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Indocyanine Green Angiographic Findings in Acute Retinal Necrosis

Hisayo Takei, Kyoko Ohno-Matsui,
Masato Hayano and Manabu Mochizuki

Department of Ophthalmology and Visual Science,
Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Purpose: To clarify indocyanine green (IA) angiographic features in patients with acute retinal necrosis (ARN).

Methods: Two patients with ARN were examined by fluorescein angiography (FA) and IA, and findings from both were compared.

Results: Fundus examination revealed widespread retinal hemorrhages and yellowish-white patches in the periphery, characteristic of ARN. In both cases, FA showed diffuse dye leakage from all retinal veins and the optic disc, and vascular obstruction in the peripheral fundus. In IA, dye leakage was localized, and extravasation of dye was evident only from the lower temporal retinal vein and the lower half of the optic disc. This pattern of indocyanine green dye leakage appeared to be continuous from the optic disc toward the lower temporal retinal vein. Also, IA clearly demonstrated choroidal vascular filling delay in one case in the early phase of the angiogram.

Conclusions: While FA showed diffuse dye leakage from all retinal veins, IA identified only the retinal vessels with the most prominent vascular damage. IA also identified choroidal vascular lesions in these patients with ARN. The information obtained by IA might be useful to detect retinal vasculitis with prominent inflammation and to determine the extent of choroidal inflammation in patients with ARN. **Jpn J Ophthalmol 2002;46:330–335**

Key Words: Acute retinal necrosis, fluorescein angiography, indocyanine green angiography.

Introduction

Acute retinal necrosis (ARN) is a potential visually devastating and insidious viral retinitis. ARN was initially reported in 1971 by Urayama and colleagues[1] who described 6 patients with intraocular inflammation, retinal vascular sheathing, large white confluent retinal infiltrates, and subsequent retinal detachment. Although the herpes zoster-varicella virus group is thought to account for most of the typical cases of ARN, herpes simplex type 1 and type 2, and rarely cytomegalovirus have also been implicated as a cause of the disease.[2–4] Studies have indicated that the natural history of classic ARN has a generally poor prognosis in untreated eyes.[5]

Fluorescein fundus angiography (FA) has been reported to be a useful tool in the diagnosis and evaluation of this disorder. In eyes with ARN, retinal vascular occlusion and dye extravasation from retinal vessels have been demonstrated using FA.[5–7] However, prominent inflammatory reaction in the vitreous and anterior chamber may prevent clear observation of retinal vascular disorders. Also, fluorescein dye leakage from retinal vessels is often rapid and diffuse; thus, it might be difficult to determine with

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Correspondence and reprint requests to: Kyoko OHNO-MATSUI, MD, Department of Ophthalmology and Visual Science Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

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FA which vessels are the most severely affected. In addition, histopathological findings have shown that the choroid also contained infiltrating cells in a patient with ARN,[8] and FA is not particularly helpful in delineating the choroidal circulation.

Recent advances in indocyanine green videoangiography (IA) have made better visualization of the choroid possible, because the light in the near infrared spectrum can penetrate the retinal pigment epithelium to a greater degree than is possible in FA.[9,10] Moreover, IA recently has been reported to have advantages over FA in the study not only of choroidal but also of retinal vasculature, as seen in cases of retinal arterial macroaneurysms and branch retinal vein occlusion.[11–13] The large molecular weight and protein-binding properties of indocyanine green (ICG) dye are considered less subject to leaking than fluorescein dye. Therefore, IA might be useful for detecting the sites of the most intense retinal vascular damage.

To our knowledge, no reports have described using IA to examine patients with ARN. To provide additional information on the pathogenesis and activity of this condition, we describe herein the detailed evolution of findings by FA and IA in 2 patients during the course of ARN.

Case Reports

Case 1

A 16-year-old young man was referred to us on May 29, 2000 for evaluation of the uveitis in his right eye. Visual acuity was 20/60 OD and 20/20 OS. "Mutton-fat" keratic precipitates were observed on the corneal endothelium, and cells were noted in the anterior chamber of the right eye. Cells and fibrous condensation were present in the vitreous.

