

# Choroidal Circulatory and Vascular Morphological Changes in Acute Macular Neuroretinopathy After Infection With Severe Acute Respiratory Syndrome Coronavirus 2: A Case Report With Literature Review

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**Abstract.** *Background/Aim:* The aim of this study was to analyze choroidal circulatory and structural changes using laser speckle flowgraphy (LSFG) and optical coherence tomography (OCT) in acute macular neuroretinopathy (AMN) after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respectively. *Case Report:* A 24-year-old woman complained of distorted vision after SARS-CoV-2 infection oculi uterque (OU) and referred to our hospital because of ellipsoid zones (EZ) disruption on OCT. Her best-corrected visual acuity (BCVA) was 1.2 OU. Color fundus photographs revealed dark red lesions in the macula, and scanning laser ophthalmoscopy infrared images showed hypointensity consistent with dark red lesions OU. We diagnosed the patient with AMN after SARS-CoV-2 infection, and posterior sub-Tenon injections of triamcinolone acetonide were performed OU. Five months after the initial visit, her BCVA was 1.2 OU, and EZ disruption improved. The rate of change in macular blood flow assessed by the mean blur rate on LSFG was 20.4% and 29.6% increase oculus dexter (OD) and oculus sinister

(OS) 5 months after the initial visit, respectively. The central choroidal thickness showed 13.5% increase OD and 16.1% increase OS. The binarization technique demonstrated that the ratio of luminal areas in choroidal area increased by 12.6% OD and 14.2% OS, and stromal areas increased by 7.3% OD and 16.9% OS. *Conclusion:* Before and after treatment for AMN, the luminal component may have increased with improvement of acute choroidal circulatory disturbance caused by SARS-CoV-2, and increased stromal components may be due to chronic inflammation and tissue remodeling of the stroma.

The coronavirus infection (COVID-19) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a serious global problem that has threatened human health and vision since 2019. SARS-CoV-2, a ribonucleic acid (RNA) virus, causes not only respiratory disorders, but also multiple systemic complications including myocardial infarction, deep venous thromboembolism, and cerebrovascular events, which are associated with hyperinflammatory and coagulopathic conditions (1). In addition, 2% to 32% of COVID-19 cases have been found to lead to various ophthalmic manifestations (2). Conjunctivitis is a relatively common manifestation in patients with COVID-19, while it can cause various retinal vascular disorders (3-5).

Recently, a binarization using enhanced depth imaging-optical coherence tomography (OCT) images has made it possible to noninvasively quantify retinal structures as well as the luminal and stromal areas of the choroid over time (6, 7). In general, the binarization method clinically allows quantitative evaluation of presumed histological intravascular and extravascular regions of the choroid, respectively (8). Laser speckle flowgraphy (LSFG) is a blood flow imaging device that uses laser scattering to noninvasively visualize the fundus circulation in two

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**Key Words:** Acute macular neuroretinopathy, severe acute respiratory syndrome coronavirus 2, laser speckle flowgraphy, optical coherence tomography, binarization method.



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dimensions. We have used LSFG to observe fundus circulation in various retino-choroidal diseases, such as optic disc melanocytoma (9), choroidal macrovessel (10), sclerochoroidal calcification (11), juxtapapillary retinal capillary hemangioblastoma (12), and choroidal lymphoma (13). Recently, we reported a case of leukemic retinopathy and analyzed choroidal circulatory and structural changes using LSFG and OCT with the binarization method simultaneously, and there was a correlation between mean blur rate (MBR) as relative blood flow values and the ratio of luminal area (LA) /total choroidal area (CA) following the binarization (14). Acute macular neuroretinopathy (AMN) is a rare disease characterized by wedge-shaped dark reddish-brown lesions in the macula, which might be caused by oral contraceptive use, vasoconstrictor and sympathomimetic use, as well as a nonspecific viral illness or fever including SARS-CoV-2 infection (15). However, little is known about the alterations of choroidal circulatory changes and vascular structures in AMN following SARS-CoV-2 infection.

We herein present a case of AMN after infection with SARS-CoV-2 and analysis of the choroidal circulatory and structural changes using LSFG and OCT with the binarization method, respectively. We further reviewed the literature regarding COVID-19-related AMN and compared it with the current findings.

