Case Report

Long-term observation of outer retinopathy-like sequelae in intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage using multimodal imaging

Renpan Zeng [*], Lixia Du, Li Chen

Department of Ophthalmology, Sichuan Provincial Corps Hospital, Chinese People's Armed Police Forces, Leshan, 614000, China

1. Background

Intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage (IHAPSH) is a rare disorder of fundus oculi, which presents most often in young myopic adults with a tilted, crowded disc that may predispose patients to bleeding from the optic disc. Bleeding often extends into the peripapillary subretinal space and vitreous[1] and usually causes sudden blurry vision and floater symptoms. Previous clinical and experimental studies have shown that subretinal hemorrhage can cause photoreceptor cell apoptosis and presents as outer retinopathy-like lesions.[2–4] The damage mechanism is thought to be due to iron toxicity and blockage of the diffusion of nutrient substances vital to the outer retina from the choroidal circulation by subretinal hemorrhage.[5,6] However, interestingly, Patrick Sibony et al. described 10 white women with IHAPSH. Subretinal hemorrhage resolved without sequelae over 3–6 months in all patients.[7] Most recently, Ming Zou et al. reported thirty-eight eyes of 37 consecutive IHAPSH patients, and all patients were followed for 2 years. After a mean follow-up of 2.85 months, the hemorrhage resolved spontaneously without sequelae.[8] The two studies indicated that IHAPSH was a benign syndrome, and the photoreceptor cells were not affected by subretinal hemorrhage secondary to IHAPSH. Here, we present a young male who suffered from IHAPSH with sequelae of outer retinopathy-like lesions in long-term observation using multimodal imaging. To our knowledge, this is the first IHAPSH case that presents sequelae of outer retinopathy-like lesions, and we demonstrated the long-term evolution of sequelae using multimodal imaging.

2. Case presentation

A 35-year-old male of Asian ethnicity (Han Chinese) presented with decreased vision and sensation of floaters in his left eye for four days. He had no ocular trauma and no past ocular history except myopia. On initial examination, he denied scotoma and photopsia, best-corrected visual acuity (BCVA) was 20/20 in the right eye and 20/40 in the left eye, manifest refraction was - 3.50 dioptres in both eyes, and intraocular pressure was 11 mmHg (right) and 10 mmHg (left). The pupils were sensitively reactive to light without relative afferent pupillary defects. The anterior segment examination was normal, and there were no inflammatory cells in the anterior chamber or vitreous in either eye. Fundus examination of the right eye was unremarkable except for a tilted, crowded optic disc (see Appendices A). In the left eye, fundus examinations showed an elevated optic disc with intrapapillary, adjacent peripapillary hemorrhage and vitreous hemorrhage (Fig. 1A, B, C). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) demonstrated blocked hypofluorescence due to hemorrhage without definite leakage throughout the overall angiogram. Localized staining of the disc where it was not covered by bleeding was shown on FA (Fig. 1D, E, F). Spectral-domain optical coherence tomography (SD-OCT) revealed that the optic disc and its surroundings were elevated prominently on the nasal and superior sides. Focal detachment of neurosensory retina with subretinal hemorrhage was located on the nasal side of the optic disc. Hyperreflectivity of hemorrhage was seen in the optic nerve head, subretinal space, vitreous and surface of the optic papilla (Fig. 1G and H). Flicker electroretinogram (FERG) and pattern visual evoked potentials were normal in both eyes. B-scan ultrasonography showed vitreous haze and raised optic discs without space-occupying lesions such as tumors or optic disc drusen in the left eye.

His medical history, family history and systemic investigations were unremarkable. Blood tests for inflammatory and immunologic factors within normal limits were screened. The tuberculosis-infected T cell spot test was negative, and chest X-ray was normal. Serological tests for antibodies against hepatitis C virus, Treponema pallidum, human immunodeficiency virus, herpes simplex virus, cytomegalovirus and varicella zoster virus were negative. Computed tomography of the brain was unremarkable.

* Corresponding author. Department of Ophthalmology, Sichuan Provincial Corps Hospital, Chinese People's Armed Police Forces, 548 East Baiyang Road, Leshan, 614000, China.

