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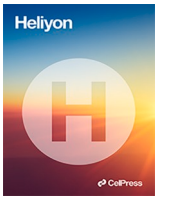

Research article

Spectrum of retinal microvascular ischemia in patients with COVID-19 based on multimodal imaging

Min Zhang [a,1], Junran Sun [a,1], Chanchan Wang [b], Li Su [a], Jieqiong Chen [a], Yimin Wang [c], Xiaodong Sun [a,d,e,f,g], Yuanyuan Gong [a,**], Suqin Yu [a,*]

[a] Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Affiliated Eye Hospital of Nanchang University, Nanchang, China
[c] Zhongshang Hospital of Fudan University, Shanghai, China
[d] National Clinical Research Center for Eye Diseases, Shanghai, China
[e] Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai, China
[f] Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai, China
[g] Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai, China

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ABSTRACT

Purpose: To describe and evaluate the multimodal imaging findings in retinal microvascular ischemia associated with COVID-19 infection.

Methods: Patients with COVID-19 associated retinal microvascular ischemia and visiting the outpatient Department of Ophthalmology, Shanghai General Hospital from December 2022, to February 2023, were documented and their multimodal images were retrospectively reviewed. *Retinal microvascular ischemia* was defined as the presence of isolated or multiple focal retinal whitening(s) on color fundus images. Patients with retinal vessel occlusion or retinopathies secondary to systematic disorders diagnosed before infection were excluded.

Results: A total of 32 eyes from 21 patients were included, 24 (75.00 %) eyes with multiple retinal whitenings, while 8 (25.00 %) eyes with isolated lesions. When divided by the types of ischemia, 9 (28.13 %) eyes had only inner retinal involvement (known as cotton wool spot, CWS), 4 (12.50 %) eyes had only middle retinal involvement (known as paracentral acute middle maculopathy, PAMM), and 19 (59.38 %) eyes had both. In addition, 4 (12.50 %) eyes had coincident angular sign of Henle fiber layer hyperreflectivity (ASHH). Patients with hypertension tended to have multiple lesions rather than isolated lesion of retinal microvascular ischemia ($P = 0.008$). Transient uncontrolled high blood pressure or acute kidney injury was simultaneously detected in some cases.

Conclusions: Ocular manifestation of COVID-19 associated microvascular ischemia can be variable, including CWS, PAMM and ASHH. Multimodal fundus imaging technologies are useful tools to reveal involved retinal layers, extent, and severity. Moreover, ocular manifestations may serve as a window of COVID-19 related microcirculation in other systems throughout the body.

* Corresponding author. Department of Ophthalmology, Shanghai General Hospital, Wujin Road 85, Hongkou District, Shanghai, China.
** Corresponding author. Department of Ophthalmology, Shanghai General Hospital, Wujin Road 85, Hongkou District, Shanghai, China.
E-mail addresses: gyydr@126.com (Y. Gong), sq-yu@163.com (S. Yu).
[1] These two authors contributed equally to this manuscript and should be considered as co-first authors.

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1. Introduction

The Coronavirus disease-2019 (COVID-19) pandemic was declared in 2020 and its pooled prevalence was estimated to be 0.43 globally in 2022 [1]. It was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The infection mainly caused flu-like symptoms [2] and could develop into multi-system inflammatory syndrome [3] and thrombi-embolic diseases [4]. Moreover, the higher transmissible but milder omicron variants brought infection surges with serious repercussions in many areas [5]. Unprecedented challenges have been brought to emergency departments, internal medicine, as well as ophthalmology.

COVID-19 associated retinal manifestations have been noted since the pandemic, varying from the cotton wool spot (CWS) [6] and tortuous vessels [7], to visually significant retinopathies such as acute macular neuroretinopathy (AMN) [8] and retinal vascular occlusions [9,10]. Retinal microvascular impairment is highly involved in these pathologies and is in causal relationships. Previous case-control optical coherence tomography angiography (OCTA) studies [11–15] have quantified retinal perfusion deficits in COVID-19 patients. COVID-19 associated cases of Purtscher-like retinopathy were also reported [16]. These reports generally described the retinal manifestations and quantified the retinal perfusion with COVID-19 infection, but COVID-19 associated microvascular ischemia was not fully focused. The retinal pathologies with multimodal imaging, was not adequately demonstrated, either. Their roles in indicating concomitant COVID-19 associated systematic microvascular impairments needed to be illustrated as well.

With the infection incidence quickly peaking in Shanghai from December 2022 to January 2023, retinal microvascular ischemia was more frequently observed than usual. To demonstrate the spectrum of retinal ischemic lesions, COVID-19 associated medical histories of these cases were aimed to be collected, and their multimodal images were reviewed. Here, we present a case series of COVID-19 associated microvascular ischemia observed during this outbreak.