## Case Report

A 24-year-old female complained of distorted vision one day after a fever due to SARS-CoV-2 infection oculi uterque (OU). There were no special notes in her medical or family history. She had received mRNA vaccination against SARS-CoV-2 twice, and no adverse reactions were observed at the time of vaccination. Her smoking history was 4 years of 15 cigarettes per day. Physical history included childhood asthma, atopic dermatitis, and influenza pneumonia. She was referred to our clinic 14 days after infection because of distorted vision and ellipsoid zones (EZ) disruption on OCT. At an initial examination, her best-corrected visual acuity (BCVA) was 1.2 OU with myopia, and intraocular pressure was normal OU. Slit-lamp microscopy did not detect any findings OU. Color fundus photography showed dark red lesions in the macula (white arrowheads, Figure 1A and B), and scanning laser ophthalmoscopy (SLO) infrared images showed hypointensity consistent with dark red lesions OU (red arrowheads, Figure 1C and D). Swept-source (SS)-OCT on horizontal scans through the fovea showed minor irregularity of EZ and expansion of interdigitation zone (IZ) loss (red arrowhead, Figure 1E and F). Fluorescein angiography (FA) showed no obvious abnormality, and indocyanine green angiography (ICGA) showed no obvious abnormality in the early phase, but dark red lesions in the macula were slightly hypofluorescent in the late phase.

Humphrey field analyzer 10-2 showed paracentral scotoma OU. Based on the clinical findings, this patient was diagnosed with AMN that developed after SARS-CoV-2 infection. Since her ocular symptoms did not improve, sub-Tenon injections of triamcinolone acetonide (STTA) of 40 mg were performed in the right and left eyes at 14 and 29 days following infection, respectively, after informed consent was given. Twenty weeks after the initial visit, her BCVA was 1.2 OU, the ocular symptom of distorted vision improved, and EZ and IZ disruption on OCT resolved. The institutional review board of Hokkaido University waived ethical assessment of this clinical study because it was a single case report with a non-invasive study. This study adhered to the tenets of the Declaration of Helsinki.

## Methods.

*Analysis of LSFG measurement.* In the present study, LSFG was used to evaluate changes in choroidal blood flow in AMN. Blood flow velocity was measured quantitatively by LSFG software (LSFG-NAVI, version 3.1.39.2, Softcare Ltd., Fukuoka, Japan), and relative blood flow values were determined as the MBR in accordance with previous reports (16). The pupils of the patient were dilated with 0.4% tropicamide (Mydrin-M; Santen Pharmaceutical Co., Ltd., Osaka, Japan) before examination. Ophthalmologic examinations were performed after the complete disappearance of light reflex in the pupils of both eyes. The macular area in the LSFG image was marked manually, and the vessels were automatically segmented using threshold values defined in the system's software (LSFG Analyzer, version 3.0.47.0). A circle with a diameter of 1,500  $\mu\text{m}$  to the fovea was defined as the region of interest on the LSFG (Figure 2A and B, small circle). Four to five consecutive measurements were taken for each circle, and the mean values were used for analysis. All tests were performed by an experienced operator. Ocular perfusion pressure (OPP) was calculated using the patient's blood pressure and intraocular pressure, in accordance with previous reports (16).

*Analysis of SS-OCT-based choroidal structural parameters.* The central choroidal thickness (CCT) in SS-OCT was measured manually by two experienced examiners from the lower edge of the retinal pigment epithelium layer to the scleral border. The choroidal structure of SS-OCT images (DRI OCT Triton; Topcon Inc., Tokyo, Japan) was analyzed by selecting a 1,500  $\mu\text{m}$  region of the OCT image as the region of interest corresponding to the LSFG analysis range, using the semi-automatic analysis software EyeGround developed by Sonoda *et al.* (6). The brightness of each pixel in the OCT image was binarized using the Niblack method in EyeGround. The bright and dark pixels in the generated images corresponded to the choroidal stromal and luminal regions, respectively (Figure 2C and D; at initial visit). The