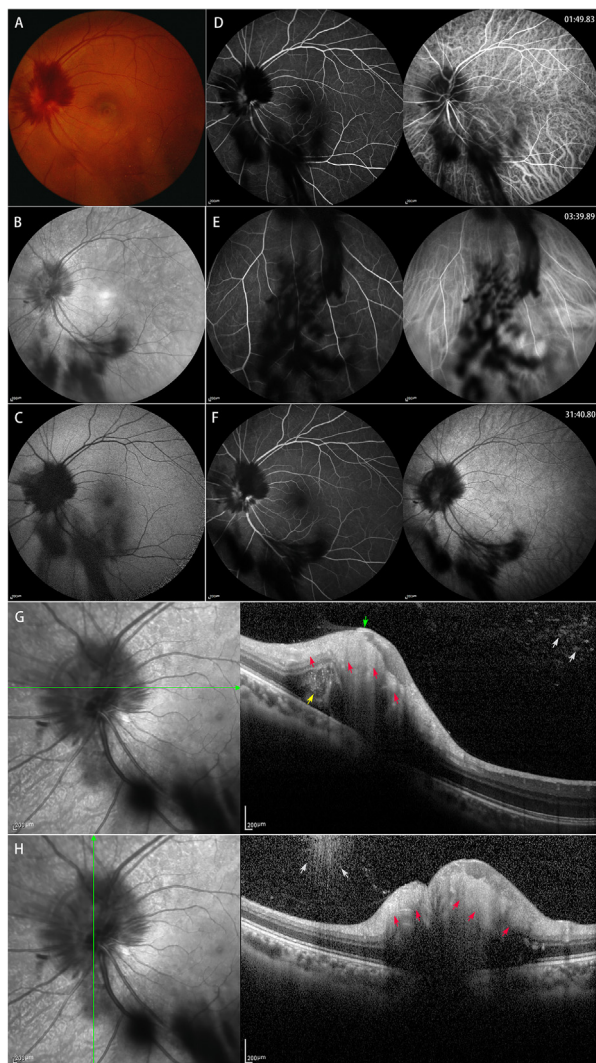*E-mail address:* kindman198247@163.com (R. Zeng).

Fig. 1. Multimodal imaging of the left eye at the initial presentation. (**A**) Fundus photograph, (**B**) infrared radiation imaging, and (**C**) fundus autofluorescence showed intrapapillary hemorrhage with adjacent peripapillary hemorrhage and vitreous hemorrhage. (**D** and **E**) Early phase of fluorescein angiography and indocyanine green angiography. (**F**) Late phase of fluorescein angiography and indocyanine green angiography demonstrated blocked hypofluorescence due to hemorrhage without definite leakage from retinal and choroidal vessels. Localized staining was seen at the disc where it was not covered by bleeding. (**G** and **H**) Spectral-domain optical coherence tomography revealed that the optic disc and its surroundings were elevated prominently with hyperreflectivity of hemorrhage in the optic nerve head (red arrow), subretinal space (yellow arrow), vitreous (white arrow) and surface of the optic papilla (green arrow).

IHAPSH was diagnosed by typical fundus manifestations, history and auxiliary examinations that excluded other diseases, such as optic neuritis, anterior ischemic optic neuropathy, Terson syndrome, optic disc phlebitis, intracranial hypertension and optic disc drusen. The patient was treated orally with a drug (compound Xueshuantong capsule) to improve microcirculation. After three weeks, the vitreous hemorrhage had completely resolved, and the BCVA had improved to 20/20 in his left eye; however, the intrapapillary hemorrhage and adjacent peripapillary hemorrhage had partially resolved (Fig. 2A). After 2 months, the hemorrhage had almost resolved, and a distinct yellowish arcuate line located on the nasal and superonasal sides of the optic disc became visible (Fig. 2B). Fundus autofluorescence (FAF) demonstrated an annular band and scattered spots of hypoautofluorescence surrounding the optic disc (Fig. 2C). The elevated optic disc and nasal peripapillary focal

detachment of the neurosensory retina had regressed, and a tilted, crowded optic disc was shown on SD-OCT (Fig. 2E). Meanwhile, irregularity of the external limiting membrane (ELM) and ellipsoid zone (EZ) with hyperreflectivity of linear vertical deposits were seen within the peripapillary lesion corresponding to the hypoautofluorescence area in FAF (Fig. 2D, E, F). The visual field illustrated a mildly enlarged physiological scotoma (see Appendices B).

