Case report

Changes in blood flow velocity and thickness of the choroid in a patient with leukemic retinopathy

Akari Takita, Yuki Hashimoto, Wataru Saito, Satoru Kase, Susumu Ishida

Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
Kaimido Eye and Dental Clinic, Sapporo, Japan

1. Introduction

Leukemia often involves the eye. Leukemia cells infiltrate the retina and causes leukemic retinopathy that is characterized by intra-retinal hemorrhages often with Roth spots, vitreous hemorrhage, dilated and tortuous retinal veins, and cotton-wool spots. The choroid is an ocular tissue that is easiest for leukemia cells to infiltrate, regardless of whether patients are symptomatic or asymptomatic. Clinically, patients with leukemic choroidopathy involve serous retinal detachment (SRD) at the macula. Histopathologically, diffuse leukemic infiltrates were observed mainly in the posterior choroid. Recently, enhanced depth imaging optical coherence tomography (EDI-OCT) revealed choroidal thickening in the acute stage of a leukemia patient with SRD. These observations suggest that impairment of the retinal pigment epithelium (RPE) following choroidopathy causes subsequent SRD development. To our knowledge, however, choroidal circulation hemodynamics in patients with leukemic retinopathy and/or choroidopathy has not been examined quantitatively.

Laser speckle flowgraphy (LSFG) is a non-invasive device that is capable of quantitatively examining ocular blood flow velocity. LSFG targets moving erythrocytes, which produces blurring within the speckle pattern using a diode laser of a wavelength of 830 nm to illuminate the ocular fundus. The mean blur rate (MBR), automatically calculated from variations in the degree of blurring, is a quantitative index of the relative blood flow velocity and the measurement results show high reproducibility. Because the MBR derives mainly from the choroid, the value represents choroidal circulation hemodynamics, especially at the macula. Therefore, LSFG is suitable to monitor the time course of choroidal circulation hemodynamics in various choroidal diseases.

We used LSFG and EDI-OCT to quantitatively investigate the time course of changes in circulation hemodynamics and thickness of the choroid in a patient with leukemic retinopathy.
1.1. Case report

A 15-year-old boy presented with sudden central scotoma of his right eye for one day. The patient's medical and family histories were unremarkable.

The patient's best-corrected visual acuity (BCVA) was $0.09 \times -2.0$ diopters OD and $1.2 \times -2.0$ diopters OS and his intraocular pressure (IOP) was 21 mmHg OD and 18 mmHg OS. Slit-lamp examination revealed no abnormal findings OU. Funduscopy revealed a sub-inner limiting membrane (ILM) hemorrhage (Fig. 1a and b, arrowheads) at the fovea OD and the temporal side of the fovea OS, intra-retinal hemorrhages with Roth spots (Fig. 1a and b, arrows) OU, and dilatation and tortuosity of retinal vessels OU. We did not perform fluorescein or indocyanine green angiography because of the patient's systemic condition. EDI-OCT demonstrated hyper- and hypo-reflectivities beneath the ILM corresponding to the sub-ILM hemorrhages (Fig. 1c and d, arrowheads) and temporal side of the fovea (b, arrowheads) and intra-retinal hemorrhages with Roth spots (arrows). White circles indicate the measurement area of mean blur rate (MBR) on laser speckle flowgraphy (LSFG) in Fig. 1e, f, and 2e, f. Horizontal images of enhanced depth imaging optical coherence tomography (EDI-OCT) showing hyper-reflectivity (c) and hypo-reflectivity with punctate hyper-reflectivities inside (d) corresponding to the sub-ILM hemorrhages (arrowheads). Choroidal thicknesses were measured at the central fovea and neighboring temporal and nasal sites with 500-μm intervals up to 2,500 μm away from the central fovea (lines). Sites with shadowing due to sub-ILM hemorrhage at the fovea were excluded from the measurements because of poor visibility. Choroidal thickness was 334 μm at the nasal side of 1.0 mm away from the fovea (c, red line) and 175 μm at the fovea (d, red line). e, f, On LSFG color map, circles were set at the peri-fovea sparing the sub-ILM hemorrhage (c) and at the fovea (f). Size and position of the circles are identical to those in Fig. 1a and b. The blue color indicates low MBR, and the red color high MBR. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

There were no recurrences of leukemia or leukemic retinopathy during the follow-up.