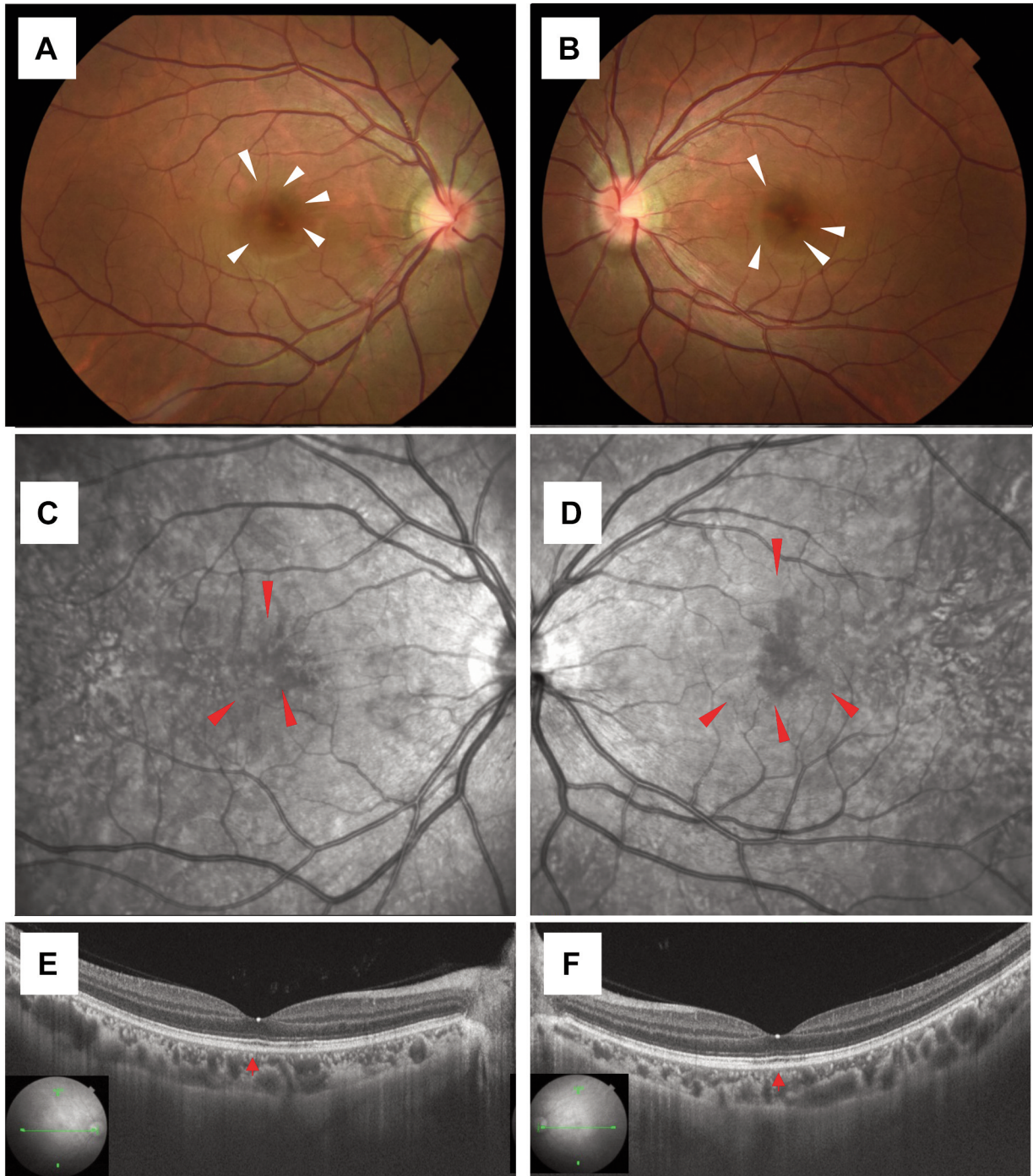


Figure 1. Initial findings on color fundus photography (CFP), scanning laser ophthalmoscopy (SLO) infrared images, and swept-source optical coherence tomography (SS-OCT) in the present case of leukemic retinopathy. A, B) CFP showed dark red lesions in the macula (white arrowheads). C, D) SLO infrared images showed hypointensity consistent with dark red lesions oculi uterque (OU) (red arrowheads). E, F) SS-OCT on horizontal scans through the fovea revealed minor irregularity of ellipsoid zones and expansion of interdigitation zone loss OU (red arrowheads).

areas of both regions were measured and quantitatively evaluated using a binarization method. The primary measurements were CA, LA, stromal area (SA), and the

ratios of the luminal area/choroidal area (L/C). Two experienced examiners measured the parameters, and the mean values were shown.