2. Methods

This study involved patients with COVID-19 associated retinal microvascular ischemia who visited the outpatient Department of Ophthalmology, Shanghai General Hospital from December 15, 2022, to February 15, 2023. Patients with signs of retinal microvascular ischemia on multimodal imaging were documented and reviewed retrospectively. The infections of COVID-19 were confirmed by polymerase chain reaction assay or the fast COVID-19 antigen tests. The associations of retinal microvascular ischemia to COVID-19 were defined as newly onset visual symptoms and/or fundus findings within 4 weeks post-COVID-19 infection. In addition, the retinal microvascular retinopathies ischemia should not be attributed to other medical history or conditions with ocular involvement before the COVID-19 infection, such as systematic lupus erythematosus [17] and pancreatitis [18].

Retinal microvascular ischemia was defined as the presence of isolated or multiple focal retinal whitening(s) on color fundus images. This definition was made on ophthalmoscopic examination only, and did not intend to identify isolated angular sign of Henle fiber layer hyperreflectivity (ASHH). ASHH is a novel descriptive OCT terminology for AMN-like lesions, while AMN is a disease entity [19]. Definitions for all types of lesions in terms of OCT and color fundus images were summarized as Table 1. A recent complaint of acute onset scotoma(s), paracentral scotoma(s), blurred vision, and/or visual acuity decline was recorded. Eyes with multiple, white retinal patches, with or without superficial retinal hemorrhage or papillitis, were classified into the multiple lesions group.

For eligible patients, de-identified medical records were collected, including age, sex, visual acuity, intraocular pressure, concomitant systemic and ocular disorders as well as medications. Blood pressures at the first visit were collected. All patients underwent slit-lamp examination with multimodal imaging. Multimodal imaging included color fundus photography (Clarus 500, Carl Zeiss), fundus fluorescein angiography (FFA; Spectralis HRA, Heidelberg), spectral domain optical coherence tomography (OCT) and near-infrared reflectance (NIR; Spectralis HRA, Heidelberg), fundus autofluorescence (excitation wave length: 488 nm; Optos) and swept-source OCTA (central wave length: 1050 nm, scan rate: $\geq$200,000 A-scans/second; VG200D, SVision). This study was conducted adhered to the tenets of the Declaration of Helsinki and was approved by the institutional board of Shanghai General Hospital. Written informed consent was waived by the board due to its retrospective, observational design.

3. Results

3.1. Patient demographics

A total of 35 eyes from 23 patients had signs of retinal microvascular ischemia on multimodal images. One patient was excluded for pancreatitis and one was excluded due to visual symptoms onset before the COVID-19 infection. Finally, 32 eyes from 21 patients were

Table 1
Definitions for all types of lesions in terms of OCT and color fundus images.

	Color fundus image	OCT B scan	
		Acute phase	Chronic phase
CWS	White, white-yellowish, and/or white-grayish lesions	Thickening and increased reflectivity of RNFL	Thinning of RNFL
PAMM	White-grayish lesions	Increased reflectivity of INL/OPL	Thinning of INL
ASHH	No finding	Increased reflectivity of HFL in ONL	Thinning of ONL

CWS = cotton wool sport, PAMM = paracentral acute middle maculopathy, ASHH = Henle fiber layer hyperreflectivity, RNFL = retinal nerve fiber layer, OPL = outer plexiform layer, ONL = outer nuclear layer, HFL = Henle fiber layer.

included in our series, of which 11 (52.38 %) were male and 10 (47.62 %) were female. The median age of the patients was 45 years old (range, 25–75 years old). Regarding their medical history, 8 (38.10 %) patients with a history of hypertension before the COVID-19 infection, and 3 (14.29 %) patients had newly diagnosed hypertension. When referring to patients' blood pressure levels at their first visit to our department, a total of 6 patients reported transient elevated blood pressure over 140/90 mmHg. Three patients had a medical history of diabetes and 1 had overweight; Case #19 has long-term use of warfarin due to heart valve replacement surgery 20 years ago. Furthermore, Case #2 was transferred to the Department of Nephrology due to acute kidney injury. Table 2 summarized the demographics, medical histories, and systematic findings of the enrolled patients.

3.2. Clinical characteristics

The involvement of retinal microvascular ischemia was bilateral in 11 (52.38 %) patients and unilateral in 10 (47.62 %) patients. Only 3 (14.29 %) patients had no visual symptoms, and they all had only one eye affected. These 3 patients visited our department due to trichiasis, conjunctive hemorrhage, and follow-ups post-refractive surgery, respectively. In 18 (85.71 %) patients having visual symptoms, visual acuity decline (11, 52.38 %) was the most common complaint, followed by blurred vision (5, 23.81 %). Their visual acuity at the first visit varied from finger-counting to 20/20, depending on the involvement of the fovea or not. Nineteen (90.48 %) patients had a fever due to COVID-19 infection. They reported visual symptom(s) after the febrile episode. The median interval from the fever recovery to the onset of visual symptoms, if they had any, was 3 days (range, 0–16 days).

Table 2
Demographics, medical histories, and systematic findings of the enrolled patients.