Fundus examination (Figure 1A) showed an edematous optic disc and retina in the macular region. All major retinal veins were slightly dilated. Vascular sheathing was seen along the major retinal veins in the periphery. Ill-defined white patches were confluent over 300° in the peripheral retina, especially in the lower temporal periphery anterior to the equator (Figure 1B). No abnormal findings were noticed in the left fundus. No systemic abnormality was found. FA performed at the initial presentation showed occlusion of retinal veins and arteries in the peripheral fundus (Figure 1C). Non-perfused capillaries were documented anterior to the site of occluded retinal vessels. In the late phase of the FA angiogram (Figure 1D), diffuse dye leakage was evident from almost all the retinal veins and the optic disc in the patient's right eye.

IA was performed on the same day as FA. In the early phase of the IA, no choroidal vascular filling delay was observed. Capillary dilation and hyperfluorescence were seen in the lower half of the optic disc in the early angiographic phase. While FA demonstrated diffuse dye leakage from all major retinal veins, the late phase of IA revealed an intense dye leakage only from the lower temporal retinal vein and the lower half of the optic disc (Figure 1E). This dye leakage appeared to be continuous from the lower half of the optic disc toward the lower temporal retinal vein.

Intravenously administered acyclovir (45 mg/kg per day) and orally administered predonisolone (50 mg per day) were started on May 30. Serum antibody tests for herpes simplex virus and herpes zoster virus were carried out, but the titers were low. Results of a polymerase chain reaction investigation of the infiltrating cells in the anterior chamber identified the genomic DNA of herpes simplex virus type 2. Vitrectomy and scleral buckling procedure were performed on June 1 to prevent any subsequent development of retinal detachment. Two weeks after the surgery, the retinitis appeared less active, and the margin of the optic disc appeared sharp (Figure 1F). Dilation of retinal veins disappeared. The FA performed 2 weeks after vitrectomy showed no dye leakage from the optic disc or retinal vessels. IA performed on the same day as FA revealed no dye leakage from the optic disc or retinal veins (Figure 1G). The patient's visual acuity has remained 20/60 in the right eye after 6 months of follow-up.

Case 2

A 44-year-old man was referred to us on June 1, 2000 for evaluation of the uveitis in his left eye. He had a history of ocular pain and blurred vision of 10-day duration in the eye, and had felt general fatigue for 1 week. On admission, visual acuity was 20/20 OD and 20/60 OS. "Mutton-fat" keratic precipitates were found on the corneal endothelium, and cells were observed in the anterior chamber of his left eye. The intraocular pressure was 15 mm Hg in each eye. Cells and fibrous condensation were present in the vitreous of the left eye.

Fundus examination (Figure 2A) showed an edematous optic disc, intense retinal hemorrhages, and dense yellowish-white intraretinal or subretinal opacities that extended over the entire retina except for the macular region. Vascular sheathing was seen along the major retinal veins in the periphery. Ill-defined white patches were found anterior to the equator,