2. Methods

2.1. LSFG measurement

The current study was approved by the ethics committee of Hokkaido University Hospital (015-0494). To quantitatively examine choroidal blood flow velocity in the present case, LSFG measurements using LSFG-NAVI (Softcare, Fukuoka, Japan) were performed for the eyes with leukemic retinopathy 5 consecutive times at the initial visit and at 2 weeks, 1 month, and 3 months after the start of chemotherapy. The mechanism and measurement method of LSFG have been published.5,9,14,15 On LSFG color map, circles were set at the nasal side of the fovea to avoid foveal sub-ILM hemorrhage OD and at the center of the macula OS (Fig. 1a, b, e, f, 2e, f). The positions of circles were determined manually by comparing the fundus photographs and the LSFG color map images at baseline. Each MBR was automatically calculated using LSFG Analyzer software (v 3.0.47; Softcare). Sequential changes in average MBR were evaluated as the changing rates of average MBR against the first measurement values, as previously described.12-16 since MBR is a quantitative index of the "relative" blood flow velocity.

2.2. Hemodynamics

Within a certain range, there is a linear relationship between choroidal blood flow and ocular perfusion pressure (OPP) in healthy subjects.17 To exclude the possibility of such physiological responses from the current results, OPP was calculated using the patient's blood pressure and IOP, as previously described.18
EDI-OCT measurements (RS-3000 Advance; NIDEK, Gamagori, Japan) were obtained for the eyes with leukemic retinopathy at initial visit and 2 weeks, 1 month, and 3 months after treatment. Choroidal thickness was determined by manually measuring the distance from the outer border of the hyper-reflective line corresponding to the RPE to the outer border of the choroid (Fig. 1c and d, 2c, d), using a horizontal scan through the fovea (scan length, 12.0 mm). Choroidal thickness values were obtained at the central fovea and neighboring temporal and nasal sites with 500-μm intervals up to 2,500 μm away from the central fovea OU (Fig. 1c, d, and 2c, d; lines). Of these, several sites with

2.3. EDI-OCT measurement

EDI-OCT measurements (RS-3000 Advance; NIDEK, Gamagori, Japan) were obtained for the eyes with leukemic retinopathy at initial visit and 2 weeks, 1 month, and 3 months after treatment. Choroidal thickness was determined by manually measuring the distance from the

![Photographs in the right eye (a, c, e) and left eye (b, d, f) after the start of chemotherapy and changes in mean blur rate (MBR) and choroidal thickness values during the 3-month follow-up period after treatment (g, h).]

a, b, Fundus photographs at 3 months after treatment showing the resolution of sub-inner limiting membrane and intra-retinal hemorrhages. c, d, The sizes of the hyper- (c) and hypo-reflectivities (d) observed at the initial visit on enhanced depth imaging optical coherence tomography was reduced at 1 month after treatment. Choroidal thicknesses measured at the same sites as the initial visit decreased to 284 μm (c, red line) and 142 μm (d, red line). e, f, On the laser speckle flowgraphy color map, the MBR within circles increased at 1 month after treatment compared with the initial visit (Fig. 1e and f). g, h, The MBR and choroidal thickness at the nasal site of 1.0 mm away from the fovea (red lines shown in Figs. 1c and 2c and the same site of circles shown in Figs. 1e and 2e) increased by 24.4–37.8% and decreased by 29.0–50.0 μm, respectively, in the right eye (g). Similarly, the MBR and choroidal thickness at the fovea (red lines shown in Figs. 1d and 2d and the same site of circles shown in Figs. 1f and 2f) increased by 13.1–26.2% and decreased by 27.0–45.5 μm, respectively, in the left eye (h). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
shadowing due to sub-ILM hemorrhage at the fovea were excluded from our measurements because of poor visibility in determining the outer border of the choroid (Figs. 1c and 2c). Two authors (AT, YH), blinded to the patient's clinical information, independently evaluated the EDI-OCT images.