Case ID/Sex/Age (years)	Systematic medical history (HTN/others)	Blood pressure (mmHg)	Laterality	BCVA		Visual symptoms
				OD	OS	
1/M/57	N	/	OU	2/20	2/20	VA decline
2/M/37	Newly diagnosed	227/138	OU	8/20	FC	VA decline
3/F/50	N/diabetes	/	OU	8/20	12/20	VA decline
4/M/40	Y	173/119	OU	16/20	20/20	VA decline
5/M/25	Newly diagnosed/overweight	242/165	OU	20/20	16/20	VA decline
6/F/34	Y/diabetes	160/110	OU	10/20	6/20	VA decline
7/M/31	Y	199/149	OU	8/20	20/20	VA decline
8/F/53	Y	117/72	OD	FC	20/20	Blurred vision
9/F/25	N	/	OU	6/20	FC	VA decline, dark shadow
10/F/48	Newly diagnosed	150/92	OU	3/20	3/20	VA decline
11/M/75	Y	121/72	OU	20/20	20/20	Binocular diplopia
12/M/31	Y	134/83	OU	16/20	16/20	VA decline
13/M/63	Y	125/88	OD	2/200	16/20	Blurred vision, dark shadow
14/F/58	N	/	OS	20/20	20/20	/
15/F/64	N	/	OD	20/20	20/20	/
16/F/57	N	/	OS	20/20	20/20	Blurred vision
17/M/45	Y	134/86	OD	20/20	20/20	Blurred vision
18/M/30	N/diabetes	160/102[a]	OD	20/20	20/20	Blurred vision
19/F/46	N/heart valve replacement surgery, warfarin	/	OD	20/20	20/20	Paracentral scotoma
20/F/72	N	/	OS	6/20	10/20	VA decline
21/M/35	N	/	OS	20/20	20/20	/

HTN = hypertension, Y = yes, N = No, OD = right eye, OS = left eye, OU = bilateral eyes, BCVA = best corrected visual acuity, VA = visual acuity, FC = finger counting.

[a] Only transient high blood pressure was detected in Case #18, and no diagnosis of hypertension was made by internal physicians.

3.3. Multimodal imaging

Retinal microvascular ischemia was presented as CWS and/or paracentral acute middle maculopathy (PAMM) on retinal examination. CWS corresponded to retinal nerve fiber layer (RNFL) swelling on OCT, and filling defects on FFA. The presentation of PAMM based on multimodal imaging included hyperreflective band(s) in the inner nuclear layer (INL)/outer plexiform layer (OPL) with OCT B scans, hyporeflective wedge-shaped lesion(s) with NIR images, and white-grayish lesions on color fundus images. Representative OCT signs of CWS and PAMM are shown in Fig. 1.

Color fundus and NIR images presented the most direct way to detect microvascular ischemia lesions. They were white, white-yellowish, or white-grayish patches. Retinopathy of multiple lesions was a common manifestation in this series, with 24 eyes (75.00 %) from 13 patients. These lesions could be merged or overlapped (Fig. 2A, E, 3A, and 3E). Hyporeflective or hyperreflective patches with explicit boundaries corresponding to the ischemia patches were found on NIR images (Fig. 3C and G). Intraretinal hemorrhage and hard exudation were always detected on fundus images in patients with multiple lesions. Ten (76.92 %) patients with multiple lesions had hypertension, previously diagnosed or newly diagnosed, significantly more than those in patients with isolated microvascular ischemia lesions ($P = 0.008$; Table 3).

OCT and OCTA helped to differentiate superficial capillary ischemia (SCI) and deep capillary ischemia (DCI) from each other. SCI was presented as focal inner retinal swelling and hyperreflective lesions on OCT (Fig. 1, left up). It corresponded to the white or white-yellowish CWS patches on fundus images (Fig. 3A). DCI mainly referred to PAMM lesions, which presented as a hyperreflective band from IPL to OPL (Fig. 1, left bottom; Fig. 5C). It corresponded to the white-grayish patches on fundus images (Fig. 5A). The ischemia in the middle retinal layer was confirmed by En face OCTA images. No abnormality was found on the superficial capillary plexus (SCP) slab (Fig. 5D) or choriocapillaris slab (Fig. 5F), but flow deficit (yellow arrowhead) on the deep capillary plexus (DCP slab; Fig. 5E). The SCI and DCI were independent of each other and can occur separately. However, coincident SCI and DCI were the most common manifestations in patients with multiple lesions (Table 3). Multiple non-perfusion areas were shown on the retinal slab of En face OCTA images (Fig. 2B and F) or FFA images (Fig. 3B and F). The distribution of ischemia types in enrolled eyes were presented in Table 4.

In addition, NIR images combined with OCT helped to detect ASHH in 4 eyes (12.50 %) from 2 patients with multiple lesions. ASHH was presented as a hyporeflective lesion in the perifovea area on NIR images (Fig. 3C and G), hyperreflective bands in Henle fiber layer (HFL)/outer nuclear layer (ONL) associated with ellipsoid zone (EZ)/interdigitation zone (IZ) disruption on OCT [20] (Fig. 3D2 and 3H3). Different from CWS, ASHH could have no significant findings on color fundus (Fig. 3A) and FFA (Fig. 3B) images. ASHH only affects the outer retina.

In addition to the morphological examination, functional assessments such as perimetry evaluated patients' visual performance. Perimetry showed persistent paracentral scotoma in Case #19 (red arrowhead, Fig. 5G).

