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Retinal autofluorescence findings after COVID-19

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Abstract

The main purpose of this study was to investigate the presence of retinal autofluorescence findings in COVID-19 patients. Observational study conducted in São Paulo in 2020. Demographic, medical history, and concomitant events, as well as medications used, hospitalization details, and laboratory test results, were obtained. Patients underwent eye examination and multimodal imaging, including color, red-free, autofluorescence fundus photography and optical coherence tomography. Eighteen patients had autofluorescence findings (6 females; average age 54 years, range 31 to 86 years; 26 eyes). Hyper-autofluorescence findings were present in 6 patients, Hypo-autofluorescence in 14 patients, and 6 patients had mixed pattern lesions. Retinal autofluorescence abnormalities were present in COVID-19 patients and may be secondary to primary or secondary changes caused by the SARS-CoV-2.

Keywords: Coronavirus, SARS-CoV-2 disease, Eye, Optical coherence tomography, Autofluorescence

Introduction

Early clinical evidence suggests that cases of COVID-19 are frequently characterized by increased inflammation, renin-angiotensin-aldosterone system (RAS) imbalance, and a particular form of vasculopathy, thrombotic microangiopathy, and intravascular coagulopathy [1].

The retina could be affected either by direct tissue damage from SARS-CoV-2 and its immunogenicity or by thrombotic complications [2, 3]. Primary or secondary retinal abnormalities mostly related to vascular structures have been reported on multimodal imaging studies [4–6].

Fundus autofluorescence (FAF) imaging provides a topographic mapping of lipofuscin distribution in the retinal pigment epithelium (RPE) cell monolayer, and other fluorophores occur with the outer retina and the sub-neurosensory space [7]. This study aims to investigate FAF findings in COVID-19 patients.

Methods

The study was approved by the institutional and national ethics research committees (Research Ethics Committee of Federal University of Sao Paulo UNIFESP #30725020.8.0000.5505 and INVITARE Pesquisa Clínica Auditoria e Consultoria Institutional Review Board Ethics Committee number 3.975.953). All patients or their representatives agreed to participate.

We conducted a observational study evaluating outpatients with confirmed COVID-19 diagnosis based on positive antibody tests (immunoglobulin G and immunoglobulin M titers) or PCR (using nasal/oral swabs). Patients with previous ophthalmological history and patients for whom fundus exam was impossible were excluded.

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Demographic and clinical information covering medical history, concomitant medical events and medications, hospitalization details, and laboratory tests were obtained. Ophthalmic examination included measurement of best-corrected visual acuity (BCVA), Goldman applanation tonometry (IOP), and both anterior and posterior biomicroscopy. Binocular indirect fundus examination and color, red-free, and autofluorescence fundus photography were performed (Topcon DRI-OCT Triton Swept-source OCT, and California Optos®). Optical coherence tomography (OCT) imaging included: Angio Retina 3.0 mm^2; HD Angio Retina 6.0 mm^2; Enhanced HD Line; Cross Line; Raster; Radial Lines; Ganglion cell complex (GCC) (Optovue RTVue-XR Avanti®).

Table 1 Patients demography (n = 18)

	Median ± SD
Age	54 ± 15 years
Female	6 (33%)
BCVA OD	0.15 ± 0.25 (20/28)
BCVA OS	0.09 ± 0.17 (20/24)
Days between symptoms onset and evaluation	44. (±24 days)
Type 2 diabetes	2 (11%)
High blood pressure	6 (33%)
Diabetes and high blood pressure concomitantly	2 (11%)

The data were analyzed using the STATA 14.0 program (StataCorp LP, College Station, TX, USA). Frequency tables were used for descriptive analyses.

Results

In late 2020, as part of the eye examination of a group of 106 patients, 18 patients with FAF changes were identified. The average time between diagnosis and the first eye exam was 44 days (±22 days), we've considered this time frame to start with symptoms onset. None of the patients had a previous ophthalmologic history, specially concerning previous ocular inflammation. All patients were evaluated at a convalescence period and disease severity ranged from mild to severe. We have considered severe cases patients whom required mechanical ventilatory support, moderate cases the ones whom required hospitalization but non-invasive ventilation and mild cases the ones without hospitalization. Of the 18 patients, 12 required previous hospital admission and were examined after hospital discharge. Table 1 presents data regarding epidemiology and clinical examination.

