes treated with IVB plus PDT. Among the remaining eyes (10 eyes treated with IVTA plus PDT and 4 eyes treated with IVB plus PDT) without occlusion of the retinal–retinal anastomosis, early-phase ICGA showed that the retinal–retinal anastomosis had narrowed in 1 of the 10 eyes treated with IVTA plus PDT and in all 4 eyes treated with IVB plus PDT. Moreover, 12 months after the initial treatment, complete occlusion of the retinal–retinal anastomosis was achieved in 2 (18.2%) of the 11 eyes treated with IVTA plus PDT and in 8 (80%) of the 10 eyes treated with IVB plus PDT.

Late-phase ICGA at baseline showed a hot spot in 11 of 12 eyes treated with IVTA plus PDT and in 12 of 13 eyes treated with IVB plus PDT. In 3 (27.2%) of the 11 eyes treated with IVTA plus PDT and in 100% of the 13 eyes treated with IVB plus PDT, the hot spot resolved 3 months after treatment. Moreover, 12 months after the initial treatment, the hot spot resolved in 2 (18.2%) of the 11 eyes treated with IVTA plus PDT and in 100% of the 13 eyes treated with IVB plus PDT. No complications, such as inflammation, increases in IOP to more than 21 mm Hg, severe vision loss, endophthalmitis, progression of cataract, or systemic events, developed.

DISCUSSION

THE CURRENT STUDY SHOWED THAT COMBINED TREATment of IVB plus PDT significantly improved the VA and reduced the number of treatments in patients with RAP compared with combined treatment of IVTA plus PDT during a 12-month follow-up.

The natural course of RAP has been reported to have poor visual outcomes compared with that of typical AMD.[5–7] The general consensus is that the disease is associated with a poor functional prognosis and resultant disciform scarring.[1,6,7] Conventional laser photocoagulation,[6,8] transpupillary thermotherapy,[6,9] surgical ablation,[10,11,30] and PDT alone[12,13] have been used to treat patients with RAP. However, poor visual outcomes usually result from these monotherapies.[6,8–13]

We reported the efficacy of IVB plus PDT for treating RAP with 6 months of follow-up.[29] In the current study, we found a significant ($P < .05$, paired t test) improvement in the mean BCVA from baseline at 12 months. The BCVA in 6 (46%) of 13 eyes increased by 3 lines or more, and 7 eyes (54%) had stable VA.

An inflammatory response and upregulation of VEGF have been reported after application of PDT.[31,32] TA has antiangiogenic, antiinflammatory, and anti-VEGF effects.[17,18] Combination therapy of PDT and TA reduced the inflammatory response and upregulation of VEGF associated with CNV and PDT. Freund and associates reported that combination therapy of IVTA plus PDT reduced or eliminated edema, achieved rapid regression of neovascularization, and stabilized or improved VA in white patients with RAP.[19] Those authors speculated that verteporfin may leak into the retinal cystic spaces, and to avoid predisposing the retinal layers to photochemical damage, they applied PDT 1 week after IVTA (referred to as pharmacology-pause-PDT). Because this method was well conceived, we administered IVTA plus PDT accordingly. Nevertheless, a significant ($P < .05$, paired t test) decline in the mean BCVA from baseline was observed at 12 months. The reason why pharmacology-pause-PDT was ineffective for treating Japanese patients in the current study is unknown.

Intraretinal neovascularization, subretinal neovascularization, and retinal–retinal anastomosis are evidence of RAP lesions.[1] Surgical lysis of the feeding arterioles and draining venules was effective because it eliminated high-flow blood supply to the RAP lesions.[33] Achieving complete occlusion of the retinal–retinal anastomosis is important for reducing RAP lesions. In patients with RAP, several injections of IVB monotherapy were needed but did not achieve complete occlusion of the feeder vessels.[34,35] We reported the efficacy of IVB plus PDT for RAP for achieving complete occlusion of retinal–retinal anastomosis during a 6-month follow-up.[29] In the current study, complete occlusion of the retinal–retinal anastomosis was achieved in 2 (18.2%) of the 11 eyes treated with IVTA plus PDT and in 8 (80%) of the 10 eyes treated with IVB plus PDT 12 months after treatment. IVB plus PDT can reduce the high-flow blood supply to RAP lesions over a long period.

Rouvas and associates compared ranibizumab, ranibizumab combined with PDT, and IVTA plus PDT with a minimum 6-month follow-up.[20] In that report, the mean VA at baseline to the end of the follow-up decreased from 0.83 to 0.85 logMAR in eyes treated with ranibizumab, decreased from 0.61 to 0.63 logMAR in eyes treated with ranibizumab plus PDT, and improved from 0.92 to 0.61 logMAR ($P = .183$) in eyes treated with IVTA plus PDT. The authors concluded that all therapies resulted in

stabilized disease, whereas IVTA plus PDT achieved better functional and anatomic results compared with the other treatments. In the current study, the mean BCVA improved significantly from 0.25 at baseline to 0.37 at 12 months in eyes treated with IVB plus PDT ($P < .05$). The investigators suggested that bevacizumab has a longer half-life than ranibizumab, so they did not observe any differences in ranibizumab and ranibizumab in combination with PDT as when using bevacizumab.

We performed PDT 1 or 2 days after administering IVB. Overexpression of VEGF in the retina (photoreceptors) is sufficient to cause intraretinal and subretinal neovascularization in animal models,[36] which is similar to the neovascular process of RAP. Using injections of intravitreal anti-VEGF agents combined with PDT is reasonable for inhibiting VEGF-induced PDT and the neovascularization of RAP. Rouvas and associates administered PDT 7 ± 2 days after ranibizumab was injected intravitreously.[20] The ideal interval between intravitreal injection of anti-VEGF agents and PDT is unknown and remains controversial. Freund and associates reported that 1 intravitreal ranibizumab injection to treat RAP resulted in rapid resolution of the intraretinal edema, hemorrhage, and neovascular lesions.[2] In typical AMD eyes, the central retinal thickness measurements decreased immediately after injection of ranibizumab.[37,38] The clinical efficacy may depend on the suppression of CNV using anti-VEGF agents. Verteporfin may accumulate minimally in the suppressed neovascular complex after injection of intravitreal anti-VEGF agents. For this reason, we applied PDT as soon as possible after IVB. Applying PDT simultaneously with intravitreal anti-VEGF agents also may be effective.

Development of complications after PDT, such as severe vision loss of approximately 4.5% in the first year[30] or the enlargement of the hypofluorescence on ICGA, has been reported.[39] The complications after IVTA include elevated IOP, progression of cataracts in phakic patients, and development of endophthalmitis.[40,41] In the current study, no patients had severe vision loss, IOP of more than 21 mm Hg, or cataract progression during the 12 months of follow-up.

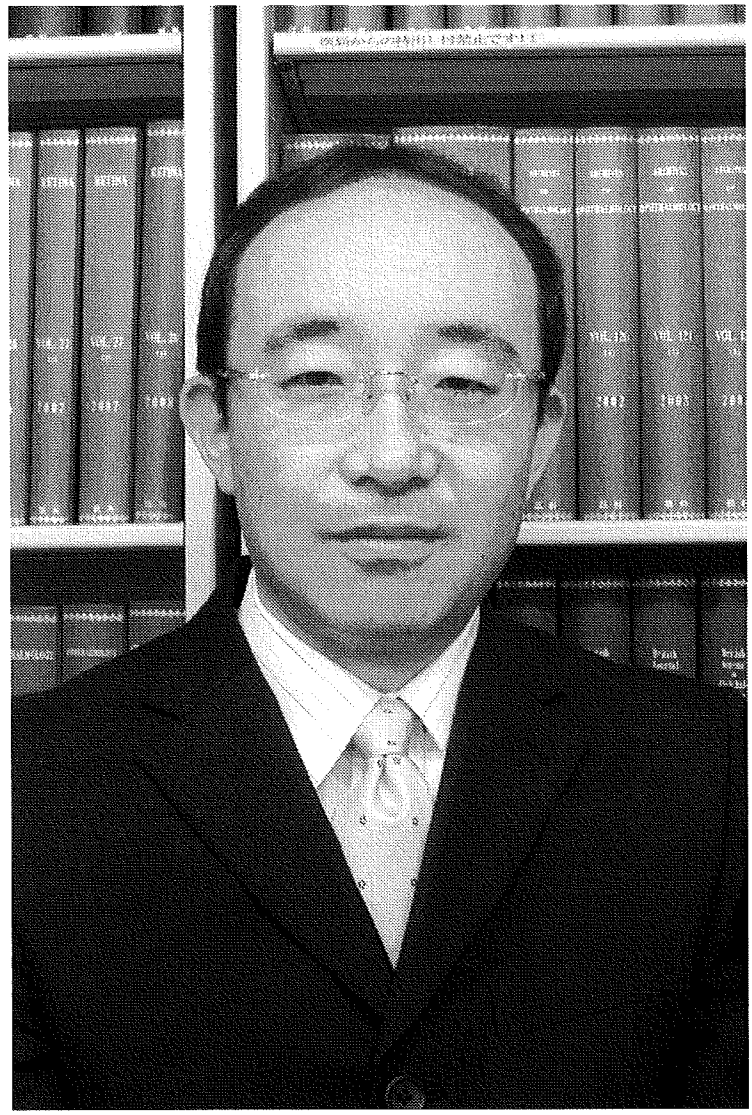
In conclusion, the results of the current study indicate that combined therapy of IVB plus PDT was significantly more effective for maintaining or improving VA and reducing the number of treatments in patients with RAP compared with combined therapy of IVTA and PDT. Because this was a pilot study, larger and long-term prospective randomized studies are needed to determine the efficacy and safety profiles of combined bevacizumab or of an anti-VEGF agent and PDT.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN AND conduct of study (M.S., T.I., F.S.); Collection, management, analysis, and interpretation of the data (M.S., C.S., M.K.); preparation, review, and revision of the manuscript (M.S., T.I.); and Approval of the manuscript (M.S., C.S., F.S., M.K., T.I.). The treatments in this study were approved by the Institutional Review Board/Ethics Committee of Fukushima Medical University and Kagawa University in Japan. After the potential risks and benefits were explained in detail, all patients provided written informed consent.