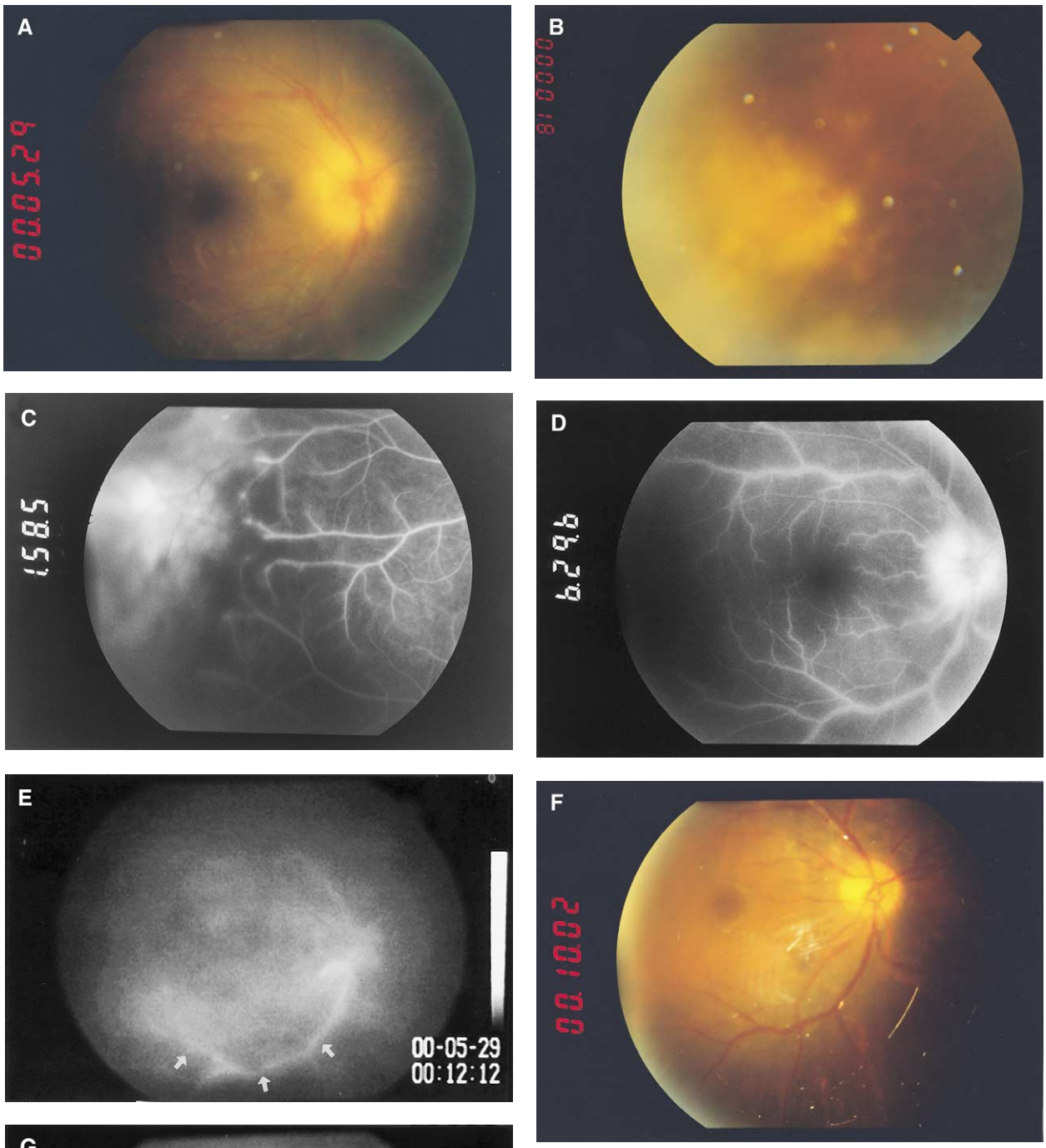

Figure 1. Case 1. (**A**) Fundus photograph at the initial presentation shows an edematous optic disc and posterior retina in the right eye of a 16-year-old young man. All major retinal veins appear slightly dilated. (**B**) In the peripheral fundus, ill-defined white patches are seen. (**C**) Fluorescein angiogram at the initial presentation shows occluded retinal veins and arteries in the peripheral fundus. (**D**) This late-phase fluorescein angiogram reveals diffuse dye leakage from almost all the retinal veins and the optic disc in the right eye. (**E**) This late-phase indocyanine green angiogram reveals intense dye leakage only from the lower temporal retinal vein and the lower half of the optic disc. This dye leakage appears to be continuous from the lower half of the optic disc toward the lower temporal retinal vein (arrow). (**F**) Right fundus photograph taken 2 weeks after vitrectomy shows resolution of retinitis and optic disc edema. (**G**) Indocyanine green angiogram taken 2 weeks after vitrectomy reveals no dye leakage from the optic disc or retinal veins. Visual acuity in the affected right eye remained at 20/60.

and the peripheral retina was yellowish. No abnormal findings were noticed in the fundus of his right eye. FA performed at the initial presentation demonstrated occluded retinal arteries and veins in the peripheral fundus (Figure 2B) and a wide area of nonperfused capillaries anterior to the site of the occluded retinal vessels. Particularly in the lower fundus, retinal veins and arteries were occluded just outside of the posterior fundus, and the lower retina had a wide area of capillary non-perfusion (Figure 2B).

IA was performed on the same day as FA. The early phase of the IA (Figure 2C) demonstrated a decreased number of visible choroidal vessels in the posterior fundus. Many hypofluorescent patches caused by choroidal filling delay were also observed (Figure 2C). While FA showed diffuse dye leakage from major retinal veins throughout the fundus, IA showed dye leakage mainly from the lower temporal retinal vein (Figure 2D). In the lower fundus, intense dye leakage was observed from the occluded end of the retinal vein (Figure 2E).