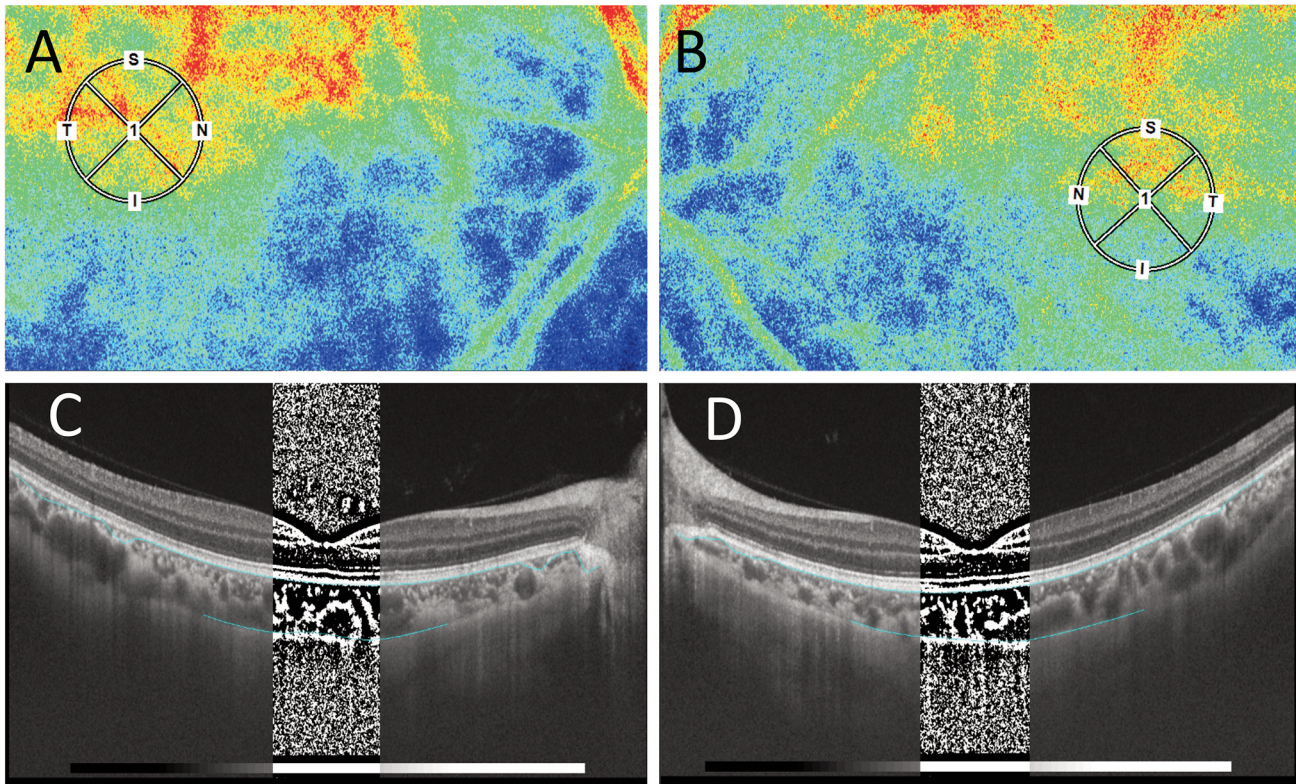


Figure 2. Initial findings on laser speckle flowgraphy (LSFG), and optical coherence tomography (OCT) images with the binarization method in the present case of leukemic retinopathy. A, B) LSFG showed a mild warm-color blood flow signal corresponding to the small circles OU. C, D) In OCT images with the binarization method, bright and dark pixels correspond to the stromal and luminal regions of the choroid, respectively.

**Results.**

**MBR and OPP assessed by LSFG.** The MBR values (arbitrary unit) oculus dexter (OD) are shown in Figure 3A as follows: 15.7, 13.2, 13.8, 14.0, and 18.9 at the initial visit, 1, 8, 13, and 20 weeks after the initial visit, respectively. The rate of change assessed by MBR was 20.4% increase OD 20 weeks after the initial visit. The MBR values oculus sinister (OS) are shown in Figure 3B as follows: 12.5, 11.5, 9.5, 14.2, and 16.2 at the initial visit, 1, 8, 13, and 20 weeks after the initial visit, respectively. The rate of change assessed by MBR was 29.6% increase OS 20 weeks after treatment. MBR of both eyes decreased temporarily but gradually increased. OPP was 49.0, 51.4, 60.0, 56.7, and 66.7 mmHg OD and 51.1, 55.0, 59.7, 56.0 and 63.5 mmHg OS at the initial visit, 1, 8, 13, and 20 weeks after the initial visit, respectively, revealing no significant changes in either eye.