REFERENCES

1. Yannuzzi LA, Negrão S, Iida T, et al. Retinal angiomatous proliferation in age-related macular degeneration. Retina 2001;21:416–434.
2. Freund KB, Ho IV, Barbazetto IA, et al. Type 3 neovascularization: the expanded spectrum of retinal angiomatous proliferation. Retina 2008;28:201–211.
3. Cohen SY, Creuzot-Garcher C, Darmon J, et al. Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. Br J Ophthalmol 2007;91:1173–1176.
4. Maruko I, Iida T, Saito M, Nagayama D, Saito K. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. Am J Ophthalmol 2007;144:15–22.
5. Hartnett ME, Weiter JJ, Staurenghi G, Elsner AE. Deep retinal vascular anomalous complexes in advanced age-related macular degeneration. Ophthalmology 1996;103:2042–2053.
6. Bottoni F, Massacesi A, Cigada M, Viola F, Masicco I, Staurenghi G. Treatment of retinal angiomatous proliferation in age-related macular degeneration: a series of 104 cases of retinal angiomatous proliferation. Arch Ophthalmol 2005;123:1644–1650.
7. Bressler NM. Retinal anastomosis to choroidal neovascularization: a bum rap for a difficult disease. Arch Ophthalmol 2005;123:1741–1743.
8. Slakter JS, Yannuzzi LA, Schneider U, et al. Retinal choroidal anastomoses and occult choroidal neovascularization in age-related macular degeneration. Ophthalmology 2000;107:742–753.
9. Kuroiwa S, Arai J, Gaun S, Iida T, Yoshimura N. Rapidly progressive scar formation after transpupillary thermotherapy in retinal angiomatous proliferation. Retina 2003;23:417–420.
10. Sakimoto S, Gomi F, Sakaguchi H, Tano Y. Recurrent retinal angiomatous proliferation after surgical ablation. Am J Ophthalmol 2005;139:917–918.
11. Shiragami C, Iida T, Nagayama D, Baba T, Shiraga F. Recurrence after surgical ablation for retinal angiomatous proliferation. Retina 2007;27:198–203.
12. Boscia F, Furino C, Sborgia L, Reibaldi M, Sborgia C. Photodynamic therapy for retinal angiomatous proliferations and pigment epithelium detachment. Am J Ophthalmol 2004;138:1077–1079.
13. Silva RM, Cachulo ML, Figueira J, de Abreu JR, Cunha-Vaz JG. Chorioretinal anastomosis and photodynamic therapy: a two-year follow-up study. Graefes Arch Clin Exp Ophthalmol 2007;245:1131–1139.
14. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. Invest Ophthalmol Vis Sci 1996;37:1929–1934.

15. Kliffen M, Sharma HS, Mooy CM, Kerkvliet S, de Jong PT. Increased expression of angiogenic growth factors in age-related maculopathy. Br J Ophthalmol 1997;81:154–162.
16. Oh H, Takagi H, Takagi C. The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. Invest Ophthalmol Vis Sci 1999;40:1891–1898.
17. Penfold PL, Wen L, Madigan MC, King NJ, Provis JM. Modulation of permeability and adhesion molecule expression by human choroidal endothelial cells. Invest Ophthalmol Vis Sci 2002;43:3125–3130.
18. Hori Y, Hu DE, Yasui K, Smither RL, Gresham GA, Fan TP. Differential effects of angiostatic steroids and dexamethasone on angiogenesis and cytokine levels in rat sponge implants. Br J Pharmacol 1996;118:1584–1591.
19. Freund KB, Klais CM, Eandi CM, et al. Sequenced combined intravitreal triamcinolone and indocyanine green angiography-guided photodynamic therapy for retinal angiomatous proliferation. Arch Ophthalmol 2006;124:487–492.
20. Rouvas AA, Papakostas TD, Vavvas D, et al. Intravitreal ranibizumab, intravitreal ranibizumab with PDT, and intravitreal triamcinolone with PDT for the treatment of retinal angiomatous proliferation: a prospective study. Retina 2009; 29:536–544.
21. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338–346.
22. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351: 2805–2816.
23. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006;26:383–390.
24. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
25. Brown DM, Kaiser PK, Michels M, et al. ANCHOR Study Group Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
26. Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA, Tewari A. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration. Retina 2006;26:988–993.
27. Ladas ID, Kotsolis AI, Papakostas TD, Rouvas AA, Karagiannis DA, Vergados I. Intravitreal bevacizumab combined with photodynamic therapy for the treatment of occult choroidal neovascularization associated with serous pigment epithelium detachment in age-related macular degeneration. Retina 2007;27:891–896.
28. Kaiser PK, Registry of Visudyne AMD Therapy Writing Committee, Boyer DS, Garcia R, et al. Verteporfin photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2009;116:747–755.
29. Saito M, Shiragami C, Shiraga F, Nagayama D, Iida T. Combined intravitreal bevacizumab and photodynamic therapy for retinal angiomatous proliferation. Am J Ophthalmol 2008;146:935–941.
30. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP Report 1. Arch Ophthalmol 1999;117:1329–1345.
31. Tatar O, Adam A, Shinoda K, et al. Influence of verteporfin photodynamic therapy on inflammation in human choroidal neovascular membranes secondary to age-related macular degeneration. Retina 2007;27:713–723.
32. Tatar O, Adam A, Shinoda K, et al. Expression of VEGF and PEDF in choroidal neovascular membranes following verteporfin photodynamic therapy. Am J Ophthalmol 2006;142: 95–104.
33. Borrillo JL, Sivalingam A, Martidis A, Federman JL. Surgical ablation of retinal angiomatous proliferation. Arch Ophthalmol 2003;121:558–561.
34. Meyerle CB, Freund KB, Iturralde D, et al. Intravitreal bevacizumab (Avastin) for retinal angiomatous proliferation. Retina 2007;27:451–457.
35. Joeres S, Heussen FM, Treziak T, Bopp S, Joussen AM. Bevacizumab (Avastin) treatment in patients with retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol 2007;245:1597–1602.
36. Okamoto N, Tobe T, Hackett SF, et al. Transgenic mice with increased expression of vascular endothelial growth factor in the retina: a new model of intraretinal and subretinal neovascularization. Am J Pathol 1997;151:281–291.
37. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143: 566–583.
38. Kiss CG, Geitzenauer W, Simader C, et al. Evaluation of ranibizumab-induced changes in high-resolution optical coherence tomographic retinal morphology and their impact on visual function. Invest Ophthalmol Vis Sci 2009;50: 2376–2383.
39. Rouvas AA, Papakostas TD, Ladas ID, Vergados I. Enlargement of the hypofluorescent post photodynamic therapy treatment spot after a combination of photodynamic therapy with an intravitreal injection of bevacizumab for retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol 2008;246:315–318.
40. Spaide RF, Sorenson J, Maranan L. Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularization. Ophthalmology 2003; 110:1517–1525.
41. Bhavsar AR, Ip MS, Glassman AR, DRCRnet and the SCORE Study Groups. The risk of endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE clinical trials. Am J Ophthalmol 2007;144:454–456.



Biosketch

Masaaki Saito, MD, was born and raised in Gunma prefecture, Japan. He graduated from the Fukushima Medical University School of Medicine, Fukushima, Japan in 1996. Dr Saito is currently an Assistant Professor of the Department of Ophthalmology, Fukushima Medical University School of Medicine, Fukushima, Japan.

One-Year Results of Reduced-Fluence Photodynamic Therapy for Polypoidal Choroidal Vasculopathy

AYANA YAMASHITA, FUMIO SHIRAGA, CHIEKO SHIRAGAMI, AOI ONO, AND KAORI TENKUMO

• PURPOSE: To report 1-year results of reduced-fluence photodynamic therapy (PDT) for polypoidal choroidal vasculopathy (PCV) in Japanese patients.
• DESIGN: Prospective interventional case series.
• METHODS: In the present study, 28 treatment-naïve eyes of 28 consecutive patients underwent PDT with a reduced laser fluence of 25 J/cm^2. Patients were followed up at baseline and 1 week and 3, 6, 9, and 12 months after PDT. Choroidal perfusion changes were evaluated by indocyanine green angiography (ICGA) and leakage from PCV lesions and exudative changes by fluorescein angiography and optical coherence tomography. Treatment safety was assessed according to visual acuity (VA) and adverse events. The best-corrected VA (BCVA) obtained by Landolt ring tests was converted into the logarithm of the minimal angle of resolution (logMAR).
• RESULTS: At baseline, the mean logMAR BCVA was 0.45 (geometric mean: 7/20). At 12 months, the mean logMAR BCVA significantly improved to 0.29 (geometric mean: 10/20) ($P = 0.0001$). The logMAR BCVA was stable or improved by ≥0.2 in 26 eyes (93%) at 1-year follow-up. In 10 eyes with VA better than 20/40 at baseline, the mean logMAR BCVA was significantly improved compared with baseline at 12 months. Although 16 of 28 eyes (57%) showed mild to moderate nonperfusion of choriocapillaris in early ICGA at 1 week, 27 eyes (96%) showed recovery to pretreatment levels at 3 months. Mean number of treatment sessions during the 12 months was 1.3. No severe side effects related to treatment were encountered.
• CONCLUSIONS: Reduced-fluence PDT is an effective treatment for PCV and could improve vision even in eyes with VA better than 20/40. (Am J Ophthalmol 2010;149:465–471. © 2010 by Elsevier Inc. All rights reserved.)