As the bleeding had been absorbed, the compound Xueshuantong capsule was replaced by a neurotrophic drug (citoline sodium tablets), which may be beneficial for photoreceptor cells. Then, the patient was followed up irregularly at 5 months, 10 months and 27 months after initial presentation. During the whole follow-up period, there was no recurrent hemorrhage, and the patient's BCVA remained 20/20 in both eyes. The yellowish arcuate line located on the nasal and superonasal sides of the optic disc faded with time (Fig. 3A, B, C). The hyperautofluorescence of the arcuate line and hypoautofluorescence of scattered small spots in FAF also faded with time, while the hypoautofluorescence of the annular band surrounding the optic disc was the same as that initially observed (Fig. 3D, E, F). On SD-OCT, the hyperreflectivity of linear vertical deposits in the outer retina resolved over time, and the structures of the ELM and EZ were reconstructed gradually over time but had not completely resolved at the last follow-up (Fig. 3G, H, I, J, K, L). The patient's visual field (see Appendices B) and FERG testing were normal in both eyes at the last follow-up.

3. Discussion

The exact pathogenetic mechanism of IHAPSH remains unclear. The main risk factors for IHAPSH related to the anatomical characteristics of the optic disc include myopic eye, tilted, crowded disc, narrowed sclera tube, etc.[1] The unique architecture of the elevated nasal and superior margins of a tilted myopic disc results in the dragging of the choroidal and retinal tissues over the elevated edge.[9] The choroidal capillary supply of the prelaminar optic nerve in such a dragging area may predispose patients to bleeding, which may be spontaneous or precipitated by an acute event, such as the Valsalva maneuver or acute disc edema. Another proposed mechanism of IHAPSH is vitreopapillary traction, which acts on a morphologically vulnerable crowded and tilted optic disc predisposed to hemorrhage.[1] Katz and Hoyt[10] theorized partial posterior vitreous detachment based on a glial tag on the optic disc and reported findings of partial attachment of the vitreous to the optic disc by B-scan ultrasonography. In our case, the vitreopapillary relationship was assessed carefully using SD-OCT. It is well known that SD-OCT is very useful in delineating subtle vitreomacular traction and vitreopapillary traction, which cannot be well visualized on biomicroscopic examination and ultrasonography. However, vitreopapillary traction was not observed at the time of acute bleeding in our case (Fig. 1G and H) and was not reported by Kokame.