Intravenously administered acyclovir (45 mg/kg per day) and orally administered predonisolone (60 mg per day) were started from the following day. The titer of serum antibody test for varicella zoster virus was high (160×). Results of a polymerase chain reaction investigation of the infiltrating cells in the anterior chamber identified the genomic DNA of varicella zoster virus. Pars plana vitrectomy and scleral buckling procedure were performed on June 3 in an effort to prevent any subsequent development of retinal detachment. Silicone oil tamponade was also performed. Ten days after the surgery, retinal detachment occurred. The patient underwent another vitrectomy using silicone oil on June 13. Two weeks after the second surgery, the retinitis appeared less active, and the retina remained attached (Figure 2F). His visual acuity had decreased to 6/200 in the left eye 3 months after the surgery.

Discussion

To our knowledge, this is the first report describing IA findings in patients with ARN. IA has recently been reported to be a useful tool in examining retinal vascular lesions as well as choroidal lesions.[11–13] The clinical appearance of the present 2 cases was characteristic of ARN: acute onset of uveitis, retinal vasculitis, massive yellowish exudates in the peripheral retina, and retinal necrosis. FA demonstrated the occlusion of retinal arterioles and capillaries, with leakage of dye from surviving vessels. FA demonstrated diffuse dye leakage from all major retinal veins and the optic disc in the late angiographic phase.

Compared with the diffuse dye leakage pattern from all retinal veins shown by FA, the dye leakage observed by IA was very limited and restricted. ICG dye leakage was evident only from the lower temporal retinal vein and the lower half of the optic disc in the two cases. The ICG dye leakage appeared to be continuous from the optic disc toward the lower temporal retinal vein, which was different from the leakage observed by FA.

The difference in patterns of dye leakage between FA and IA appear to be attributed to the difference in molecular size and affinity to serum protein. Namely, the fluorescein sodium used for FA is smaller in molecular size and less protein-bound than the ICG molecule. Because of this property, fluorescein dye can easily extravasate from all retinal vessels even when there is only mild vascular damage. This theory was supported by the findings of McDonell and co-workers,[14] who showed the difference in dye leakage of fluorescein sodium and ICG from retinal vessels in an animal model with platelet-fibrin embolisms. Because the ICG molecule is large and highly bound to serum proteins, the dye leaks very slowly and only at the site of severe retinal vascular damage. Based on this feature, IA may be able to detect only the sites of the most severely affected retinal vessels.

In both cases described here, ICG dye leakage appeared to be continuous from the optic disc toward the lower temporal retinal vein. This pattern could suggest continuous progression of inflammation through the optic disc toward the retinal vessels. The mechanism by which viruses spread and affect retinal vessels in ARN has remained unclear. However, these IA findings suggest that the retinal vasculitis may have resulted from the contiguous spread of viruses from the optic nerve, as partly shown by Whittum et al[15] in an animal model of ARN. IA taken shortly after the disease onset could provide additional information about the progressive pattern of retinal vasculitis through the optic disc, although it would be difficult because ARN progresses extremely rapidly.

Histopathologic findings have shown the choroidal vasculature to be involved in this disorder.[8] Although one report described choroidal hypofluorescence in the early phase of FA,[16] FA is not a suitable tool to clearly demonstrate choroidal vascular lesions. In our patient (case 2), IA clearly detected the decrease of visible choroidal vessels in the posterior pole, and many patchy choroidal areas of nonperfusion were identified as hypofluorescent patches in the early phase of the angiogram. If IA is performed