VERTEPORFIN THERAPY REDUCES THE RISK OF VISION loss in patients with subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD).[1–4] The Japanese Age-Related Macular Degeneration Trial (JAT)[5] showed superior efficacy of photodynamic therapy (PDT) for Japanese patients compared with the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study,[1–4] which mainly investigated Caucasians. Guidelines for the use of verteporfin in Japan[6] demonstrated that verteporfin was effective in maintaining visual acuity (VA) for 12 months for all lesion types, as demonstrated previously in the JAT, and a significant improvement in VA was observed for eyes with polypoidal choroidal vasculopathy (PCV) ($P < .001$),[6] the prevalence of which is postulated to be higher in Asian populations than in Caucasians.[7–9] However, a decline in VA was observed for eyes with VA better than 20/40.[6]

On the other hand, several studies have shown that PDT damages the physiological choriocapillary layer beyond the irradiated area, and repeated PDT leads to persistent choriocapillary nonperfusion in most eyes.[10,11] Choroidal ischemia consecutively induces a secondary angiogenic response with increased expression of vascular endothelial growth factor (VEGF).[12] The influence of verteporfin therapy on the physiological choroid may be the reason for further vision loss and the need for repeated treatment. The Visudyne in Minimally Classic Choroidal Neovascularization (VIM) Study Group[13] showed there was no difference in the proportion of patients having acute severe vision decrease in the reduced-fluence group as compared with the standard-fluence group. Michels and associates[14] reported that reduced-fluence treatment leads to much less damage of the choriocapillaris when compared to standard-fluence. Thus, since the efficacy of PDT was reported in eyes with PCV,[15–17] we aimed to study the effect and safety of reduced-fluence PDT for PCV in Japanese patients.

METHODS

TWENTY-EIGHT EYES OF 28 CONSECUTIVE PATIENTS (24 men, 4 women) who had been diagnosed with PCV and had no previous treatment of any type for PCV were enrolled in this prospective study between July 1, 2007 and March 31, 2008. All 28 patients were Japanese and the median patient age was 73.5 years (range, 47–85 years). The prospective interventional case-control study was approved by the Institutional Review Board of Kagawa University Faculty of Medicine.

Patients received verteporfin (Visudyne; Novartis Pharma, Tokyo, Japan) injection at 6 mg/m^2 body surface area over 10 minutes and then underwent PDT with a light fluence of 25 J/cm^2 using a Visulus PDT system 690S (Carl Zeiss Meditec AG, Jena, Germany) 5 minutes after the completion of infusion. The laser spot size was chosen to

Accepted for publication Sept 30, 2009.
From the Department of Ophthalmology, Kagawa University Faculty of Medicine, Miki-cho, Kida-gun, Kagawa, Japan.
Inquiries to Ayana Yamashita, Department of Ophthalmology, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kida-gun, Kagawa 761-0793, Japan; e-mail: bourjois@med.kagawa-u.ac.jp

0002-9394/10/$36.00
doi:10.1016/j.ajo.2009.09.020

TABLE. Indocyanine Green Angiographic Findings Before and After Reduced-Fluence Photodynamic Therapy in 28 Eyes With Polypoidal Choroidal Vasculopathy

Case No.	Age	VA		ICGA Findings at Month 3		Choriocapillary Nonperfusion After PDT[a]		No. of Treatments
		At Baseline	12 Months	Branching Vascular Network	Polypoidal Vascular Lesions	Week 1	Month 3	
1	61	20/250	20/120	persistent	disappeared	no	no	1
2	77	20/30	20/20	disappeared	disappeared	not significant	no	1
3	82	20/60	20/25	persistent	disappeared	moderate	no	1
4	47	20/20	20/10	disappeared	disappeared	moderate	no	1
5	59	20/30	20/20	disappeared	disappeared	no	no	1
6	59	20/200	20/100	persistent	disappeared	moderate	no	1
7	85	20/200	20/100	persistent	disappeared	no	no	1
8	73	20/50	20/100	persistent	recurrent	no	no	3
9	77	20/50	20/22	persistent	disappeared	not significant	no	1
10	75	20/40	20/60	persistent	disappeared	moderate	no	2
11	71	20/40	20/22	disappeared	disappeared	moderate	not significant	2
12	76	20/25	20/28	persistent	disappeared	not significant	no	3
13	84	20/200	20/200	persistent	persistent	no	no	2
14	55	20/30	20/16	persistent	disappeared	not significant	no	1
15	77	20/30	20/25	persistent	disappeared	not significant	no	1
16	71	20/40	20/30	persistent	disappeared	no	no	2
17	64	20/28	20/30	persistent	disappeared	no	no	1
18	77	20/40	20/25	persistent	disappeared	not significant	no	1
19	68	20/28	20/16	persistent	disappeared	no	no	1
20	75	20/28	20/28	persistent	disappeared	moderate	no	1
21	79	20/120	20/120	persistent	disappeared	no	no	1
22	68	20/50	20/28	persistent	disappeared	no	no	1
23	70	20/60	20/28	persistent	disappeared	moderate	no	1
24	83	20/60	20/28	persistent	disappeared	no	no	1
25	78	20/50	20/22	persistent	disappeared	moderate	no	1
26	70	20/200	20/120	disappeared	disappeared	no	no	1
27	71	20/100	20/50	persistent	disappeared	moderate	no	1
28	74	20/30	20/50	persistent	disappeared	moderate	no	2

PDT = photodynamic therapy; VA = visual acuity.
[a]Based on grading of verteporfin therapy's effect on the choriocapillaris as documented by indocyanine green angiography.[14]

cover the entire PCV vascular lesions, including the polypoidal lesions and branching vascular network vessels, as shown on indocyanine green angiography (ICGA), plus an extra margin of 1000 μm.[15,17]

Patients were seen for regular follow-up visits within 7 days before PDT (baseline) and at 1 week and 3, 6, 9, and 12 months after PDT. Best-corrected VA (BCVA) and optical coherence tomography (OCT) using an OCT3000 or Cirrus HD-OCT system (Carl Zeiss Meditec, Dublin, California, USA) were performed at each visit. Fluorescein angiography (FA) using the TRC50IX system with ImageNet2000 (Topcon, Tokyo, Japan) and ICGA using a Heidelberg Retina Angiograph 2 (HRA2) (Heidelberg Engineering GmbH, Heidelberg, Germany) were performed before PDT, and at 1 week and 3 months after PDT. We evaluated choroidal perfusion changes by ICGA, leakage from polypoidal vascular lesions by FA, and exudative changes by OCT. Grading of effect on choriocapillaris was based on a report by Michels and associates.[14]

The PDT endpoint was achieved when complete absence of leakage was seen on FA, or when the absence of exudative changes including pigment epithelial detachment, serous retinal detachment, and retinal edema was seen on OCT. Rendering disappearance of polypoidal vascular lesions on ICGA was unnecessary. Eyes with no exudative changes on OCT were observed rather than treated, even though there was minimal leakage.

Safety of treatment was assessed based on BCVA and adverse events. The BCVA obtained by Landolt ring tests was converted into the logarithm of the minimal angle of resolution (logMAR), with a change of 0.2 or more in logMAR VA considered significant. Improvement in BCVA was defined as an increase of ≥0.2 logMAR units, and worsening in BCVA was defined as a decrease of ≤0.2 logMAR units. For comparison of BCVA outcomes to baseline, the paired *t* test was used.

RESULTS

PATIENT CHARACTERISTICS ARE SHOWN IN THE TABLE.