Among the 18 patients, 10 had findings only in one eye and 8 in both eyes. Most of these were depicted at posterior pole (16 eyes) and 4 other eyes had alterations contiguous to the optic nerve. Hyper-autofluorescence (HyperFAF) (Fig. 1) was present in 6 eyes of 5 patients (27.8%–5/18), and one eye presented with uniquely HyperFAF. OCT of those areas was associated with the outer retina findings, mainly in the interdigitation and ellipsoid zones (Fig. 1). Hypo-autofluorescence

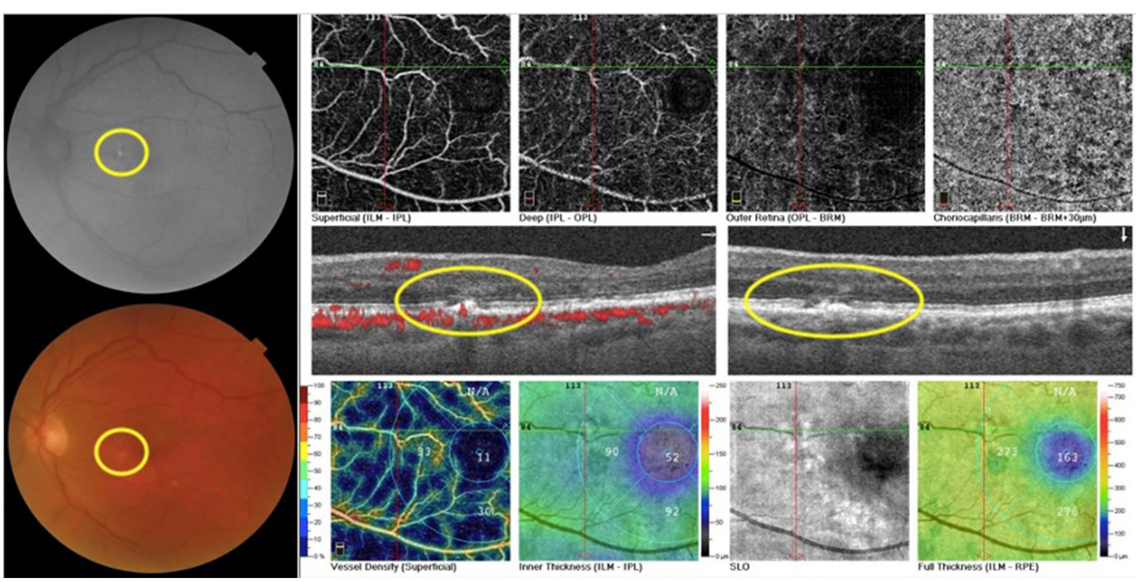

Fig. 1 Composite of the left eye of patient 7. Composite depicts a hypopigmented area in the papillomacular bundle more evident as a hyper-autofluorescent lesion on FAF. OCT B-scan of the lesion displays RPE irregularity with adjacent cell loss in the ellipsoid zone

(HypoFAF) (Fig. 2) was present in 18 eyes of 14 patients (77.8%–14/18). OCT of those areas was associated with outer retina cell loss and RPE elevation. One eye also presented with subretinal fluid.

Seven eyes of 6 patients (33.3%–6/18) showed mixed patterns of hyper-autofluorescence and hypo-autofluorescence. These findings were predominantly seen adjacent to vascular structures, especially veins, in different retinal areas (Figs. 3 and 4). OCT findings of retinal thinning were associated with a disturbance of the ellipsoid zone, photoreceptors outer segments, and interdigitation zone (Figs. 3 and 4).

Table 2 presents the correlation between autofluorescence patterns, OCT findings and patient data.

Discussion

FAF is a non-invasive diagnostic tool that documents the metabolic status of lipofuscin levels throughout the eye's posterior pole. It can be a helpful marker of outer retinal health helpful in monitoring various ophthalmic