3. Results

3.1. LSFG data

On LSFG color map, the MBR increases in both eyes were clearly visualized at 3 months after the initial visit compared with baseline (Fig. 1e, f, and 2e, f). Changes in the average macular MBR values are shown in Fig. 2g and h. The values were as follows: 4.5 ± 0.2, 5.7 ± 0.4, 6.2 ± 0.1, and 5.6 ± 0.2 OD at the initial visit and 2 weeks, 1 month, and 3 months after treatment, respectively, and 6.1 ± 0.4, 7.2 ± 0.4, 7.7 ± 0.7, and 6.9 ± 0.5 OS at the same evaluation points. When the changing rates in MBR were compared with the baseline values (100%), 26.7%, 37.8%, and 24.4% increments were noted OD with equivalent elevations of 18.0%, 26.2%, and 13.1% OS at 2 weeks, 1 month, and 3 months, respectively (Fig. 2g and h).

3.2. OPP data

OPP was 38.5, 41.3, 26.5, and 26.8 mmHg OD and 41.5, 43.3, 26.5, and 26.8 mmHg OS at baseline and 2 weeks, 1 month, and 3 months after the baseline measurement, respectively. It slightly decreased OU during the follow-up.

3.3. Changes in choroidal thickness

Changes in macular choroidal thickness in the eyes with leukemic retinopathy are shown in Table 1. Choroidal thickness values at 3 months after treatment decreased as compared with baseline data at all the sites measured (Fig. 1c, d, and 2c, d).

4. Discussion

In the present study, we quantitatively evaluated changes in choroidal blood flow velocity and choroidal thickness in the macular area using LSFG and EDI-OCT in a patient with leukemic retinopathy. During the 3-month follow-up period after the start of chemotherapy, the MBR increased by 24–38% OD and 13–26% OS. The macular choroidal thickness values decreased by 7–60 μm OD and 8–46 μm OS. In the acute stage, moreover, macular choroidal thickness values before treatment were much higher than the mean values at the corresponding 500-μm interval sites in normal eyes with refractive errors less than ~6.0 diopters. There were also improvements in the BCVA and retinal findings. Since the OPP slightly decreased during the follow-up, we determined that the increase of MBR in this patient were due to changes in choroidal blood flow velocity, but not systemic hemodynamics. Therefore, our results suggest that choroidal blood flow velocity decreases and choroidal thickness increases in the acute stage of a patient with leukemic retinopathy.

Histopathological studies reported that entry of leukemia cells into the eye was frequently observed intravascularly and extravascularly, especially at the posterior choroid. Therefore, the reason why MBR decreased and choroidal thickness increased in the acute stage of this patient may be explained as follows: leukemia cell adhesion to the inner wall of choroidal vessels and vascular compression by extravasated leukemia cells cause reduction of choroidal blood flow velocity, and increased infow of fluids to the choroidal interstitial tissue due to blood flow congestion and choroidal infiltration of leukemia cells result in choroidal thickening.

We previously showed that choroidal blood flow velocity decreased and choroidal thickness increased in the acute stage of choroiditis such as in Vogt-Koyanagi-Harada disease and serpiginous choroiditis. In contrast, both the blood flow velocity and thickness of the choroid increased in the acute stage of patients with acute central serous choriorretinopathy (CSCR). These circulatory and morphologic patterns in choroiditis and CSCS may be called the inflammatory pattern and sympathetic pattern, respectively. Interestingly, unilateral acute idiopathic maculopathy, a series of diseases in the acute zonal occult outer retinopathy complex, and acute posterior multifocal placoid pigment epitheliopathy also showed inflammatory patterns. Because the pattern of choroidal flow and thickness changes in the present case was similar to that of choroiditis, it may be termed as a “pseudo-inflammatory” pattern, which is also supported by the previous histopathological observations.