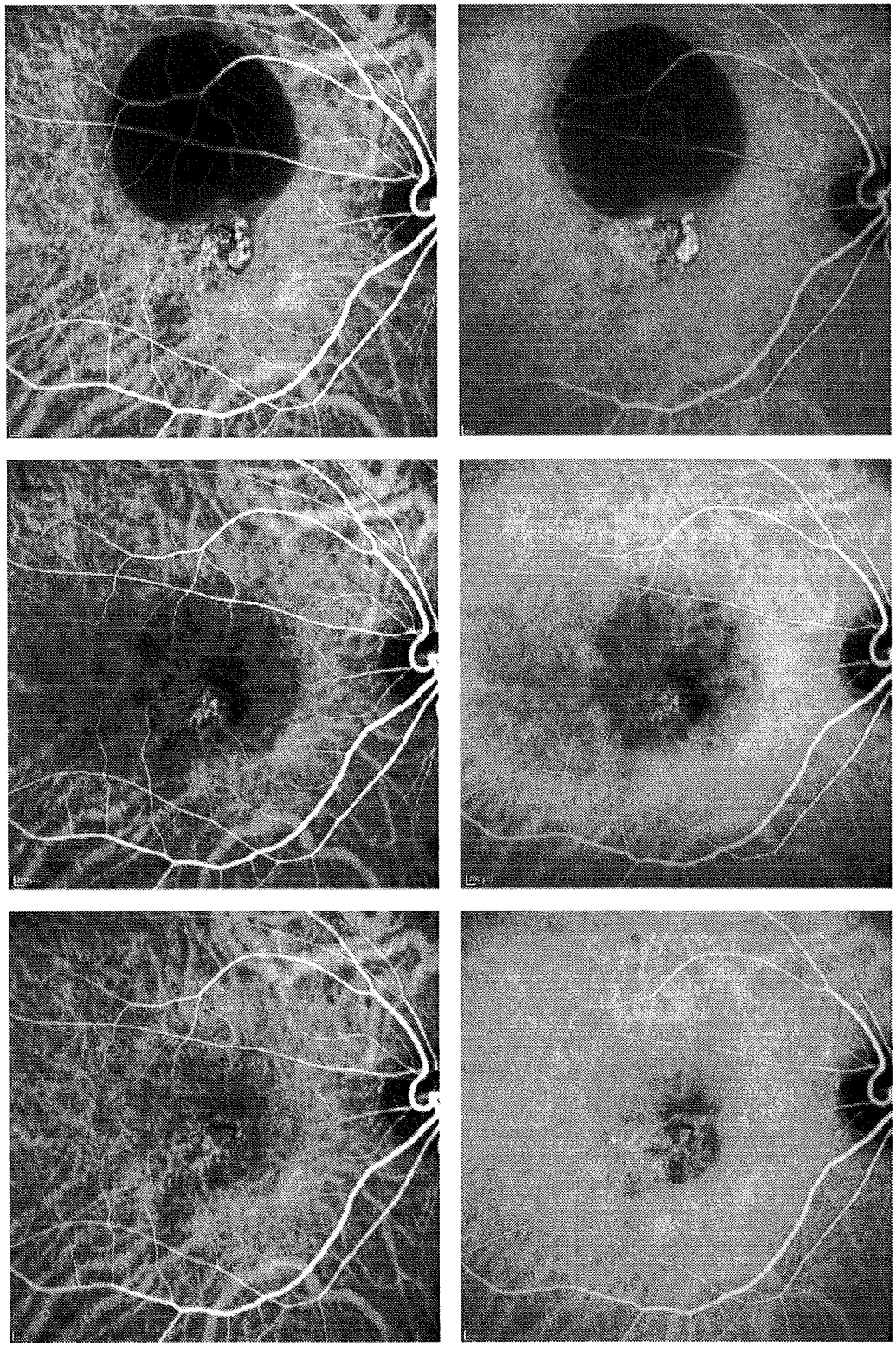


FIGURE 1. Choroidal perfusion before and after reduced-fluence photodynamic therapy (light dose of 25 J/cm^2) (RFPDT) for polypoidal choroidal vasculopathy. (Top left) Early and (Top right) late indocyanine green angiograms (ICGA) before treatment demonstrate a branching vascular network and polypoidal vascular lesions. (Middle left) Early and (Middle right) late ICGA at 1 week after RFPDT show no significant choriocapillary nonperfusion. (Bottom left) Early and (Bottom right) late ICGA at 3 months after RFPDT do not show any effect on choriocapillaris. Polypoidal vascular lesions are not seen.

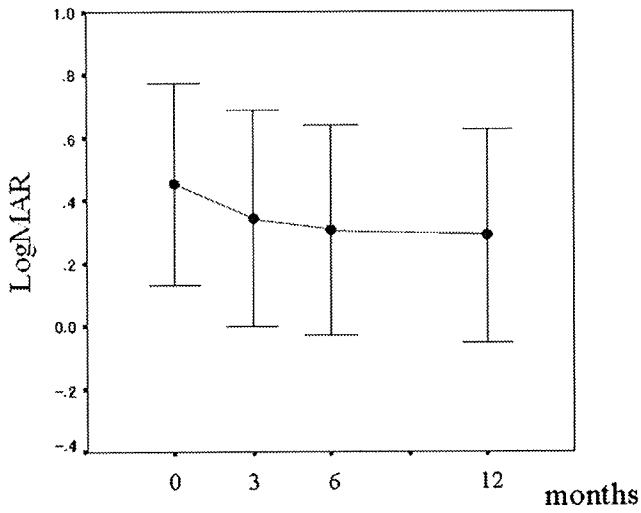


FIGURE 2. Changes in logarithm of the minimal angle of resolution (logMAR) visual acuity of 28 patients received reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. The logMAR (mean ± SD) was 0.45 ± 0.32 at baseline, 0.34 ± 0.34 at month 3, 0.30 ± 0.33 at month 6, and 0.29 ± 0.34 at month 12. Changes in BCVA showed statistically significant differences compared with baseline at 3, 6, and 12 months ($P = .004$, $P = .0003$, and $P = .0001$, respectively). Bars indicate standard error.

• PDT-INDUCED CHOROIDAL PERFUSION CHANGES: Sixteen of 28 eyes (57%) showed mild (not significant) to moderate nonperfusion of choriocapillaris in early ICGA at 1 week, but 27 of 28 eyes (96%) showed recovery to pretreatment levels at 3 months (Figure 1, Table). Only 1 eye showed mild choriocapillary nonperfusion at 3 months.

• VISUAL OUTCOMES: The logMAR BCVA (mean ± standard deviation) was 0.45 ± 0.32 (geometric mean: 7/20) at baseline, 0.34 ± 0.34 (geometric mean: 9/20) at 3 months, 0.30 ± 0.33 (geometric mean: 10/20) at 6 months, and 0.29 ± 0.34 (geometric mean: 10/20) at 12 months. The logMAR BCVA at 12 months was improved by ≥0.2 or maintained as compared to that at baseline in 26 eyes (93%). Changes in BCVA showed significant differences compared with baseline at 3, 6, and 12 months ($P = .004$, $P = .0003$, and $P = .0001$, respectively) (Figure 2).

Furthermore, in all 10 eyes with VA better than 20/40 at baseline, logMAR BCVA (mean ± standard deviation) was significantly improved from 0.17 ± 0.07 (geometric mean: 14/20) at baseline to 0.05 ± 0.18 (geometric mean: 18/20) at 12 months ($P = .038$).

• REPEAT TREATMENT RATE: Mean number of treatment sessions for angiographic leakage activity and exudative changes as identified on OCT during the 12-month study period was 1.3 (range, 1–3). Twenty-one of 28 eyes (75%) underwent a single PDT session during the 12-month study period (Figure 3).

• ADVERSE EVENTS AND COMPLICATIONS: Although 6 of 28 eyes (21%) showed subretinal hemorrhage within 1 disc area within 3 months after PDT, no severe hemorrhage was encountered. All 6 eyes with minimal subretinal hemorrhage displayed complete resolution during the study period, and loss of vision ≥3 lines did not occur. No systemic side effects related to treatment were encountered.

DISCUSSION

PDT WITH VERTEPORFIN FOR PCV RESULTS IN A SIDE EFFECT of subretinal hemorrhage in some eyes, but shows good results.[16,17] Although anti-VEGF monotherapy is currently the standard of care for neovascular AMD, Gomi and associates reported that intravitreal injection of bevacizumab is insufficient for the treatment of PCV.[18]

To date, the only parameters of PDT used for the treatment of CNV in AMD have been those recommended by the TAP guidelines.[1–4] The fact that the TAP regimen regularly leads to damage to the physiological choroid has been demonstrated by ICGA showing early and often persistent nonperfusion of the surrounding choroid,[10,19] by histology showing dose-dependent thrombosis of the choriocapillaris,[20] and by immunostaining demonstrating reactive upregulation of VEGF.[12] However, overtreatment can be prevented by selecting optimal parameters, so pathologic new vessels can be occluded without damaging the physiological choroidal vasculature.[13,14,21] In our study, although mild to moderate choriocapillary nonperfusion of the irradiated area on ICGA at 1 week after treatment was seen in 57% of the studied 28 eyes, choriocapillary perfusion was restored at 3 months in 97%. The damage to the choroid was thus prevented compared to standard-fluence PDT (Figure 4).

Michels and associates[14] reported that ICGA at 3 months after treatment demonstrated at least moderate perfusion changes of the choriocapillaris in 80% of the standard-fluence PDT (light dose, 50 J/cm^2) group, while no choriocapillary perfusion changes of moderate or worse severity were present at 3 months in the reduced-fluence PDT group.

In previous studies of standard-fluence PDT for PCV, Akaza and associates[22] reported improved or maintained VA (logMAR 0.2 or better) in 29 of 35 eyes (83%) at 6 months and 28 of 35 eyes (80%) at 12 months. Mean logMAR VA was 0.67 at baseline, 0.67 at 6 months, and 0.69 at 12 months, with a mean of 2.2 treatment sessions after 1 year of follow-up. Chan and associates[17] reported that the mean logMAR VA was significantly improved at 12 months; during 1 year of follow-up, there was a mean of 1.6 treatment sessions. Kurashige and associates[23] reported maintained or improved VA in 35 of 41 eyes. In our study, during 12 months of follow-up, the rate of improved or maintained VA was 93% and the number of treatment sessions was 1.3.