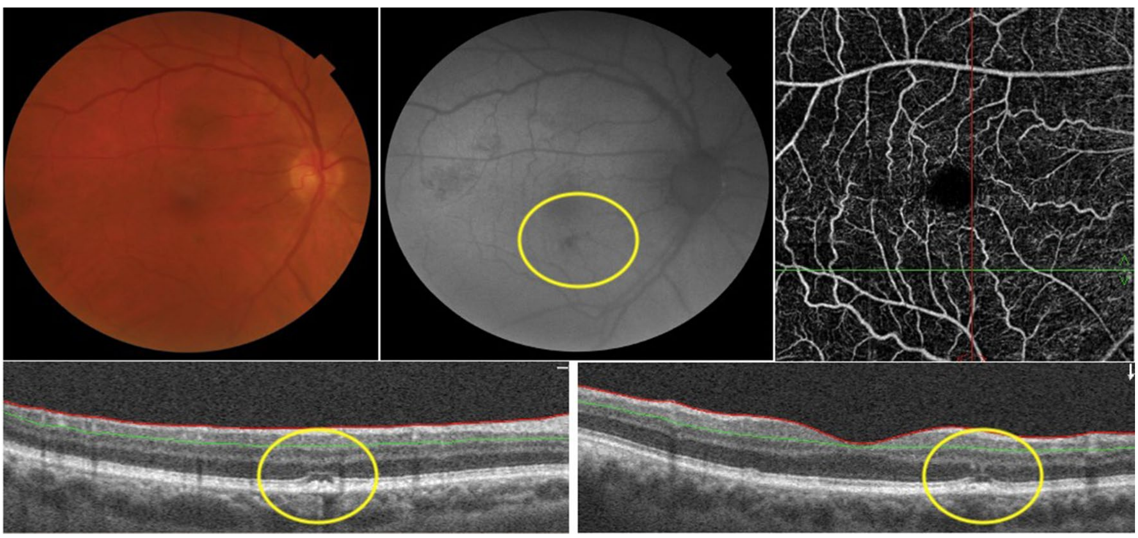

Fig. 2 Composite of the right eye of patient 7. Image shows a hypopigmented area in the papillomacular bundle more evident as a hypo-autofluorescent lesion on FAF. OCT B-scan of the lesion displays RPE irregularity with adjacent cell loss in the ellipsoid zone

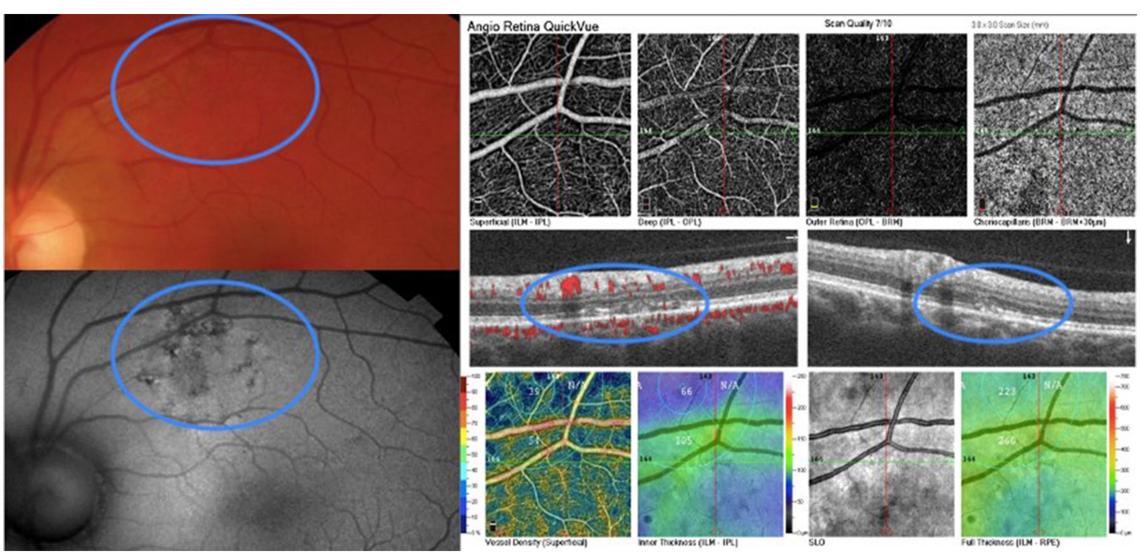

Fig. 3 Composite of the left eye of patient 6. FAF shows a retinal alteration more prominent at FAF with a mixed pattern of hyper-hypoFAF. OCT B-scan of the area displays disruption of the interdigitation zone, outer segment layer, and ellipsoid zone