3.4. Treatments

A total of 3 eyes with macular edema received intravitreous anti-vascular endothelial growth factor (VEGF) treatment (Conbercept, Kanghong Biotech), and one patient (Case #10) received intravenous methylprednisolone pulse therapy from another clinic before her

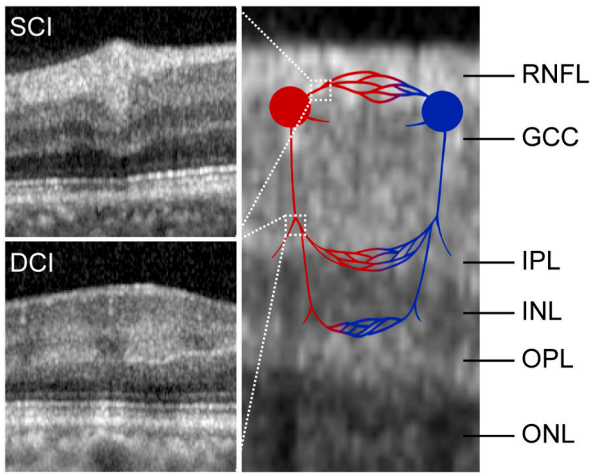

Fig. 1. Schematic diagram of retinal superficial capillary ischemia (SCI) and deep capillary ischemia (DCI) based on OCT images. Retinal arteries and arterioles were in red, while veins and venules were in blue. The capillary network connected the arterioles and veins. The retinal superficial capillary plexus is located at the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) layer. The middle and deep capillary plexus are located on either side of the inner nuclear layer (INL). Pre-capillary arterioles with pathological occlusions are indicated by white dashed squares. Representative resulting OCT signs of SCI and DCI were presented with the magnified OCT B scans on the left column. IPL = inner plexiform layer, OPL = outer plexiform layer, ONL = outer nuclear layer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

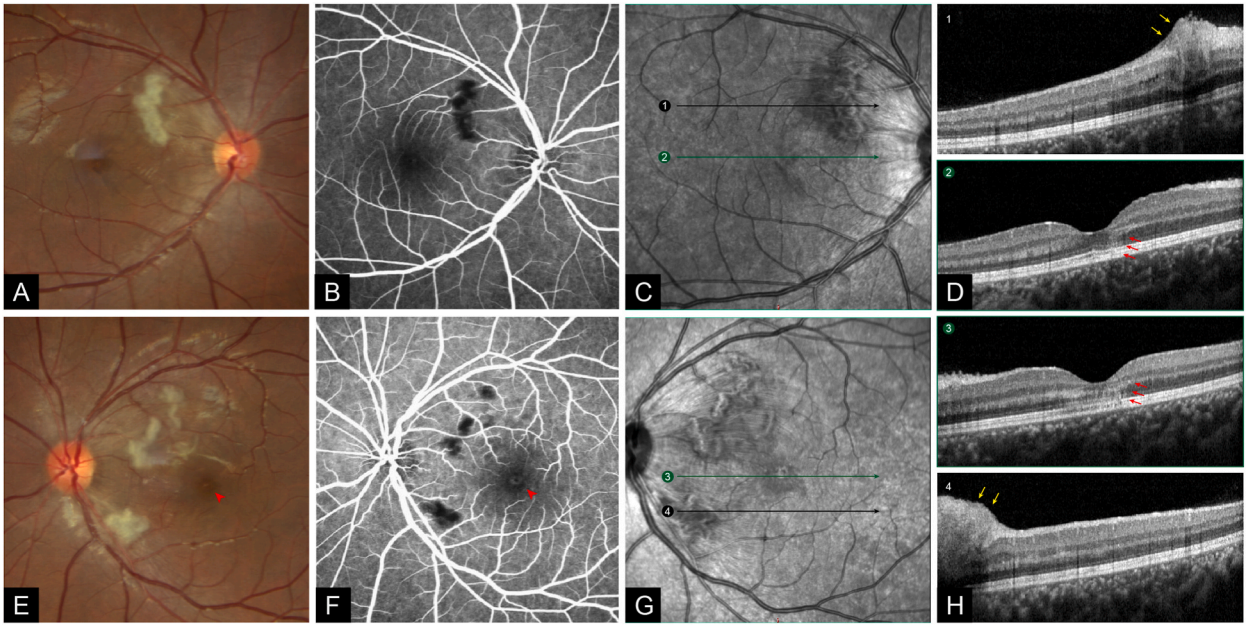

Fig. 2. A case of bilateral multiple lesions of CWS and PAMM (Case #2). (A)–(D), the right eye; (E)–(H), the left eye. (A) and (E), color fundus images. (B) and (F), En face OCTA image of the retinal slab, (C) and (G), NIR images. (D) and (H), OCT B scans. CWS, PAMM, retinal edema, and hard exudation were observed. Red arrows indicated PAMM lesions. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