[9,11] There may be other acute events to induce bleeding, such as acute disc edema or Valsalva maneuvers. Specific to our case, he had moderate myopia with a tilted, crowded disc, and disc hemorrhage extending into the peripapillary subretinal space and vitreous. Valsalva maneuvers were denied, and typical signs of optic disc edema, such as dilated telangiectatic vessels of the optic disc and diffuse late leakage into the optic disc, were not observed by FA. Thus, we believed that our case was most likely spontaneous hemorrhage based on a tilted, crowded disc, and the elevated optic disc was secondary to acute intrapapillary hemorrhage at the initial presentation. Differential diagnoses of IHAPSH include optic nerve head drusen, optic disc vasculitis, optic neuritis, ischemic optic neuropathy, peripapillary subretinal neovascularization and Terson's syndrome, which can also cause peripapillary subretinal hemorrhage. However, in our case, multimodal imaging, including OCT, FAF and B-scan ultrasonography, did not reveal any presence of optic disc drusen. No subretinal neovascularization was demonstrated on FA and ICGA throughout the overall angiogram. FA, visual field and electrophysiological examinations did not reveal any presence of optic disc vasculitis, optic neuritis or ischemic optic
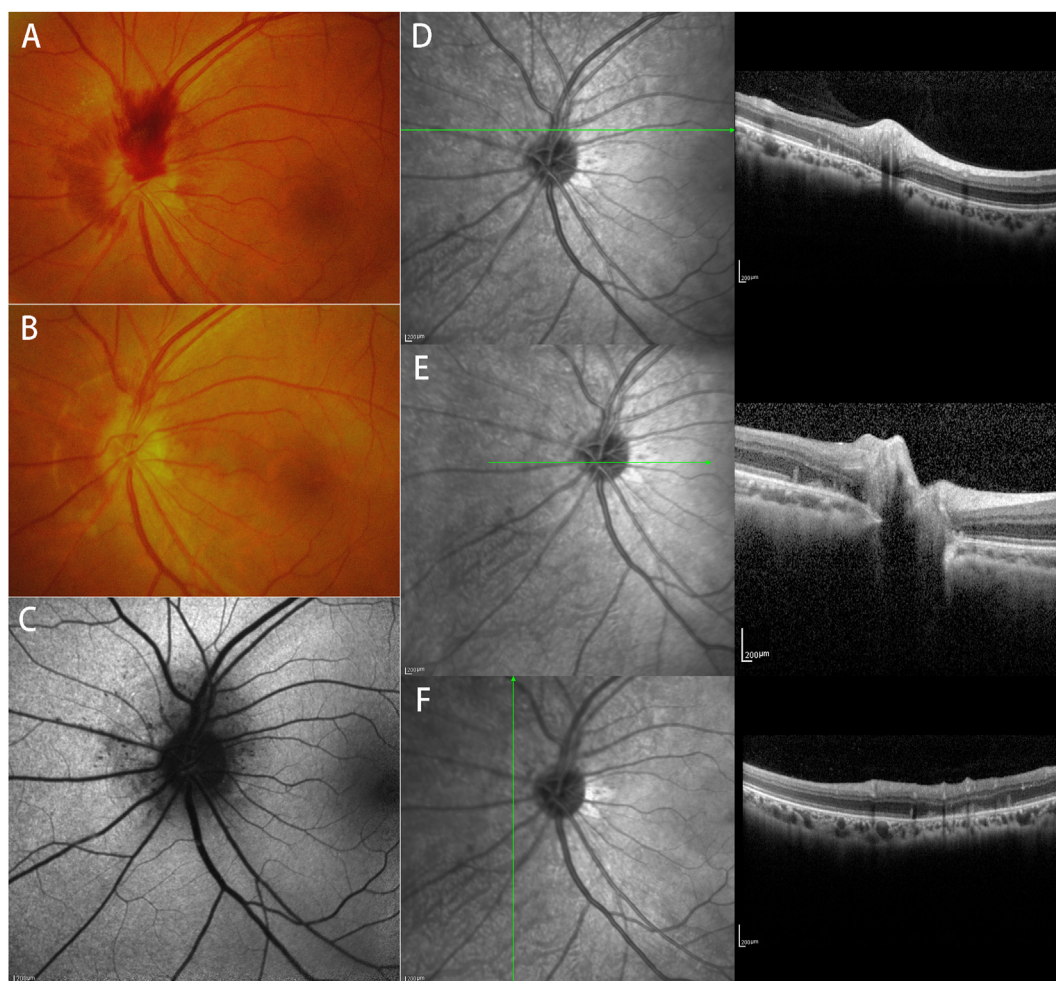
Fig. 2. Follow-up of the left eye at 3 weeks and 2 months. (**A**) Fundus photograph at 3 weeks showed that the intrapapillary hemorrhage and adjacent peripapillary hemorrhage had partially resolved, leaving a few retinal exudates on the superonasal side of the optic disc. (**B**) Fundus photograph at 2 months showed that the hemorrhage and exudates had almost resolved, and a distinct yellowish arcuate line was located on the nasal and superonasal sides of the optic disc. (**C**) Fundus autofluorescence at 2 months showed an annular band and scattered spots of hypoautofluorescence surrounding the optic disc. (**D to F**) Spectral-domain optical coherence tomography at 2 months revealed a tilted, crowded optic disc without an obvious optic cup. Meanwhile, irregularities of the external limiting membrane and ellipsoid zone with hyperreflectivity of linear vertical deposits were observed within the peripapillary annular area. Inner retinal layers were unremarkable.