**Alterations in OCT-based choroidal parameters.** The CCT values OD were 319, 268, 309, 292, and 362  $\mu$ m at the initial visit, 1, 8, 13, and 20 weeks after the initial visit, respectively (Figure 3C). The CCT values OS were 285, 273, 274, 254, and 331  $\mu$ m at the initial visit, 1, 8, 13, and 20

weeks after the initial visit, respectively (Figure 3D). The rate change of CCT showed 13.5% increase OD and 16.1% increase OS 20 weeks after treatment. The CCT of both eyes decreased temporarily after the start of treatment, and then gradually increased thereafter.

The rates of change in choroidal structures by the binarization method in the designated 1,500  $\mu$ m circle 20 weeks after treatment were as follows: L/C increased by 3.2% OD (Figure 3C) and decreased by 4.8% OS (Figure 3D); LA increased by 12.6% OD and 14.2% OS; SA increased by 7.3% OD and increased by 16.9% OS. Taken together, the L/C ratio increased for 1~8 weeks but then decreased. LA and SA decreased temporarily but gradually increased afterward.

**Discussion**

The present study demonstrated a case of AMN that developed after SARS-CoV-2 infection and analyzed choroidal circulatory and structural changes. MBR, CCT, LA, and SA decreased in the acute phase (1 week), slightly decreased around the subacute phase (after 8 weeks), and gradually increased in the chronic phase (after 13 weeks). In contrast, the L/C ratio increased OD and decreased OS in the