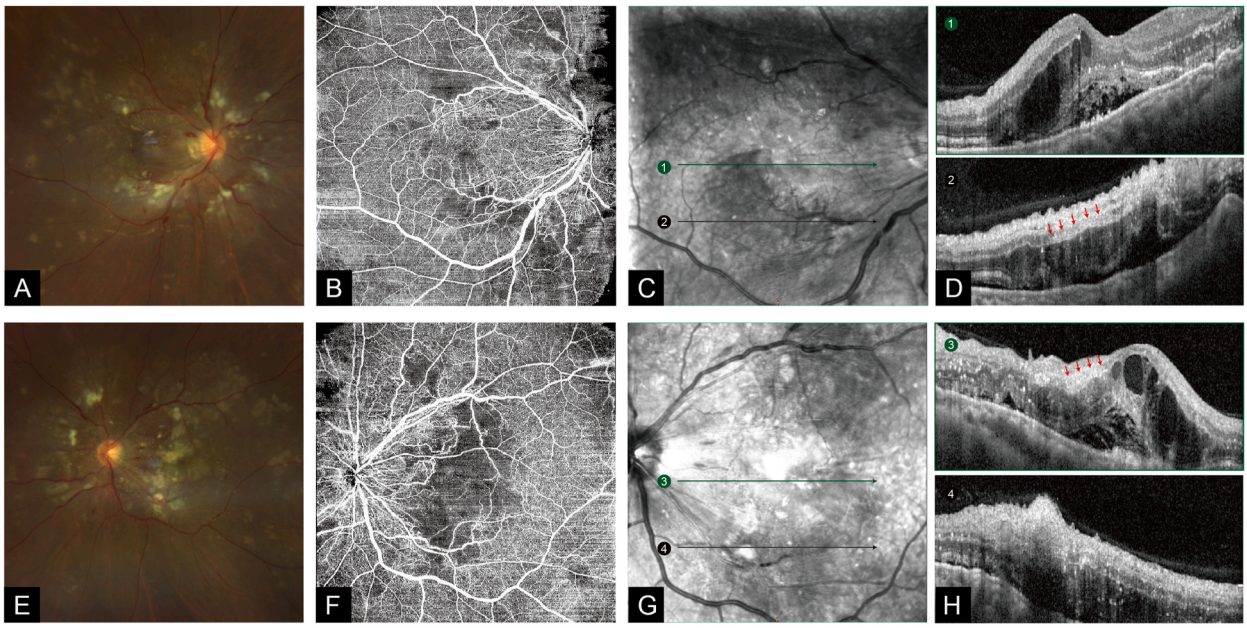

Fig. 3. A case of bilateral multiple lesions of CWS, PAMM, and ASHH (Case #9). (A)–(D), the right eye; (E)–(H), the left eye. (A) and (E), color fundus images. (B) and (F), FFA images. Red arrowheads pointed to a yellowish dot in the left fovea, with a corresponding ring-like hyperfluorescence lesion on FFA. (C) and (G), NIR images. (D) and (H), OCT B scans. Yellow arrows indicated CWS lesions. Red arrows indicated hyperreflective bands in ONL/HFL with EZ/IZ disruption, in both foveae. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Distribution of hypertension and high blood pressure levels in patients with multiple or isolated lesion(s).

Fundus manifestation	HTN	non-HTN	*P* value[a]
Multiple lesions	10	3	0.008
Isolated lesion	1	7	

HTN = hypertension.
[a] *P* value was reported by Fisher's exact test.

Table 4
Distribution of retinal ischemia types in enrolled patients.

Fundus manifestation		Types of ischemia	Number of eyes (%, N = 32)
Multiple lesions	CWS	SCI	4 (12.50)
	PAMM	DCI	1 (3.13)
	CWS + PAMM	SCI + DCI	15 (46.88)
	CWS + PAMM + ASHH	SCI + DCI	4 (12.50)
Isolated lesion	CWS	SCI	5 (15.63)
	PAMM	DCI	3 (9.38)

CWS = cotton wool sport, PAMM = paracentral acute middle maculopathy, ASHH = Henle fiber layer hyperreflectivity, SCI = superficial capillary ischemia, DCI = deep capillary ischemia.

first visit to our departement. Most patients were prescribed methylcobalamin and iodized lecithin for neurotrophic support and exudation relief.

3.5. Representative cases

3.5.1. Case #2, multiple lesions of CWS and PAMM

A 36-year-old male patient complained about acute visual loss for 1 week after COVID-19 associated fever recovery. His best corrected visual acuity (BCVA) was 8/20 of the right eye and finger-counting at 30 cm of the left eye. No medical history of hypertension was noted, but his blood pressure was 227/138 mmHg at this visit. Multiple white-yellowish and white-grayish patches, intraretinal hemorrhage, and stellate hard exudation were found in the bilateral fundus (Fig. 2A and E). Vascular twists were also detected, but no hyperemic optic disc. Corresponding hyporeflective and hyperreflective ischemic lesions were detected on NIR (Fig. 2C and G). Severe retinal swelling was confirmed by OCT B scans (Fig. 2D and H), such as intraretinal fluid, subretinal fluid, and retinal folds. The choroidal folds (Fig. 2D and H) suggested the severity of his fundus pathologies as well. OCT B scans presented the exact types of the lesions, such as CWS (Fig. 2H4) and hyperreflective PAMM lesions (red arrows, Fig. 2D2 and 2H3). Multiple non-perfusion areas were shown on the retinal slab of En face OCTA images (Fig. 2B and F).