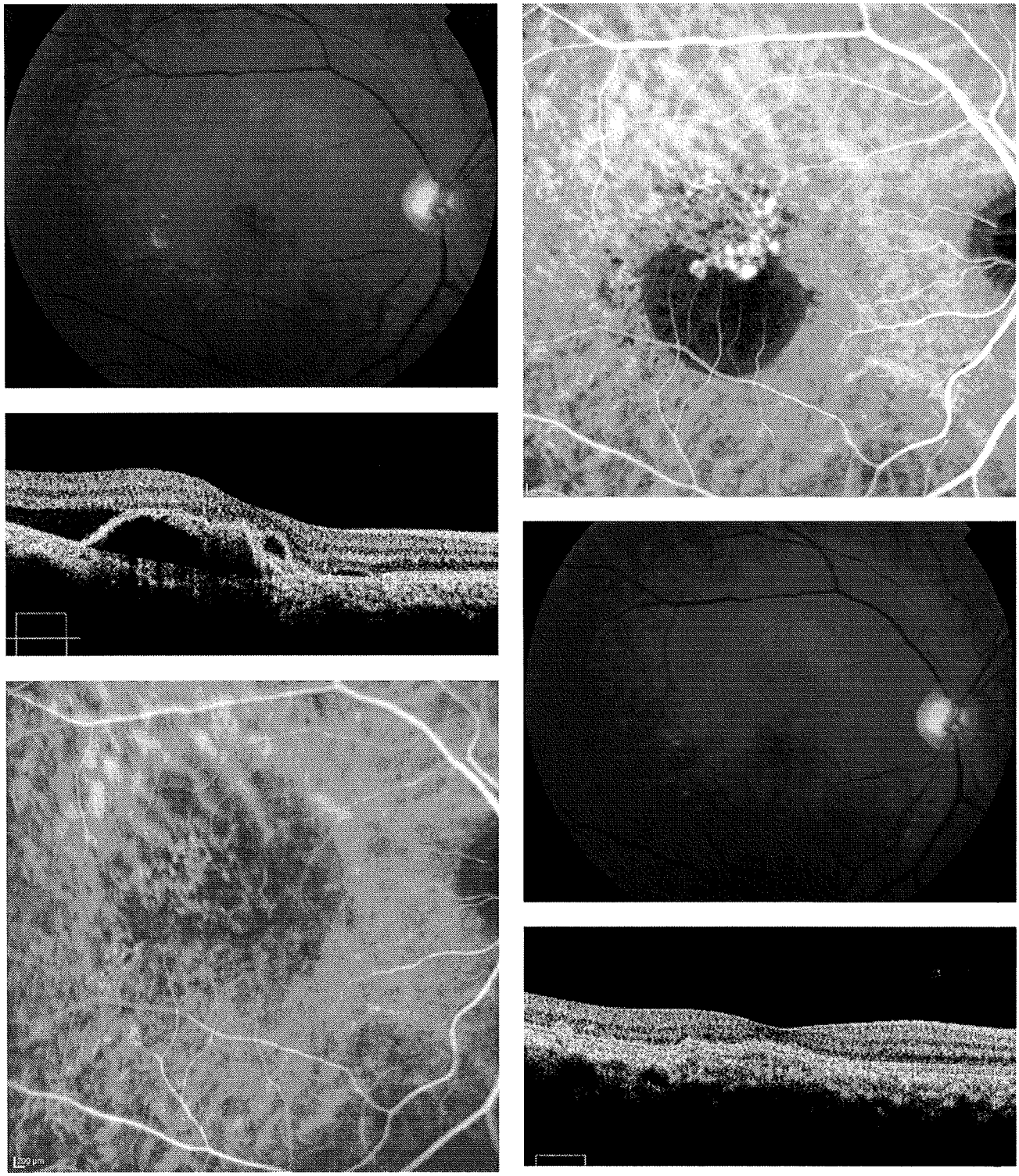


FIGURE 3. Fundus, indocyanine green angiography (ICGA), and optical coherence tomography (OCT) findings before and after reduced-fluence photodynamic therapy (RFPDT) for polypoidal choroidal vasculopathy. A 71-year-old man was successfully treated with single RFPDT. The visual acuity in his right eye improved from 20/100 at baseline to 20/50 at 12 months after single RFPDT. (Top left) Fundus photograph before treatment demonstrates hemorrhage, exudates, and pigment epithelial detachment. (Top right) ICGA before treatment demonstrates an abnormal vascular network and polypoidal vascular lesions at its border. (Middle left) OCT shows subretinal fluid and pigment epithelial detachment. (Middle right) Fundus photograph at 3 months after RFPDT demonstrates no hemorrhagic and/or exudative manifestations. (Bottom left) On ICGA at month 3, although the vascular network remains, terminal polypoidal vascular lesions are totally occluded. (Bottom right) OCT at month 6 does not demonstrate any subretinal fluid or pigment epithelial detachment.

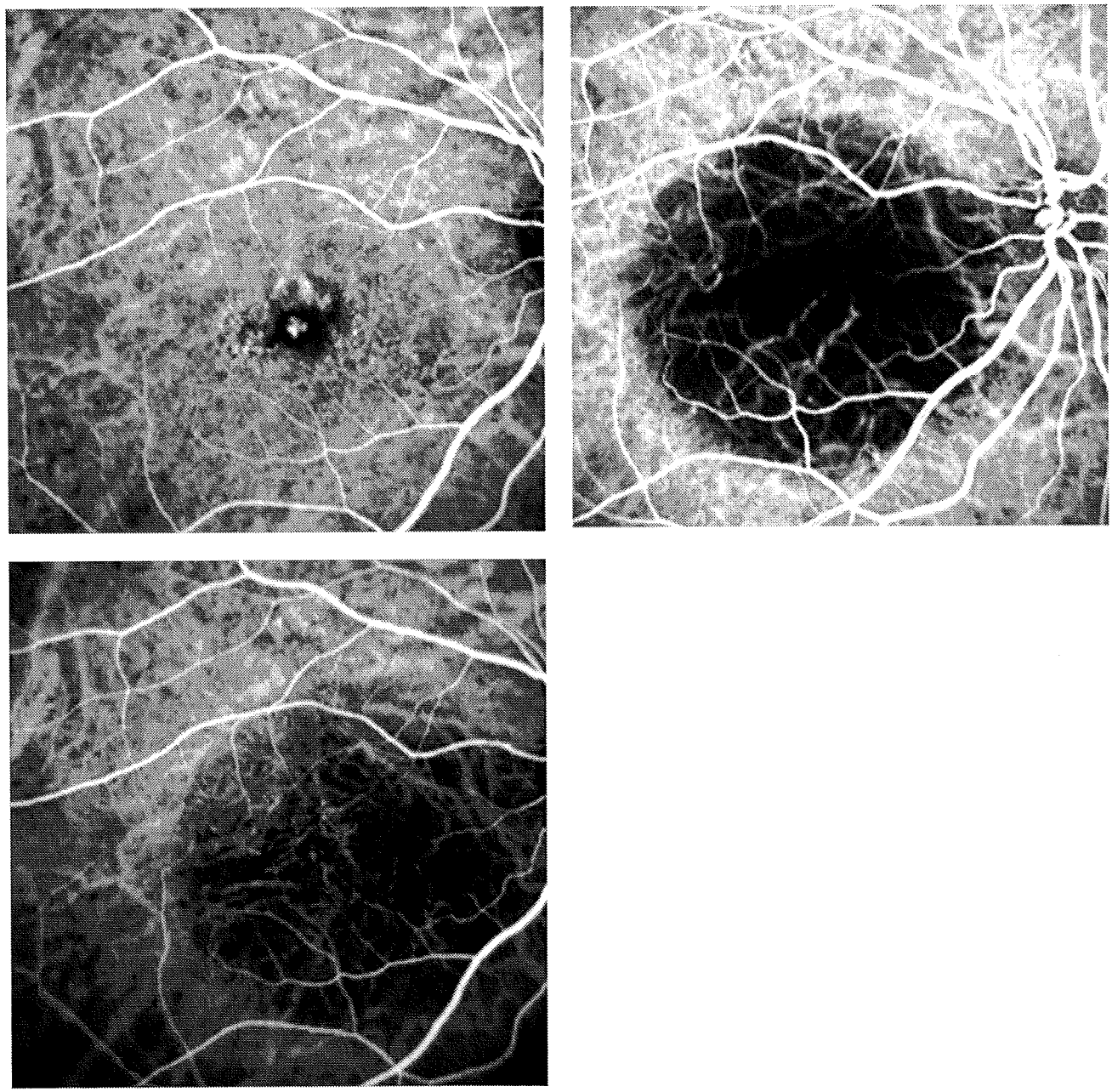


FIGURE 4. Choroidal nonperfusion after standard-fluence photodynamic therapy (SFPDT) for polypoidal choroidal vasculopathy. (Top left) Early indocyanine green angiogram (ICGA) before SFPDT demonstrates a vascular network and a polypoidal vascular lesion. (Top right) Early ICGA at 1 week after SFPDT demonstrates significant nonperfusion of choriocapillaris. (Bottom left) Early ICGA at 3 months after SFPDT demonstrates moderate nonperfusion of choriocapillaris. The polypoidal vascular lesion is not seen.

The guidelines for PDT in Japan mention a decrease in VA after PDT in patients with good VA.[5] In contrast, all 10 eyes with VA better than 20/40 in the present study showed stable or improved vision. In previous studies, mean VA decreased with increased duration of follow-up.[22,23] Further follow-up in our study should clarify whether reduced-fluence PDT is more effective than standard-fluence PDT.