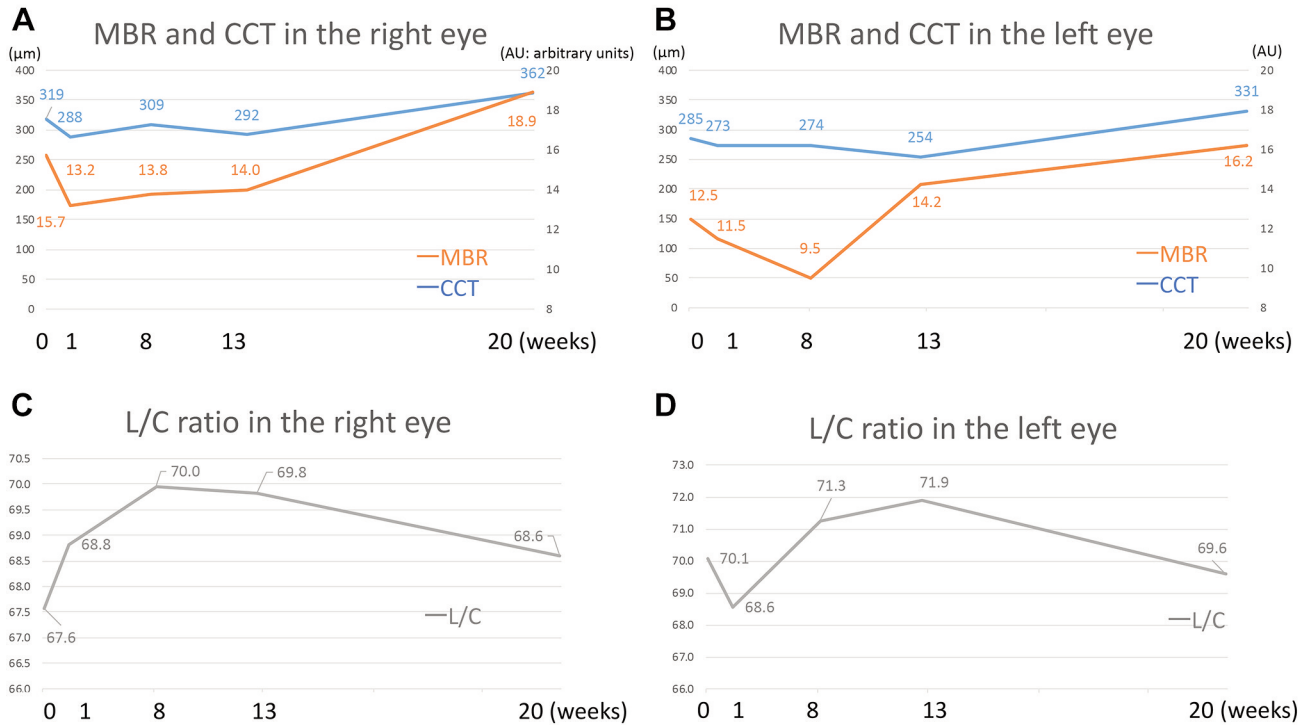


Figure 3. Mean blur rate (MBR) by laser speckle flowgraphy and the central choroidal thickness (CCT) (A, B) and luminal area /choroidal area (L/C) ratio (C, D). A, B) MBR and CCT decreased temporarily in the acute phase, flat to slightly decreased in the subacute phase, and gradually increased in the chronic phase. C, D) L/C ratio increased in the right eye and decreased in the left eye in the acute phase, increased OU in the subacute phase, and gradually decreased OU in the chronic phase.

acute phase, increased OU in the subacute phase, and gradually decreased OU in the chronic phase.

First, this study compared ophthalmic findings in the current patient with those reported on the choroidal circulation of AMN prior to the SARS-CoV-2 pandemic. Hashimoto *et al.* reported a 15-year-old male with AMN in both eyes, who recovered without treatment, and demonstrated that the thickened CCT in the acute phase decreased over time until 3 months (presumed subacute phase), whereas the MBR increased (17). Hashimoto *et al.* reported another case of AMN in a 41-year-old female who had taken oral contraceptives, and demonstrated that choroidal blood flow velocity determined by MBR on LSFG increased sequentially during systemic corticosteroid administration (18). The two cases by Hashimoto *et al.* (17, 18) showed that the MBR increased till 3 months after the onset, in which the change in MBR was consistent with that in our case. The background of the two cases, however, was different from that of our case, since the first case (17) was a young male, and the second case (18) had a history of oral contraceptives use and of systemic corticosteroid treatment for 4 months. Hirooka *et al.* reported an 11-year-old female with AMN in the right eye, who recovered without treatment, and demonstrated that CCT did not show remarkable change, whereas the MBR continuously increased 6 months

after the onset of the disease (19), which was consistent with changes in the chronic phase in our case. In particular, the acute decrease in MBR in our AMN case suggested that vascular damage might have preceded local inflammation, since SARS-CoV-2 is an infectious agent that causes vascular damages. In addition, as mentioned above, three reports in pre-COVID-19 era (17-19) have implicated the choroidal circulation impairments in the pathogenesis of AMN, but this was the first report of LSFG and OCT with a binarization method of AMN after infection with SARS-CoV-2.

Next, this study reviewed a total of 36 cases of AMN following COVID-19 based on the published literature through the PubMed website (Table I). Majumder PD *et al.* (20) reviewed 18 AMN cases after SARS-Cov-2 infection in 2023; therefore, the present study added 17 reported cases including the current case. On the other hand, cases of paracentral acute middle maculopathy without ophthalmic findings of AMN, or cases of AMN after SARS-CoV-2 vaccination were excluded in this study.

Mean age of all the patients included in this analysis was  $35.5 \pm 15.7$  years. Twenty-four cases (69%) were female, and 11 cases (31%) were male, and 26 cases had bilateral lesions. Ocular symptoms appeared an average of  $12.1 \pm 26.6$  days after SARS-CoV-2 infection. This case is a young woman,

Table I. Review of literature of AMN cases in COVID-19 patients.