The following blood test reported a creatinine of 1241.20 μmol/L (reference, 57–111 μmol/L), indicating renal microvascular impairment as well. Therefore, this patient was referred to internal medicine and hemodialysis was applied by physicians. He also received bilateral intravitreous anti-VEGF treatment (Conbercept) in our department, once each, due to the macular edema. Restricted by his poor systematic conditions, this patient was followed via telephone. Two-month follow-ups showed great improvements in visual function, with his right visual acuity of 20/20.

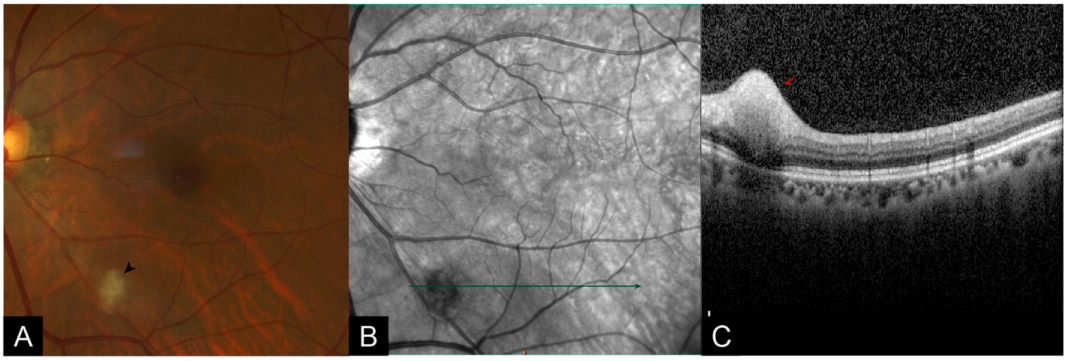

Fig. 4. A case with isolated CWS in the left eye (Case #16). A CWS was detected on the color fundus image (A), indicated by the black arrowhead. (B) and (C) were NIR and the OCT B scan across the lesion, respectively. The red arrow indicated the corresponding inner retinal swelling. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.5.2. Case #9, multiple lesions of CWS, PAMM, and ASHH

A 25-year-old female patient complained about bilateral visual acuity declines 3 days after COVID-19 infection. Her BCVA was 6/20 of the right eye and finger-counting at 30 cm of the left eye. Multiple white-yellowish CWS was found in both of her eyes (Fig. 3A and E), corresponding to multiple hypofluorescence patches on FFA (Fig. 3B and F). A yellowish dot was detected in her right fovea (red arrowhead, Fig. 3E), corresponding to a ring-like hyperfluorescence lesion on FFA (red arrowhead, Fig. 3F). CWS was also confirmed by OCT showing RNFL swelling (yellow arrows, Fig. 3D1 and Fig. 3H4). The representative hyporeflective ASHH in the perifovea areas were presented on NIR images (Fig. 3C and G). OCT B scans across the lesions showed hyperreflective bands in ONL/HFL, as well as EZ/IZ disruption (red arrows, Fig. 3D2 and 3H3). Neurotropic treatment was applied. Her BCVA improved to 8/20 of the right eye and 12/20 of the left eye 9 days after her first visit.

3.5.3. Case #16, isolated CWS lesion

A 31-year-old female patient presented with blurred vision in her left eye since the COVID-19 fever recovery. The visual acuity of her affected eye remained 20/20. An isolated white-yellowish CWS (dark arrowhead) was detected on the fundus image (Fig. 4A). A corresponding hyporeflective lesion on NIR (Fig. 4B) and a hyperreflective lesion in RNFL (Fig. 4C) were also detected.

3.5.4. Case #19, isolated PAMM lesion

A 45-year-old female complained about paracentral scotoma 2 weeks after her COVID-19 associated fever recovery. Her visual acuity was 20/20 of both eyes. Color fundus photography (Fig. 5A) showed a white-grayish patch (red arrows) along the vessels, corresponding to the hyporeflective region in the NIR image (Fig. 5B) with an explicit boundary. On the OCT B scan (Fig. 5C) across the lesion, a hyperreflective band from IPL to OPL was detected. No abnormality was found on the SCP slab (Fig. 5D) or choriocapillaris slab (Fig. 5F) of the En face OCTA, but there was a flow deficit (yellow arrowhead) on the DCP slab (Fig. 5E). Only methylcobalamin was prescribed for neurotropic support. Perimetry (Fig. 5G) showed persistent paracentral scotoma (red arrowhead) 11 days after her first visit. At this follow-up, the blurred hyporeflective lesion on NIR (Fig. 5H), attenuation of the hyperreflective PAMM lesion on OCT (Fig. 5I), and the clear non-perfusion area on the DCP slab (Fig. 5K) could be found. Still, no clinically significant finding was found on the SCP slab (Fig. 5J) or choriocapillaris slab (Fig. 5L).