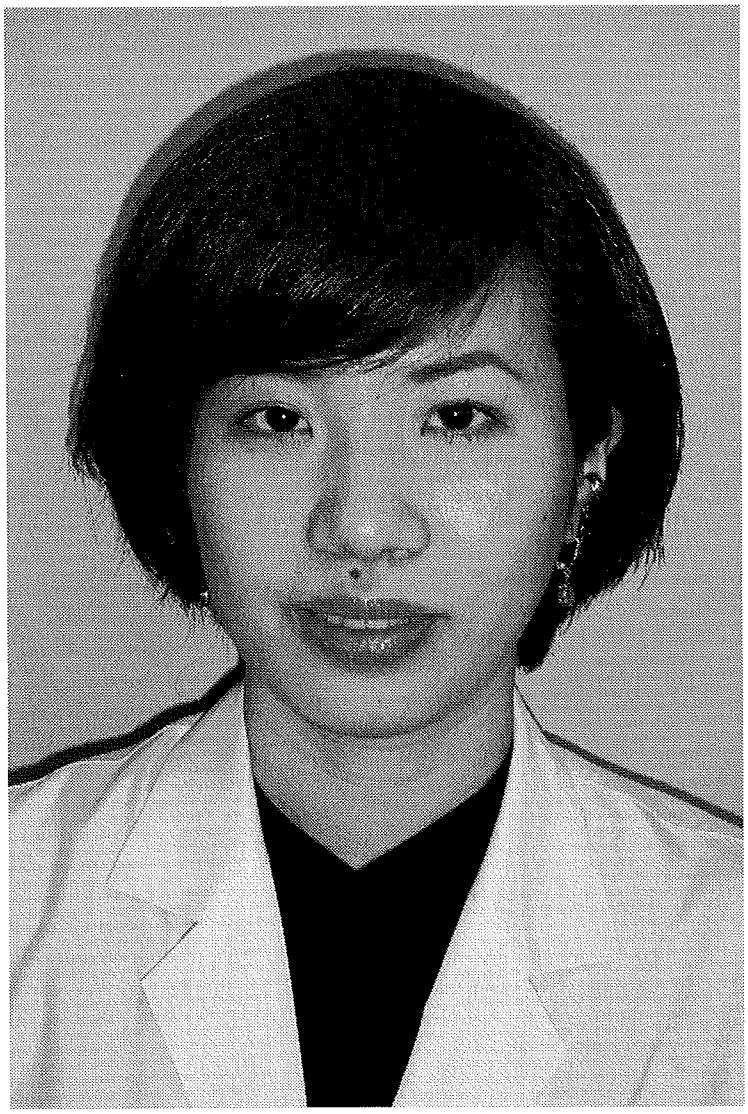
Even with changes in treatment parameters, as reported previously,[13,14,21] no influence on safety was seen. Adverse effects of PDT for the treatment of PCV include extensive subretinal hemorrhage, as reported by Akaza and associates[22] in 3 eyes (9%) and by Chan and associates[17] in 1 eye (4.5%). In addition, Kurashige and associates[23] reported vitreous hemorrhage requiring vitrectomy in 2 eyes (5%). In our study, no severe hemorrhage developed. Six eyes (21%) developed minimal subretinal hemorrhages smaller than 1 disc area within 3 months after treatment, but these hemorrhages spontaneously resolved within 3 months and VA was maintained.

Although the present study has shortcomings, including the small sample size and the lack of control, reduced-fluence PDT is an effective treatment for PCV and could improve vision even in eyes with VA better than 20/40. However, further studies with longer follow-up periods are necessary to assess treatment safety and efficacy.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. THE AUTHORS HAVE NO proprietary interest in any aspect of this study. Involved in design and conduct of study (A.Y., F.S.); data collection (A.Y., C.S., A.O., K.T.); management, analysis, and interpretation the data (A.Y., C.S., F.S.); and preparation, review, and approval of the manuscript (A.Y., F.S.). All procedures conformed to the Declaration of Helsinki and informed consent was obtained from each of the patients participating in the study. The prospective interventional case-control study was approved by the Institutional Review Board of Kagawa University Faculty of Medicine.

REFERENCES

1. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials –TAP report 1. Arch Ophthalmol 1999;117:1329–1345.
2. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials –TAP report 2. Arch Ophthalmol 2001;119:198–207.
3. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study group. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes –TAP report No. 3. Arch Ophthalmol 2002;120: 1443–1454.
4. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study group. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration : three-year results of an open-label extension of 2 randomized clinical trials –TAP report No. 5. Arch Ophthalmol 2002;120:1307–1314.
5. Japanese Age-related Macular Degeneration Trial (JAT) Study Group. One-year results of photodynamic therapy with verteporfin in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Am J Ophthalmol 2003;136:1049–1061.
6. Tano Y. Ophthalmic PDT Study Group: Guidelines for PDT in Japan. Ophthalmology 2008;115:585585.e6.
7. Yannuzzi LA, Wong DW, Sforzolini BS, et al. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 1999;117:1503–1510.
8. Uyama M, Wada M, Nagai Y, et al. Polypoidal choroidal vasculopathy: natural history. Am J Ophthalmol 2002;133: 639–648.
9. Sho K, Takahashi K, Yamada H, et al. Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. Arch Ophthalmol 2003;121:1392–1396.
10. Schmidt-Erfurth U, Michels S, Barbazetto I, Laqua H. Photodynamic effects on choroidal neovascularization and physiological choroid. Invest Ophthalmol Vis Sci 2002;43: 830–841.
11. Schmidt-Erfurth U, Laqua H, Schlötzer-Schrehard U, Viestenz A, Naumann GO. Histopathological changes following photodynamic therapy in human eyes. Arch Ophthalmol 2002;120:835–844.
12. Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 2003; 44:2147–2154.
13. The Visudyne in Minimally Classic CNV (VIM) study group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration. Arch Ophthalmol 2005;123:448–457.
14. Michels S, Hansmann F, Geitzenauer W, Schmidt-Erfurth U. Influence of treatment parameters on selectivity of verteporfin therapy. Invest Ophthalmol Vis Sci 2006;47:371–376.
15. Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography-guided photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol 2007;144:7–14.
16. Gomi F, Ohji M, Sayanagi K, et al. One-year outcomes of photodynamic therapy in age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. Ophthalmology 2008;115:141–146.
17. Chan WM, Lam DS, Lai TY, et al. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. Ophthalmology 2004;111:1576–1584.
18. Gomi F, Sawa M, Sakaguchi H, et al. Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. Br J Ophthalmol 2008;92:70–73.
19. Michels S, Schmidt-Erfurth U. Sequence of early vascular events after photodynamic therapy. Invest Ophthalmol Vis Sci 2003;44:2147–2154.
20. Schlötzer-Schrehardt U, Viestenz A, Naumann GO, Laqua H, Michels S, Schmidt-Erfurth U. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. Graefes Arch Clin Exp Ophthalmol 2002;240:748–757.
21. Sacu S, Varga A, Michels S, et al. Reduced fluence versus standard photodynamic therapy in combination with intravitreal triamcinolone: short-term results of a randomised study. Br J Ophthalmol 2008;92:1347–1351.
22. Akaza E, Yuzawa M, Matsumoto Y, Kashiwakura S, Fujita K, Mori R. Role of photodynamic therapy in polypoidal choroidal vasculopathy. Jpn J Ophthalmol 2007;51:270–277.
23. Kurashige Y, Otani A, Sasahara M, et al. Two-year results of photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol 2008;146:513–519.



Biosketch

Ayana Yamashita, MD, is an assistant professor of the department of Ophthalmology at the Kagawa University Hospital, Kagawa, Japan. She graduated Kagawa Medical School, Japan and received a MD in 1997.

小児に認められた傍中心窩毛細血管拡張症の2例

杉山 千晶 有澤 章子 久保木香織 長央由里子
西川 真生 永井 由巳 髙橋 寛二

関西医科大学附属枚方病院眼科

要約 **目的**：小児に発症した傍中心窩毛細血管拡張症2例の報告。**症例**：6歳と7歳の男児が学校検診で片眼の視力低下を指摘され受診した。**所見**：矯正視力はそれぞれ0.2と0.08であった。両症例とも，傍中心窩に散在する網膜毛細血管瘤，斑胞様黄斑浮腫，輪状の硬性白斑があった。蛍光眼底造影では傍中心窩領域の全域に網膜毛細血管拡張，毛細血管瘤，色素漏出があり，Gass分類の1A群，Yannuzzi分類の血管瘤型の傍中心窩毛細血管拡張症と診断した。レーザー光凝固を行い，斑胞様黄斑浮腫は軽快し，視力はそれぞれ0.4，0.1に改善した。**結論**：小児にも傍中心窩毛細血管拡張症が起こることがある。光凝固の是非については，将来の瘢痕拡大の問題があるので慎重に対応する必要がある。

Juxtafoveolar retinal telangiectasis in two children

Chiaki Sugiyama Akiko Arisawa Kaori Kuboki Yuriko Nagao
Maki Nishikawa Yoshimi Nagai Kanji Takahashi

Dept of Ophthalmol, Kansai Med Univ Hirakata Hosp

Abstract. **Purpose**：To report idiopathic juxtafoveolar retinal telangiectasis in two children. **Cases**：Unilateral impairment of visual acuity was detected in two schoolboys aged 6 and 7 years during routine health check. **Findings**：Corrected visual acuity was 0.2 and 0.08 each. Both cases showed retinal capillary microaneurysm in the perifoveal area, cystoid macular edema (CME), and circinate exudates. Fluorescein angiography showed telangiecatasia and capillary microaneurysms around the fovea with dye leakage. Both cases were diagnosed with juxtafoveolar retinal telangiectasis corresponding to group 1A by Gass or aneurysmal type by Yannuzzi. Laser photocoagulation was followed by remission of CME and improved visual acuity to 0.4 and 0.1 respectively. **Conclusion**：These cases illustrate that idiopathic juxtafoveolar retinal telangiectasis may develop in children. Precaution is necessary regarding photocoagulation because of the possibility of atrophic creep later.