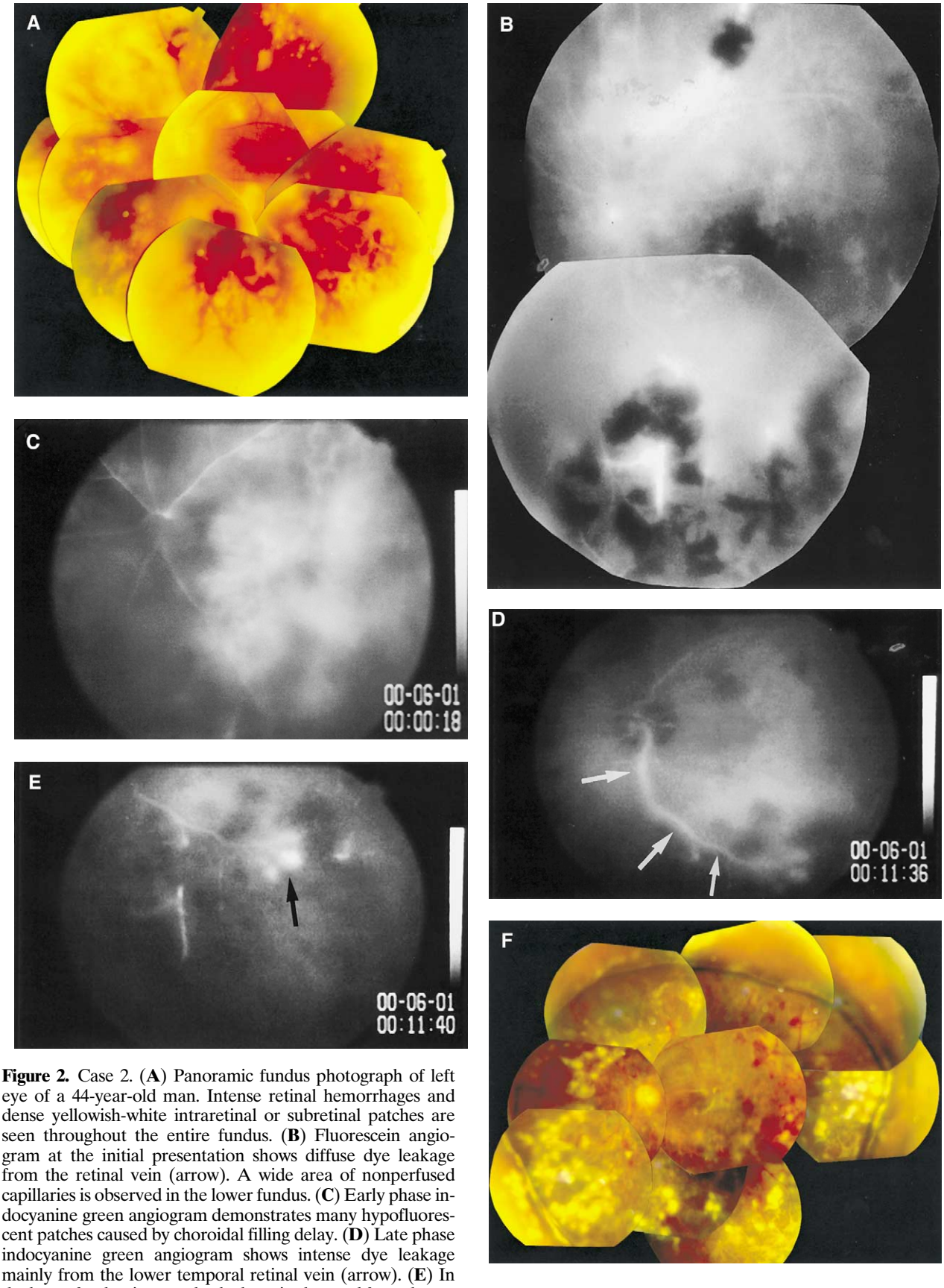

Figure 2. Case 2. (**A**) Panoramic fundus photograph of left eye of a 44-year-old man. Intense retinal hemorrhages and dense yellowish-white intraretinal or subretinal patches are seen throughout the entire fundus. (**B**) Fluorescein angiogram at the initial presentation shows diffuse dye leakage from the retinal vein (arrow). A wide area of nonperfused capillaries is observed in the lower fundus. (**C**) Early phase indocyanine green angiogram demonstrates many hypofluorescent patches caused by choroidal filling delay. (**D**) Late phase indocyanine green angiogram shows intense dye leakage mainly from the lower temporal retinal vein (arrow). (**E**) In the lower fundus, intense dye leakage is observed from the occluded end of the retinal vein (arrow). (**F**) Panoramic fundus photograph taken 2 weeks after the second vitrectomy shows no recurrence of retinitis or atrophy of the entire fundus. The patient's visual acuity decreased to 6/200 in the left eye.

in more patients with ARN, the information might be beneficial in selecting the therapy for ARN in the future.

In summary, performing IA enabled us to identify the retinal vessels that had the most prominent vascular damage and the existence of concomitant choroidal vascular lesions in patients with ARN. The information obtained by IA may prove useful to investigate the pattern of progression and severity of the vasculitis in patients with this syndrome.

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