4. Discussion

In this series, 24 (75.00 %) eyes with COVID-19 related retinal microvascular ischemia had multiple lesions of CWS and/or PAMM, some combined with ASHH. When divided by the types of ischemia, 19 (59.38 %) eyes had combinations of SCI and DCI, 9 (28.13 %) eyes had only SCI and 4 (12.50 %) eyes had only DCI, isolated or multiple. These data must be interpreted with caution due to a possible referral bias, as patients were recruited from a terminal referral center specialized in ophthalmology.

Many studies [11,21] and meta-analysis [22] have demonstrated the high incidence of OCTA-detected, pre-clinically microvascular impairments in post-COVID-19 infection populations. Similar fundus lesion has been reported in other viral infection, such as dengue-related maculopathies [23]. Some might conclude them as post-fever retinitis [24]. Though they do not have a well-defined name, a great important role of retinal microvascular ischemia in these disorders has been recognized.

Multimodal imaging is a useful tool to detect and analyze COVID-19 related retinal microvascular ischemia. The most distinguished fundus findings were multiple white, white-yellowish, and/or white-grayish lesions (also known as Purtscher flecks in Purtscher-like retinopathy) or isolated patches on color fundus images. The color and intensity of the lesions varied depending on their ischemia types and stages. Apparent hyporeflective PAMM lesions with well-defined edges can be found on NIR during the acute stage of ischemia. Instead, the CWS lesions on NIR might be hyporeflective due to outer retinal signal blockage, or be hyperreflective due to the signal reflection from the high density of chalk-white CWS. Then with atrophy occurred, the darkening of the lesions became subtle and the edges blurred (Case #19).

The exact ischemia types had to be determined by OCT, to differentiate CWS resulting from SCI and PAMM lesions resulting from DCI. During the acute stage of ischemia, thickening and increased reflectivity of the corresponding layers was noted, possibly caused by intracellular edema secondary to ischemia. Atrophy and thinning of the corresponding layer were unavoidable in the chronic stages. Because FFA provides a two-dimensional retinal perfusion map, and OCTA provides a three-dimensional perfusion pattern and can have it segmented into different capillary complexes as well [25]. Evidence of retinal ischemia can be provided by both FFA (Case #9) and OCTA (Case #2), but only OCTA can provide information about the DCP flow deficit (Case #19) [26].

With the help of NIR and OCT images, we also detected ASHH in 12.50 % of enrolled eyes. ASHH is a descriptive OCT features referring to AMN-like lesions. Previous literature erroneously adopted the disease entity “AMN” to describe OCT changes in various retinal disorders, for example Dengue maculopathy and Whiplash maculopathy. The exact pathogenic etiology of ASHH is still controversial, choroid capillary ischemia [27], retinal DCI [28,29], or inflammation. Anatomically, the DCP mainly provides retinal perfusion to INL, and its distal ends also nourish parts of the ONL [30]. Based on no significant findings on OCTA choriocapillaris slab (Fig. 5F and L) and according to the principles of monism, we proposed retinal DCI, especially ischemia in the outermost portion of the INL as the cause of ASHH in our series. Iovino et al. [20] reported the frequent association of coincident PAMM and ASHH with retinal vein occlusion. Then they postulated that the common cause was the impairment of the venous outflow channels of the DCP [20]. It could be a possible explanation, with the high post-capillary pressure transmitted to the pre-capillary arterioles, then the infarction of the pre-capillary arterioles, and finally capillary ischemia. Therefore, pre-capillary retinal arterioles infarction in DCP should be considered as the direct pathology in coincident PAMM and ASHH.

Despite of focal retinal circulation alternation, changes of entire retinal microcirculations were also hypothesized to contribute to