The present study has some limitations. Because this is a case report, further studies with a larger number of cases are needed to establish usefulness of the MBR and choroidal thickness in the management of this disease. In this study, choroidal thickness was manually measured using an OCT B-scan. To reduce measurement bias, further studies are needed to automatically measure choroidal volume using a swept-source OCT C-scan or EDI-OCT raster scan protocol.

In conclusion, LSFG and EDI-OCT results at the macula revealed that MBR increased, choroidal thickness decreased, and visual function and fundus findings improved in a patient with leukemic retinopathy. These results suggest that choroidal circulation impairment was sub-clinically present in leukemic retinopathy regardless of the absence of choroidopathy. Thus, LSFG and EDI-OCT may be useful to non-invasively and quantitatively evaluate the activity of choroidal involvements in leukemic retinopathy and/or chorioretinopathy.

Table 1

| Site from the central fovea (mm) | Choroidal thickness (μm) |
|---------------------------------|--------------------------|
|                                 | Right eye    | Left eye    |
|                                 | Baseline     | 1W          | 1M          | 3M          | Baseline     | 1W          | 1M          | 3M          |
| Temporal 2.5                    | 350          | 344          | 328          | 328          | 301          | 293          | 276          | 274          |
| Temporal 2.0                    | 369          | 354          | 344          | 342          | 321          | 311          | 297          | 293          |
| Temporal 1.5                    | 398          | 365          | 352          | 338          | 307          | 288          | 282          | 274          |
| Temporal 1.0                    | 402          | 375          | 365          | 356          | 270          | 253          | 243          | 245          |
| Temporal 0.5                    | ND           | ND           | ND           | 352          | 342          | 167          | 157          | 145          | 144          |
| Fovea                           | ND           | ND           | ND           | 332          | 175          | 148          | 142          | 129          |
| Nasal 0.5                       | ND           | ND           | ND           | 319          | 295          | 307          | 218          | 193          | 185          | 185          |
| Nasal 1.0                       | 334          | 305          | 284          | 293          | 264          | 251          | 227          | 218          |
| Nasal 1.5                       | 286          | 262          | 233          | 247          | 231          | 222          | 189          | 189          |
| Nasal 2.0                       | 266          | 249          | 224          | 227          | 181          | 177          | 152          | 148          |
| Nasal 2.5                       | 193          | 179          | 166          | 158          | 136          | 127          | 115          | 107          |

ND, not done; W, week; M, month.

Patient consent

Informed consent was obtained in writing from the patient and his parent for the use of the patient's information for the purpose of this report.

Funding

No funding or grant support.

Conflicts of interest

The following authors have no financial disclosures: AT, VH, WS, SK, and SI.
Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgments

None.