neuropathy. There was no history of ocular trauma, and computed tomography of the brain was normal, so Terson's syndrome was not considered. The outer retinopathy-like lesion presented in our IHAPSH case after absorption of subretinal hemorrhage shares some common features with acute zonal occult outer retinopathy (AZOOR). These conditions are distinguished by symptoms and signs. AZOOR often has a photopsia and typically presents initially with minimal fundus changes, and electroretinogram examination is usually abnormal. Our case had no photopsia. The shape, size and location of the outer retinopathy-like lesion were consistent with previous peripapillary subretinal hemorrhage, and electroretinogram examination was normal.

Kokame et al.[9] reported that IHAPSH has a benign clinical course with an excellent visual prognosis. Hemorrhage spontaneously resolved within 1–7 months (mean, 2 months) without treatment.[9] In our case, the visual acuity completely recovered at 3 weeks, and the hemorrhage resolved at 2 months after initial presentation. This is consistent with Kokame's report.[9] Moreover, previous studies have shown that subretinal hemorrhage resolves spontaneously without sequelae in IHAPSH patients.[7,8] The amount of subretinal hemorrhage caused by IHAPSH is usually small and absorbed quickly. Therefore, photoreceptor cells are usually unaffected in IHAPSH patients. However, our case showed that subretinal hemorrhage secondary to IHAPSH could damage photoreceptor cells, resulting in the formation of outer retinopathy-like lesions. To our knowledge, this is the first

IHAPSH case that presents outer retinopathy-like lesions after the resolution of subretinal hemorrhage in the literature. Clinical and experimental studies have shown that subretinal hemorrhage induces photoreceptor cell apoptosis[12–14] depending on the amount and duration of bleeding.[15] Akitaka Tsujikawa et al.[16] described retinal structural changes associated with foveal subretinal hemorrhage in retinal arterial macroaneurysm patients using OCT examination. Although the retinal structure was relatively preserved at the initial visit, the foveal photoreceptor layer was substantially damaged at the subsequent visit, showing outer retinopathy-like lesions after the resolution of subretinal hemorrhage and resulting in a poor visual outcome. Yuki Muraoka et al.[17] reported similar findings in branch retinal vein occlusion with foveal subretinal hemorrhage. The damage mechanism is thought to be due to a number of effects of the hemorrhage and presents as outer retinopathy-like lesions. The main mechanisms include iron toxicity to photoreceptor cells[14] and blockage of the diffusion of oxygen, glucose, and other metabolic substances from the choroidal circulation to the outer retina.[6] Other mechanisms include mechanical shearing forces exerted on photoreceptor cells with contraction of the clot,[6] inflammation and fibrotic traction.[14] Although subretinal hemorrhage usually does not cause early acute impairment of the outer retina, it seems to cause chronic damage to the overlying photoreceptor layer, which results in sequelae of outer retinopathy-like lesions.
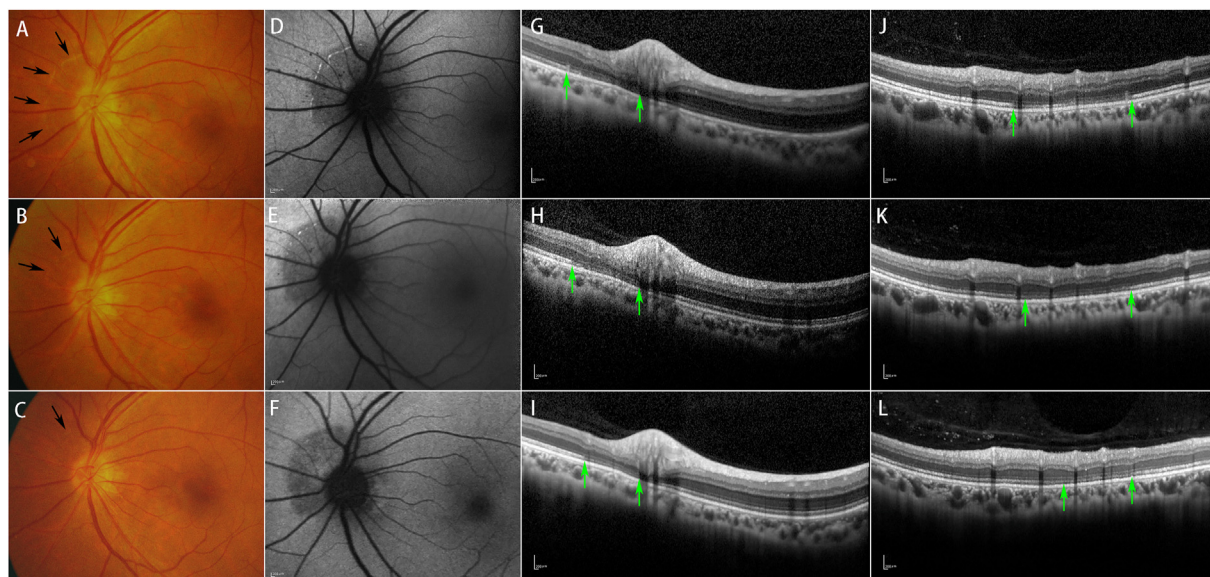
Fig. 3. Follow-up of the left eye at 5 months, 10 months, and 27 months. (**A** to **C**) Fundus photograph at 5 months (**A**), 10 months (**B**), and 27 months (**C**) showed that the yellowish arcuate line (black arrow) faded with time. (**D** to **F**) Fundus autofluorescence at 5 months (**D**), 10 months (**E**), and 27 months (**F**) showed that the hyperautofluorescence of the arcuate line and hypoautofluorescence of scattered small spots also faded with time, while the hypoautofluorescence of the annular band surrounding the optic disc was the same as that initially observed. (**G** to **L**) Spectral-domain optical coherence tomography at 5 months (**G**, **J**), 10 months (**H**, **K**), and 27 months (**I**, **L**) revealed that the hyperreflectivity of linear vertically deposited foci in the outer retina resolved with time, and the structure of the external limiting membrane and ellipsoid zone reconstructed gradually with time in the affected area (green arrows). The scanning lines of images G, H, and I were exactly the same as the scanning position of image D in Fig. 2. The scanning lines of images J, K, and L were exactly the same as the scanning position of image F in Fig. 2.