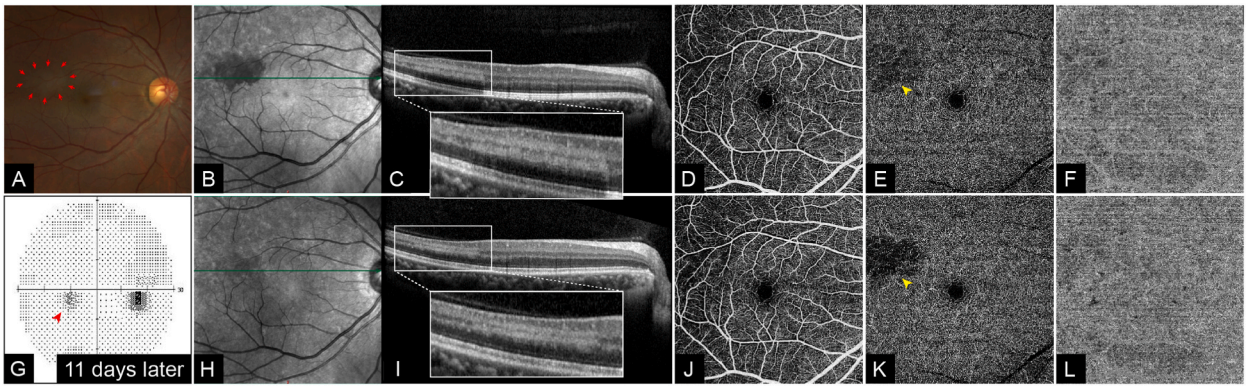

Fig. 5. A case with isolated PAMM in the left eye (Case #19). (A)–(F), multimodal images at baseline; (G)–(L), images 11 days later. (A), color fundus images. Red arrows surrounded indicated a white-grayish patch. (B), NIR and (C), OCT B scan. The PAMM lesion was magnified. No abnormality was found on the SCP slab (D) or choriocapillaris slab (F) of the En face OCTA, but there was a flow deficit (yellow arrowhead) on the DCP slab (E). (G) showed persisted paracentral scotoma (red arrowhead) on perimetry. At this follow-up, the blurred hyporeflective lesion on NIR (H), attenuation of the hyperreflective PAMM lesion on OCT (I), and the clear non-perfusion area on DCP slab (K) could be found. Still, no clinically significant finding was found on the SCP slab (J) or choriocapillaris slab (L). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

these retinal findings in patients with COVID-19. Reduced microcirculation was recognized with COVID-19 infection [31,32]. Kulikov et al. reported general nonspecific changes in retinal microvasculature in eyes with coincident PAMM and ASHH, including a decrease in the vessel density of SCP and distortion of the foveal avascular zone [33]. Preservation of perfusion in focal PAMM lesions but pruning of the plexus was found in old cases [34] as well. Thus, COVID-19 introduced retinal perfusion reduction should be considered in PAMM and in the spectrum of retinal microvascular ischemia in this study.

There is no established treatment for COVID-19 associated microvascular ischemia. Observation, neurotrophy, and corticosteroid were the 3 main treatment modalities [16,35–38]. To the best of our knowledge, this is the first report of the anti-VEGF application in COVID-19 associated retinopathy with macular edema. Quick recovery of the macular structure as well as the visual function supported the rationale of this treatment. A short-term follow-up of isolated PAMM lesion showed that atrophy occurred and visual defect persisted. Reduced retinal perfusion was still expected in these patients in the long-term, as observed in the patients recovered from COVID-19 infection [39]. We need to understand the retinal changes caused by COVID-19 mainly because not only the retinal vascular systems will be affected, but also the systemic circulatory system may be attacked. The retinal findings might be labeled as acute hypertensive retinopathy in patients with hypertensive emergency. However, considering systematic vascular disorders were closely correlated with COVID-19 infection, retinal microvascular ischemia reported in this study was always COVID-19 infection correlated, but in an indirect manner. Furthermore, Romero-Castro et al. reported clinical correlation between retinal diseases and more severe systemic organ damage, suggesting that new retinal findings with recent COVID-19 infection is a predictor of more severe illness [40]. In this study, several patients only had visual complaints and visited the department of ophthalmology first, but further systematic examination revealed life-threatening disorders such as acute renal failure and malignant hypertension. So, retinal multimodal imaging may not only reveal retinal microvascular ischemia, but also indicate systematic microvascular impairment in patients with COVID-19.

The main limitations of this case series were its retrospective nature and the relatively small sample size. A causal relationship between COVID-19 infection and retinal microvascular ischemia was not fully determined, and the quantitative correlations between the severity of COVID-19 infection, systemic complications, ischemia severity in other organs, and retinal ischemia was not established. However, this series enrolled patients with retinal microvascular ischemia during the high-incidence period of COVID-19 infection, and carefully reviewed their medical history and the course of visual impairment. These study designs empowered the association between retinal microvascular ischemia and COVID-19 infection. Further fundus examinations in a COVID-19 infection cohort are warranted. It should be noted that retinal artery/vein occlusion was not included for the involvement of the first three bifurcations of the retinal vessels (arterioles or venules). Simple ASHH was also excluded due to the possible cause of choriocapillaris ischemia.

5. Conclusions

Retinal microvascular ischemia due to COVID-19 infection could be unilateral or bilateral involvement, most shown as multiple lesions. It may present as CWS resulting from SCI, and PAMM with or without ASHH resulting from DCI. Multimodal imaging is a useful tool to detect retinal ischemic lesions, to locate the affected retinal layer, and to evaluate their pathological severities. Furthermore, it offers a unique "window" that may non-invasively reflect the microvascular impairment in other systems.

Data availability

All data to support the conclusions have been provided in the manuscript and in the Supplementary materials.

Precis

Ocular manifestations of COVID-19 associated microvascular ischemia can be variable, including CWS resulting from superficial capillary ischemia, and PAMM with or without ASHH resulting from deep capillary ischemia. They may serve as a window to indicate the influence of COVID-19 on the microvasculature of other systems throughout the body.

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CRediT authorship contribution statement

Min Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Junran Sun:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation. **Chanchan Wang:** Writing – review & editing, Methodology, Data curation. **Li Su:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Jieqiong Chen:** Writing – review & editing, Resources, Data curation. **Yimin Wang:** Writing – review & editing, Validation, Investigation, Funding acquisition, Formal analysis, Data curation. **Xiaodong Sun:** Writing – review & editing, Project administration, Funding acquisition. **Yuanyuan Gong:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Suqin Yu:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing 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.

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