Rinsho Ganka (Jpn J Clin Ophthalmol) 63(7)：1163-1167, 2009

緒言

特発性傍中心窩毛細血管拡張症（idiopathic juxtafoveolar retinal telangiectasis：以下，本症）は，中心窩近傍の網膜毛細血管拡張による黄斑浮腫，視力低下をきたす疾患で，1982年にGassら[1]により報告された。その後，1993年にGassら[2]が検眼鏡的所見，蛍光眼底造影所見および臨床的特徴により3群に分類し，2006年にYannuzziら[3]は同一疾患を特発性黄斑部毛細血管拡張症（idiopathic macular telangiectasia）と呼び，さらに簡略化させた分類を作成した。

本症は中高年に多くみられ，小児に発症することは稀である。今回，筆者らは小児に発症した本症の2例を経験したので報告する。

症例

[症例1]

患者：6歳，男児

主訴：右眼視力低下

発育歴・既往歴・家族歴：特記すべきことはない。

別刷請求先：杉山千晶（すぎやま・ちあき）〒573-1191 枚方市新町2-3-1 関西医科大学附属枚方病院眼科
Reprint requests to：**Chiaki Sugiyama** Department of Ophthalmology, Kansai Medical University Hirakata Hospital. 2-3-1 Shinmachi Hirakata 573-1191, JAPAN

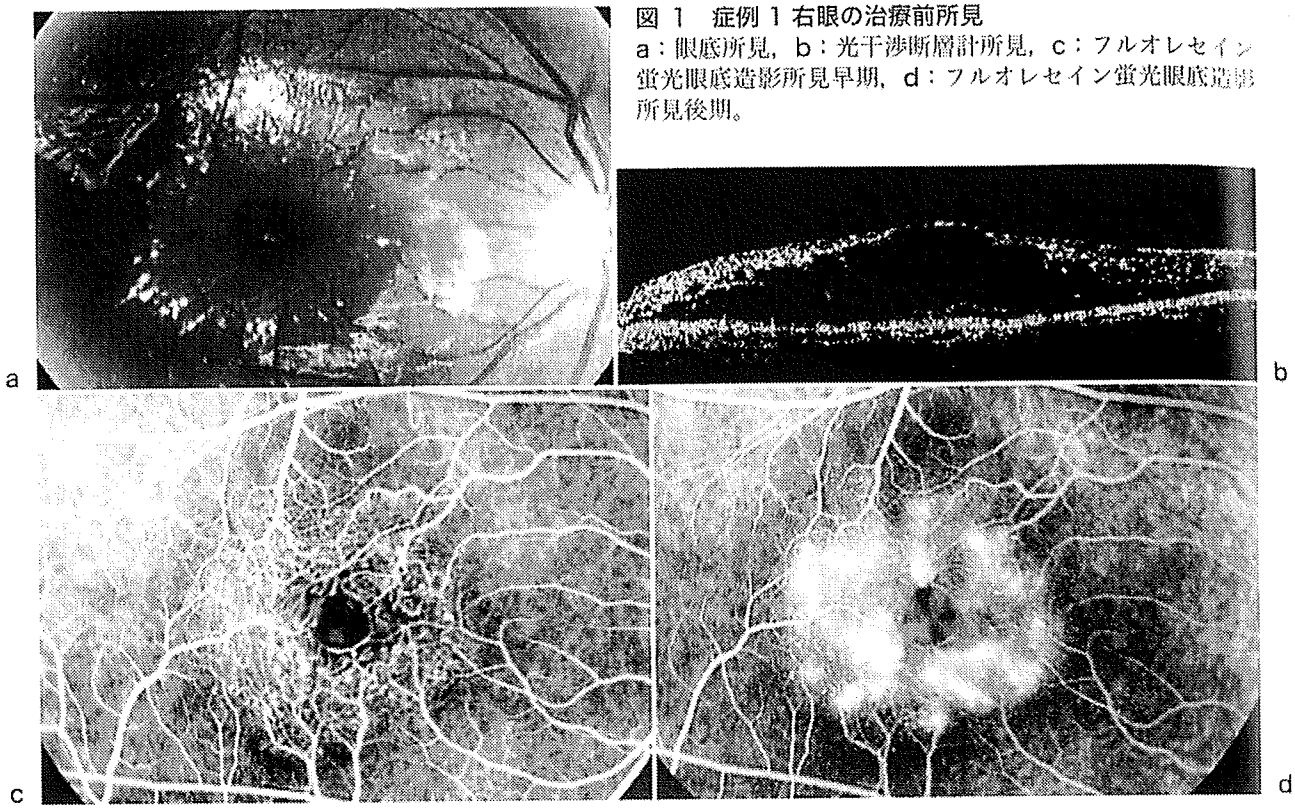


図 1　症例 1 右眼の治療前所見
a：眼底所見，b：光干渉断層計所見，c：フルオレセイン蛍光眼底造影所見早期，d：フルオレセイン蛍光眼底造影所見後期。

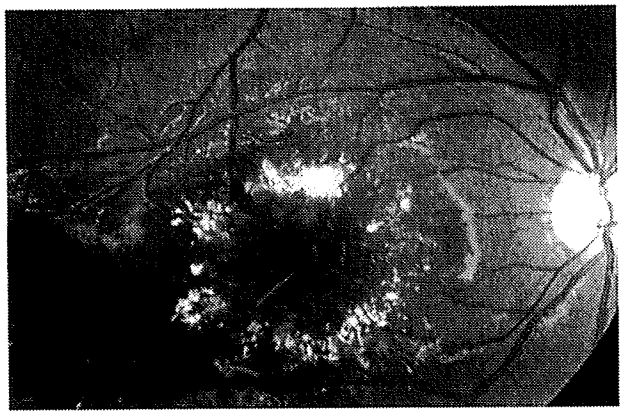


図 2　症例 1 の治療 3 年 2 か月後の眼底所見
嚢胞様黄斑浮腫は軽減し，硬性白斑は沈着範囲が縮小した。

現病歴：2005 年 5 月，学校検診にて右眼の視力低下を指摘され，近医を受診した。精査目的にて同年 5 月 30 日に当科を紹介され受診した。

初診時所見：視力は右 0.15（0.2×＋1.00D⊂cyl−2.00D 165°），左 1.5（矯正不能）で，両眼とも外眼部・前眼部・中間透光体に異常はなく，左眼眼底に特記すべきことはなかった。右眼眼底には，傍中心窩に多数の網膜毛細血管瘤と毛細血管拡張，嚢胞様黄斑浮腫（cystoid macular edema：以下，CME），輪状の配列を示す硬性白斑が認められた（図 1a）。フルオレセイン蛍光眼底造影（fluorescein fundus angiography：以下，FA）の早期では，傍中心窩領域の全周に網膜毛細血管の強い拡張と多数の毛細血管瘤が描出され，後期では同部からの強い血管外漏出がみられ（図 1c，d），本症と診断した。光干渉断層計（optical coherence tomography：以下，OCT）では黄斑部に著明な CME がみられ，中心窩網膜厚は 586 μm と網膜の強い肥厚を認めた（図 1b）。

経過：2 か月後，右眼矯正視力 0.1 と低下し，黄斑浮腫も持続していたため，FA で認められた拡張血管，毛細血管瘤に対してダイレーザー黄色波長で直接レーザー光凝固を施行した。凝固条件は，波長 577 μm，凝固サイズ 200 μm，凝固時間 0.2 秒，凝固出力 120 mW，凝固数 49 発であった。

治療 2 か月後，黄斑部の CME は軽減し，治療 3 か月後の OCT では CME の高さが低くなり，中心窩網膜厚は 462 μm と治療前よりも減少していた。治療 3 年 2 か月後，右眼眼底には軽度の光凝固瘢痕がみられ，硬性白斑は沈着範囲が縮小し，CME は中心窩に限局，周囲の網膜浮腫は軽減していた（図 2）。右眼矯正視力は 0.4 と改善していた。