Study	Age	Sex	Time from systemic symptoms to the onset of ocular symptoms	Laterality	RE BCVA	LE BCVA
Azur G <i>et al.</i> (21)	21	M	ND	Right eye	2	0
	28	F	ND	Both eyes	0	0
	27	F	ND	Both eyes	-0.1	-0.1
	22	F	ND	Right eye	0	0
Bellur S <i>et al.</i> (22)	64	F	ND	Both eyes	1	1
Capuano V <i>et al.</i> (23)	37	F	ND	Both eyes	0	ND
David JA <i>et al.</i> (24)	22	F	1	Both eyes	0	ND
Goyal M <i>et al.</i> (25)	32	M	28	Both eyes	0	0
Preti RC <i>et al.</i> (26)	70	M	-4	Left eye	0	0.7
El Matri K <i>et al.</i> (27)	75	F	84	Left eye	ND	ND
Gascon P <i>et al.</i> (28)	53	M	1	Both eyes	ND	ND
Giacuzzo C <i>et al.</i> (29)	23	F	ND	Both eyes	0	ND
Macé T <i>et al.</i> (30)	39	F	2	Both eyes	0	ND
Aidar MN <i>et al.</i> (31)	71	F	14	Left eye	ND	0.5
Diafas A <i>et al.</i> (32)	59	M	ND	Both eyes	ND	ND
	24	F	ND	Both eyes	ND	ND
Masjedi M <i>et al.</i> (33)	29	F	14	Left eye	ND	ND
Virgo J <i>et al.</i> (34)	32	M	16	ND	ND	ND
Zamani G <i>et al.</i> (35)	35	F	-9	Right eye	0	ND
Jalink MB <i>et al.</i> (36)	29	F	112	Left eye	Normal	Normal
Ferkova N <i>et al.</i> (37)	32	F	ND	Both eyes	0.3	0.3
Liu YC <i>et al.</i> (38)	19	M	5	Both eyes	0.3	0.3
	35	M	5	Both eyes	0.9	0.3
	17	F	4	Both eyes	0.05	0.01
	28	M	4	Both eyes	0.01	0.01
	37	M	2	Both eyes	1	1
	42	F	3	Both eyes	0.8	0.7
	32	F	4	Both eyes	0.4	0.2
	42	F	3	Both eyes	0.1	0.04
	19	F	1	Both eyes	1	0.02
	30	F	2	Both eyes	0.2	0.4
	49	F	5	Both eyes	0.5	0.9
	23	F	1	Both eyes	0.4	0.2
16	M	2	Both eyes	0.05	0.6	
30	F	3	Both eyes	0.4	0.5	

RE: Right eye; LE: left eye; ND: not determined; M: male; F: female.

who did not take oral contraceptives, but had a history of smoking. In fact, since smoking has been reported to have a negative effect on the coagulation system in COVID-19 (39), it should be investigated in cases of COVID-19-related AMN reports as a future issue. In one case (21) with poor vision at onset, oral prednisolone was administered. In another case (37), low molecular weight heparin was administered in a preventive dose. All other cases had been observed without treatment. The visual prognosis was generally good, but the patient with poor vision at onset had persistent scotomas (21). The current patient developed AMN 1 day after infection with SARS-CoV-2, the duration of which was relatively short compared to previous reports. While the patient with poor vision in the previous report was treated, this patient had good vision but suffered from distorted

vision. Therefore, STTA were performed in both eyes, and her ocular symptom of distorted vision eventually improved.

It is known that adhesion of SARS-CoV-2 has a close relation with receptors (angiotensin-converting enzyme 2: ACE2), which are histologically located in the ocular adnexal tissues (40) as well as vascular systems including the choroidal middle-large vessels and choriocapillaris (41). In fact, viral particles following infection with SARS-CoV-2 possibly cause choroidal vasculopathy (42). Bellur *et al.* and Liu *et al.* reported that the choriocapillaris vascular density was reduced in AMN after SARS-CoV-2 infection using OCT angiography (22, 38). In our case, SARS-CoV-2 virion attached presumed ACE2-positive choroidal vessels, led to acute choroidal bloodstream congestion, and impaired choroidal circulation, which subsequently reduced stromal and



luminal areas at the acute phase of infection. At this acute phase, there were no dark spots even on ICGA, suggesting that inflammation of the choroid had yet happened or the inflammation did not involve the choroidal vascular structures. Pathologically diffuse lymphocytic infiltration and fibrosis can occur in the chronic phase after SARS-CoV-2 infection of the ocular adnexa (40). In our case, since the vasculopathy improved as the infection recovered and the lumen was enlarged presented as increased L/C ratio, lymphocyte infiltration into the stroma caused inflammation and an increase in stromal components observed by OCT. In addition, STTA controlled inflammation, led to stromal remodeling, and maintained stromal area from the subacute to chronic phase.

In conclusion, before and after treatment of this case, the luminal component increased with improvement of acute choroidal circulatory disturbance due to SARS-CoV-2 infection, and the interstitial component may have increased due to chronic inflammation and remodeling of the stroma.

### Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

### Authors' Contributions

MM wrote the paper and acquired clinical data. SK reviewed the paper and interpreted the clinical data. KH analyzed LSFSG data. HE and YI analyzed and verified the results of binarization. SI conducted clinical revision and supervised the data interpretation. All Authors have read and approved the manuscript.

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