In our case, the yellowish-white retinal arcuate line with papillocentric configuration represents the interface separating the affected and unaffected retina in SD-OCT imaging, and the origin of the linear vertically hyperreflective deposits noted in the outer retina is unclear but likely represents the residual hemorrhage. The outer retinopathy-like lesion illustrated hypoautofluorescence in FAF without RPE and choroidal atrophy in SD-OCT, and no pigmentary changes were noted in 27 months of follow-up, unlike AZOOR, which showed varying degrees of hyperautofluorescence in FAF[1,4] and can affect both retinal photoreceptors and RPE,[11] leading to retinal pigment epithelium (RPE) changes including pigmentary migration, proliferation or atrophy accompanied by the resolution of the lesion in long-term follow-up.[4] The pattern of FAF in our case is consistent with that reported by S. Amal Hussnain in neovascular age-related macular degeneration patients, which show areas of hypoautofluorescence in the absence of RPE atrophy during and after subretinal hemorrhage resolution.[18] A potential mechanism for the development of this FAF pattern is proposed. Iron toxicity is implicated in the direct injury effect to the RPE that is not detectable upon OCT but can impair its ability to process bisretinoids and lead to hypoautofluorescence, which is distinct from that attributable to geographic atrophy and complete RPE loss and outer retinal atrophy.[18]

We demonstrated long-term evolution of the outer retinopathy-like lesion in our case using multimodal imaging. During the 27-month follow-up period, there was no recurrent hemorrhage. A fundus photograph showed that the yellowish arcuate line faded with time. FAF showed hyperautofluorescence of the arcuate line and hypoautofluorescence of scattered small spots that also faded with time, while the hypoautofluorescence of the annular band surrounding the optic disc was the same as that initially observed. SD-OCT revealed that the hyperreflectivity of linear vertically deposited foci in the outer retina resolved with time, and the structure of the ELM and EZ reconstructed gradually with time in the outer retinopathy-like lesion. Further investigation with OCT angiography, a noninvasive vascular imaging modality, may provide more information about the microvascular abnormality of IHAPSH.

4. Conclusions

In summary, we first reported outer retinopathy-like sequelae in an IHAPSH patient using multimodal imaging. Long-term observation of the case demonstrated that the outer retinopathy-like sequelae gradually improved. Our case also confirmed that IHAPSH was a benign disorder with a good prognosis.

punctuation, and phrasing by Elsevier Language Editing Services.

Funding

This work was supported by the key science and technology plan project of Leshan [grant number 20SZD125].

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

IHAPSH	Intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage
BCVA	Best-corrected visual acuity
FA	Fluorescein angiography
ICGA	Indocyanine green angiography
SD-OCT	Spectral-domain optical coherence tomography
FERG	Flicker electroretinogram
FAF	Fundus autofluorescence
ELM	External limiting membrane
EZ	Ellipsoid zone
RPE	Retinal pigment epithelium
AZOOR	Acute zonal occult outer retinopathy

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2021.100009.