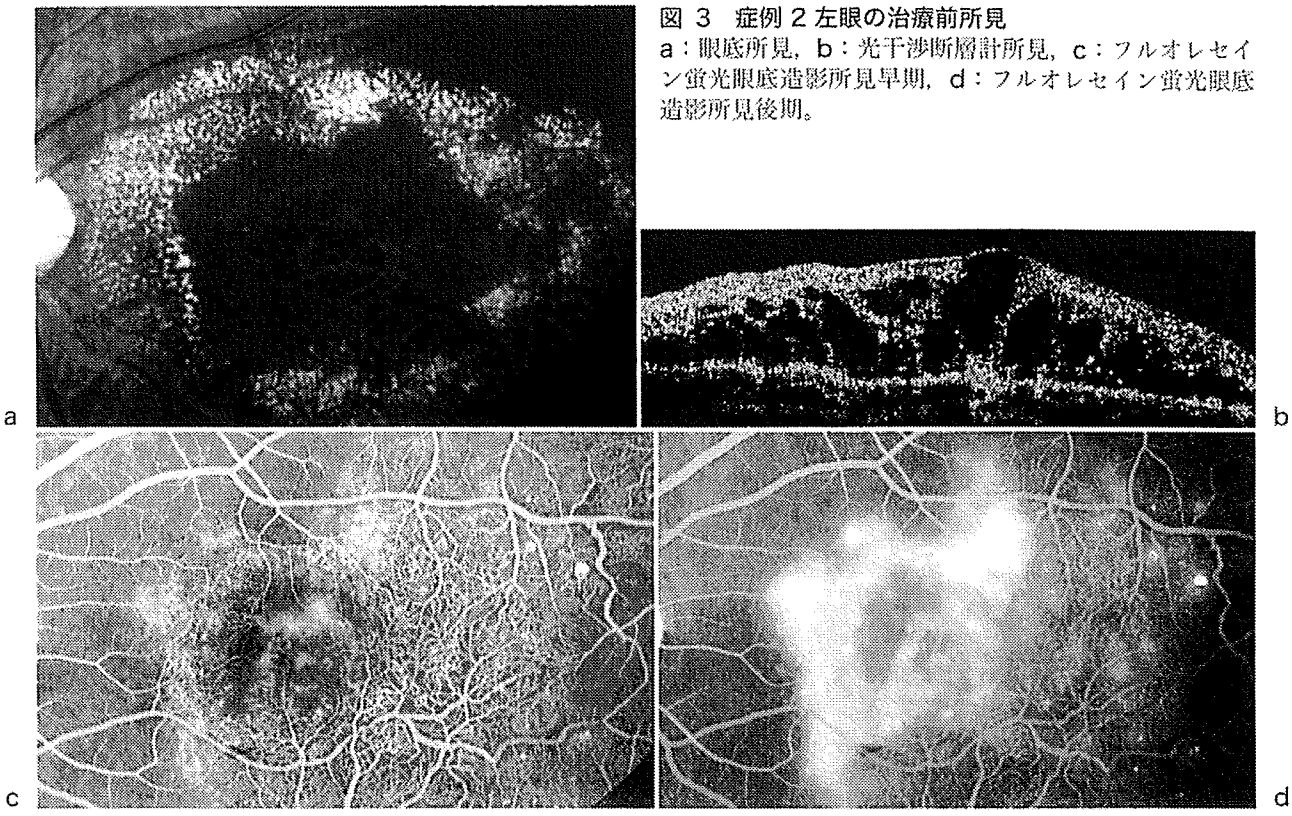


図 3　症例 2 左眼の治療前所見
a：眼底所見，b：光干渉断層計所見，c：フルオレセイン蛍光眼底造影所見早期，d：フルオレセイン蛍光眼底造影所見後期。

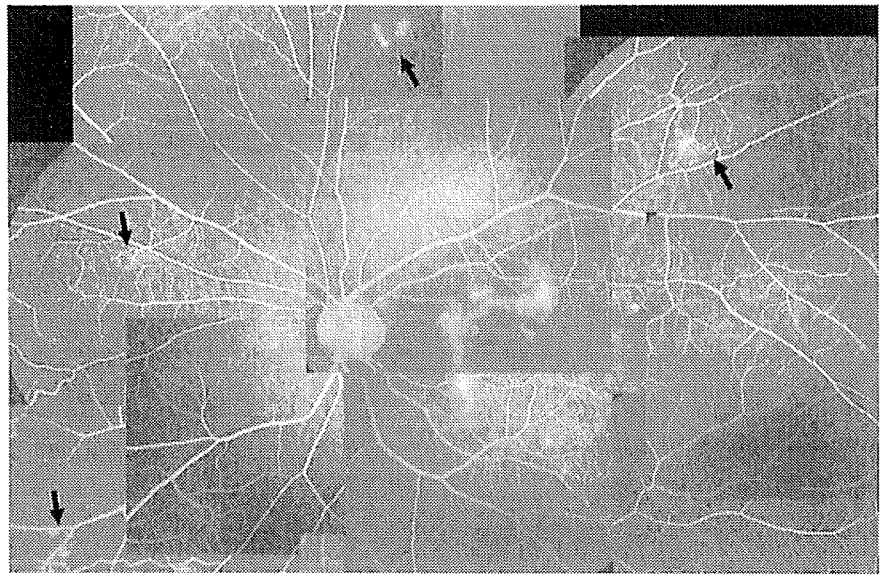


図 4　症例 2 の初診時フルオレセイン蛍光眼底造影パノラマ
中間周辺部にも毛細血管拡張（矢印）を数か所認めた。

［症例 2］
患者：7 歳，男児
主訴：左眼視力低下
既往歴：外耳道ヘルペス（2002 年）
発育歴・家族歴：特記すべきことはない。
現病歴：2007 年秋に学校検診にて左眼視力低下を指摘され，近医を受診した。精査目的で同年 10 月 17 日に当科を紹介され受診した。

初診時所見：視力は右 1.2（1.5× +1.00D⊂cyl −0.75 180°），左 0.07（0.08×S+1.50D⊂cyl −1.00D 180°）で，外眼部・前眼部・中間透光体に異常はなく，右眼眼底に特記すべきことはな

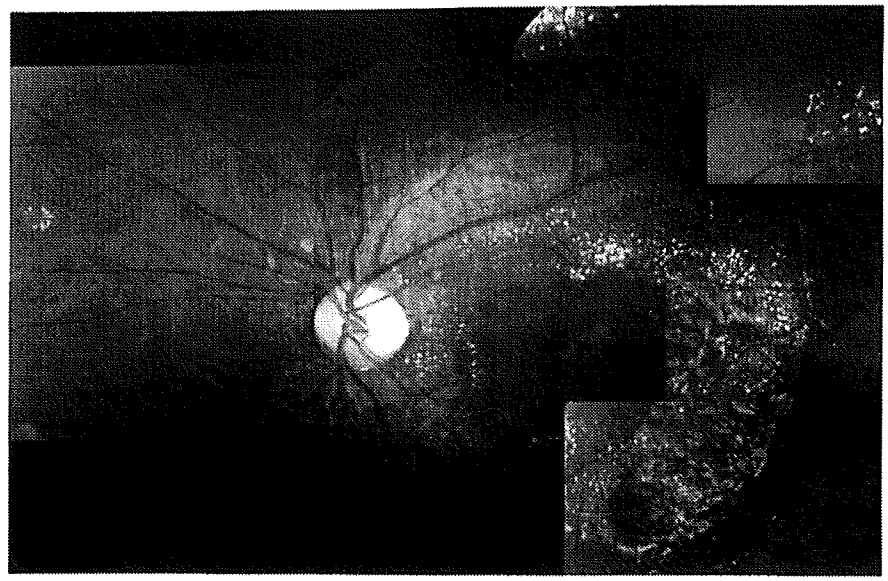


図 5　症例 2 の治療 9 か月後の眼底所見
嚢胞様黄斑浮腫は持続していたが，毛細血管瘤，硬性白斑は減少した。

かった。左眼眼底には，傍中心窩に網膜毛細血管拡張と毛細血管瘤を認め，黄斑部に CME，周囲に輪状硬性白斑が認められた（図 3a）。FA 早期では，傍中心窩領域全周に毛細血管拡張と毛細血管瘤（図 3c），眼底の中間周辺部（眼底上方，耳上側，鼻上側，鼻下側）にも小範囲の毛細血管拡張を 4 か所に認め（図 4），後期では毛細血管拡張部から血管外漏出がみられた（図 3d）。以上の所見から，Coats 病の所見を合併した本症と診断した。OCT では黄斑部に著明な CME がみられた（図 3b）。

経過：小児でありレーザー光凝固が可能かどうかを確認するため，初診 9 日後に，まず眼底上方の毛細血管拡張部にマルチカラーレーザー黄色波長で毛細血管瘤への直接レーザー光凝固を施行した。凝固条件は，波長 568 μm，凝固サイズ 300 μm，凝固時間 0.2 秒，凝固出力 180 mW，凝固数 23 発であった。その後も左眼矯正視力 0.08 と不変で，黄斑部の浮腫が持続しており，固視も良好であったため，レーザー可能と判断し，初診 1 か月半後に傍中心窩の拡張血管，毛細血管瘤への直接レーザー光凝固を施行した。凝固条件は，波長 568 μm，凝固サイズ 200 μm，凝固時間 0.2 秒，凝固出力 100 mW，凝固数 46 発であった。

初診 10 か月後（傍中心窩へのレーザー治療後 9 か月），CME は持続していたが，毛細血管瘤・硬性白斑はレーザー施行前に比べ減少し，視力は 0.1 とやや改善した（図 5）。

考按

本症は中心窩近傍の網膜毛細血管が拡張し，拡張血管からの滲出によって黄斑浮腫，CME，硬性白斑，視力低下をきたす症候群である。

臨床的に本症にはさまざまな病型がみられ，1993 年に Gass ら[2]が，2006 年に Yannuzzi ら[3]が本症の分類を行っている。Gass ら[2]は大きく 3 群に分類し，それぞれをさらに 6 病型に分類した。

1 群は男性に多くみられ，片眼性で，網膜毛細血管瘤，毛細血管拡張が容易に確認され，黄斑浮腫や硬性白斑などの滲出性変化がみられる。このうち拡張血管病巣の範囲により，病巣が中心窩周囲 60° 以上のものを 1A，60° 未満のものを 1B に分類している。

2 群は両眼性で毛細血管拡張が主体で，家族性のないものを 2A，家族性があり若年性に発症するものを 2B に分類している。3 群は両眼性で毛細血管閉塞が主体のもので，中枢神経系の血管異常合併のない例を 3A，合併例を 3B と分類している。

その後，この Gass ら[2]による分類は Yannuzzi ら[3]により簡素化され，1 群は血管瘤型，2 群は血管拡張型，3 群は血管閉塞型と分類された。

筆者らが経験した 2 症例の特徴として，①片眼性，②検眼鏡的に毛細血管瘤が観察可能であったこと，③黄斑浮腫と滲出斑などの滲出性変化を認