References

1. Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. Surv Ophthalmol. 1983;27(4):211–232.
2. Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukemia: the ophthalmologist’s role. Eye (Lond). 2004;18(7):663–672.
3. Kincaid MC, Green WR, Kelley JS. Acute ocular leukemia. Am J Ophthalmol. 1979;87(5):698–702.
4. Leonardy NJ, Rupani M, Dent G, Klintworth GK. Analysis of 135 autopsy eyes for measurement of retinal microcirculation using laser speckle phenomenon. Ophthalmol Vis Sci. 1994;35(11):3825–3834.
5. Bajenova NV, Vanderbeek BL, Johnson MW. Change in choroidal thickness after chemotherapy in leukemic choroidopathy. Retina. 2012;32(1):203–205.
6. Adam MK, Pitcher JD, Shields CL, Maguire MJ. Enhanced depth imaging optical coherence tomography of precursor cell leukemic choroidopathy before and after chemotherapy. Middle East Afr J Ophthalmol. 2015;22(2):249–252.
7. Robb RM, Ervin ID, Sallan SE. An autopsy study of eye involvement in acute leukemia in childhood. Med Pediatr Oncol. 1979;6(2):171–177.
8. Tamaki Y, Arai M, Kawamoto E, Eguchi S, Fujii H. Noncontact, two-dimensional measurement of retinal microcirculation using laser speckle phenomenon. Invest Ophthalmol Vis Sci. 1994;35(11):3825–3834.
9. Sugiyama T. Basic technology and clinical applications of the updated model of laser speckle flowgraphy to ocular diseases. Photonics. 2014;1(3):220–234.
10. Aizawa N, Yokoyama Y, Chiba N, et al. Reproducibility of retinal circulation measurements obtained using laser speckle flowgraphy-NAVI in patients with glaucoma. Clin Ophthalmol. 2011;5:1171–1176.
11. Isoho H, Kishi S, Kimura Y, Hagihara N, Konishi N, Fujii H. Observation of choroidal circulation using index of erythrocytic velocity. Arch Ophthalmol. 2003;121(2):225–231.
12. Saito M, Saito W, Hashimoto Y, et al. Macular choroidal blood flow velocity decreases with regression of acute central serous chorioretinopathy. Br J Ophthalmol. 2013;97(6):775–780.
13. Saito M, Saito W, Hashimoto Y, et al. Correlation of choroidal blood flow velocity and choroidal thickness to the pathogenesis of acute zonal occult outer retinopathy. Clin Exp Ophthalmol. 2014;42(2):139–150.
14. Hirooka K, Saito W, Namba K, et al. Relationship between choroidal blood flow velocity and choroidal thickness during systemic corticosteroid therapy for Vogt-Koyanagi-Harada disease. Graefe’s Arch Clin Exp Ophthalmol. 2015;253(4):609–617.
15. Hashimoto Y, Saito W, Saito M, et al. Decreased choroidal blood flow velocity in the pathogenesis of multiple evanescent white dot syndrome. Graefe’s Arch Clin Exp Ophthalmol. 2015;253(9):1457–1464.
16. Hashimoto Y, Saito W, Saito M, et al. Increased choroidal blood flow velocity with regression of unilateral acute idiopathic maculopathy. Jpn J Ophthalmol. 2015;59(4):252–260.
17. Riva CE, Titze P, Hero M, Petrig BL. Effect of acute decreases of perfusion pressure on choroidal blood flow in humans. Invest Ophthalmol Vis Sci. 1997;38(9):1752–1760.
18. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus-HD optical coherence tomography. Am J Ophthalmol. 2010;150(3):325–329.
19. Takahashi A, Saito W, Hashimoto Y, Saito M, Ishida S. Impaired circulation in the thickened choroid of a patient with serpiginous choroiditis. Ocul Immunol Inflamm. 2014;22(5):409–413.
20. Saito M, Saito W, Hirooka K, et al. Pulse waveform changes in macular choroidal hemodynamics with regression of acute central serous chorioretinopathy. Invest Ophthalmol Vis Sci. 2015;56(11):6515–6522.
21. Hashimoto Y, Saito W, Saito M, et al. Relationship between choroidal thickness and visual impairment in multiple evanescent white dot syndrome. Acta Ophthalmol. 2016;94(8):e804–e806.
22. Hirooka K, Saito W, Hashimoto Y, Saito M, Ishida S. Increased macular choroidal blood flow velocity and decreased choroidal thickness with regression of punctate inner choroidopathy. BMC Ophthalmol. 2014;14:73.
23. Hirooka K, Saito W, Noda K, Ishida S. Enhanced-depth imaging optical coherence tomography and laser speckle flowgraphy in a patient with acute macular neuroretinopathy. Ocul Immunol Inflamm. 2014;22(6):485–489.
24. Hashimoto Y, Saito W, Saito M, et al. Relationship between choroidal thickness and visual field impairment in acute zonal occult outer retinopathy. J Ophthalmol. 2017;2017:2371032.
25. Hirooka K, Saito W, Saito M, et al. Increased choroidal blood flow velocity with regression of acute posterior multifocal placoid pigment epitheliotropism. Jpn J Ophthalmol. 2016;60(3):172–178.
26. Chhablani J, Bartessi G, Wang H, et al. Repeatability and reproducibility of manual choroidal volume measurements using enhanced depth imaging optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(4):2274–2280.