References

1. Teng Y, Yu X, Xu B, et al. Evaluation of crowded optic nerve head and small scleral canal in intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(2):241–248. https://doi.org/10.1007/s00417-013-2459-4.
2. Dunaief JL, Dentchev T, Ying G-S, et al. The role of apoptosis in age-related macular degeneration. *Arch Ophthalmol*. 2002;120(11):1435–1442. https://doi.org/10.1001/archopht.120.11.1435.
3. Bhisitkul RB, Winn BJ, Lee O-T, et al. Neuroprotective effect of intravitreal triamcinolone acetonide against photoreceptor apoptosis in a rabbit model of subretinal hemorrhage. *Investig Ophthalmol Vis Sci*. 2008;49(9):4071–4077. https://doi.org/10.1167/iovs.08-1892.
4. Notomi S, Hisatomi T, Murakami Y, et al. Dynamic increase in extracellular ATP accelerates photoreceptor cell apoptosis via ligation of P2RX7 in subretinal hemorrhage. *PLoS One*. 2013;8(1), e53338. https://doi.org/10.1371/journal.pone.0053338.
5. Glatt H, Robert Machemer MD. Experimental subretinal hemorrhage in rabbits. *Am J Ophthalmol*. 1982;94(6):762–773. https://doi.org/10.1016/0002-9394(82)90301-4.
6. Toth CA, Morse LS, Hjelmeland LM, et al. Fibrin directs early retinal damage after experimental subretinal hemorrhage. *Arch Ophthalmol*. 1991;109(5):723–729. https://doi.org/10.1001/archopht.1991.01080050139046.
7. Sibony P, Fourman S, Honkanen R, et al. Asymptomatic peripapillary subretinal hemorrhage: a study of 10 cases. *J Neuro Ophthalmol : Off J North Am Neuro-Ophthalmol Soc*. 2008;28(2):114–119. https://doi.org/10.1097/WNO.0b013e318175cd90.
8. Zou M, Zhang Y, Huang X, et al. Demographic profile, clinical features, and outcome of peripapillary subretinal hemorrhage: an observational study. *BMC Ophthalmol*. 2020;20(1):1–7. https://doi.org/10.1186/s12886-020-01426-9.
9. Kokame GT, Yamamoto I, Kishi S, et al. Intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage. *Ophthalmology*. 2004;111(5):926–930. https://doi.org/10.1016/j.ophtha.2003.08.040.
10. Katz B, Hoyt WF. Intrapapillary and peripapillary hemorrhage in young patients with incomplete posterior vitreous detachment. Signs of vitreopapillary traction. *Ophthalmology*. 1995;102(2):349–354. https://doi.org/10.1016/s0161-6420(95)31018-4.
11. GT K. Intrapapillary, peripapillary, and vitreous hemorrhage. *Ophthalmology*. 1995;102(7):1003–1004. https://doi.org/10.1016/s0161-6420(95)30923-2.
12. Bhisitkul RB, Winn BJ, Lee O-T, et al. Neuroprotective effect of intravitreal triamcinolone acetonide against photoreceptor apoptosis in a rabbit model of subretinal hemorrhage. *Investig Ophthalmol Vis Sci*. 2008;49(9):4071–4077. https://doi.org/10.1167/iovs.08-1892.
13. Dunaief JL, Dentchev T, Ying G-S, et al. The role of apoptosis in age-related macular degeneration. *Arch Ophthalmol*. 2002;120(11):1435–1442. https://doi.org/10.1001/archopht.120.11.1435.
14. Winn BJ, Pereira DS, Wong J, et al. Retinal toxicity induced by subretinal vs. Sub–RPE hemorrhage in a rabbit model of macular degeneration. *Investig Ophthalmol Vis Sci*. 2005;46(13):243. https://iovs.arvojournals.org/article.aspx?articleid=2399679&resultClick=1.
15. Bennett SR, Folk JC, Blodi CF, et al. Factors prognostic of visual outcome in patients with subretinal hemorrhage. *Am J Ophthalmol*. 1990;109(1):33–37. https://doi.org/10.1016/S0002-9394(14)75575-8.
16. Tsujikawa A, Sakamoto A, Ota M, et al. Retinal structural changes associated with retinal arterial macroaneurysm examined with optical coherence tomography. *Retina*. 2009;29(6):782–792. https://doi.org/10.1097/IAE.0b013e3181a2f26a.
17. Muraoka Y, Tsujikawa A, Murakami T, et al. Branch retinal vein occlusion-associated subretinal hemorrhage. *Jpn J Ophthalmol*. 2013;57(3):275–282. https://doi.org/10.1007/s10384-013-0236-x.
18. Hussnain SA, Dolz-Marco Rosa, et al. Speckled hypoautofluorescence as a sign of resolved subretinal hemorrhage in neovascular age-related macular degeneration. *Retina*. 2019;39(10):1925–1935. https://doi.org/10.1097/IAE.0000000000002367.