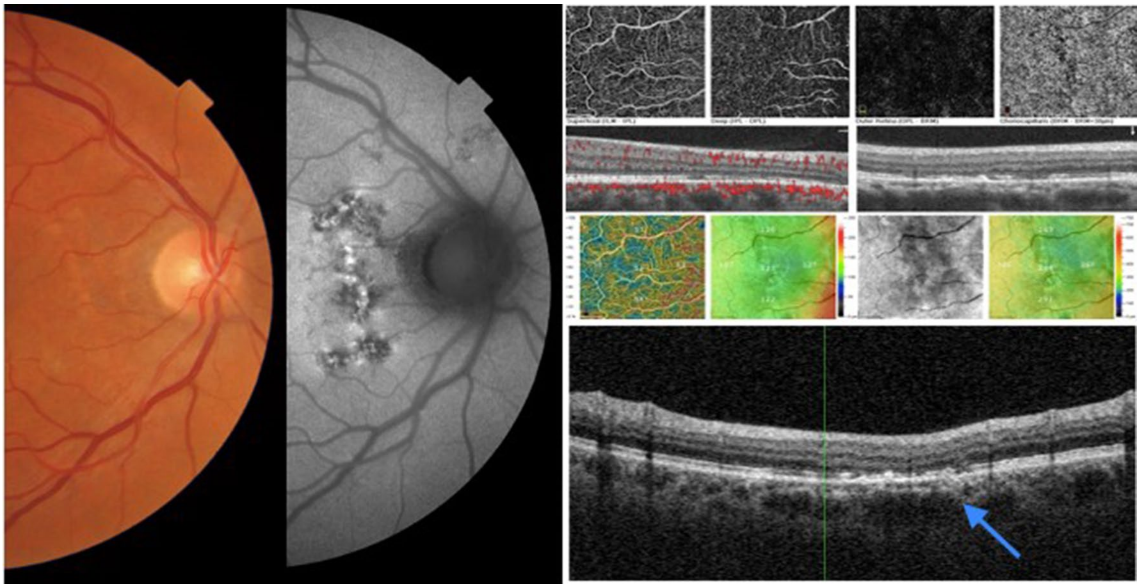

Fig. 4 Composite of the right eye of patient 10. This composite shows a retinal alteration more prominent at FAF with a mixed pattern of hyper-hypoFAF. OCT B-scan displays retinal thinning due to loss of external retina layers and outer nuclear layer

conditions, including uveitis or photoreceptor diseases. HyperFAF patterns are often related to active retinal pigmentary epithelium inflammation, and HypoFAF patterns are found in chronic and scar lesions.

The FAF patterns reported here appeared similar to those previously described in other diseases, such as syphilis [8], tuberculosis [9], inflammatory maculopathies [10], and even age-related macular degeneration [11] and may implicate pathogenic mechanisms. Our small sample prevented us the use of multiple logistic regressions to assess whether comorbidities, treatment performed, or changes in laboratory tests were related to the ophthalmological findings. Since the descriptive nature of the study aiming to report the FAF findings in patients its valuable to emphasize the multiple confusing factors, specially the heterogeneity of the population involved.

Fundus autofluorescence results from the interaction between natural fluorophores and the adjacent tissues, and variety of clinical COVID-19 presentations [12–15] can explain the broad spectrum of findings [12]. Schmitz-Valckenberg et al. have previously reported that inflammatory diseases may present different pattern of FAF over time [16], and according to the affected area, it can appear hypo-autofluorescent early and mixed later on.

Previous publications have reported retinal findings in COVID19 patients [5, 12–15, 17, 18]. FAF alterations have been presented among case reports [17–19] and the frequency has increased since the beginning of the pandemic. To our knowledge this is the biggest number of cases congregated and, in face of a new and still poorly understood disease, a more detailed analysis of the RPE-choriocapillaris complex may contribute to the better understand of COVID-19 pathophysiology in the eye ant it's presumed effect, bring new light in it's pathophysiology. The high prevalence of a hyper-hypo-autofluorescence pattern near vascular structures suggests that vessels may be preferentially affected, which agrees with other studies suggesting a vascular component to the SARS-CoV-2 pathogenesis [20, 21].

Conclusions

Autofluorescence may be an useful resource to detect lesions otherwise missed. The presence of hyper-autofluorescence speaks in favor of acuter lesions and towards a somewhat neglected RPE-choriocapillaris complex disfunction. Further investigation is mandatory to better understand the pathophysiology and presumed long term implications.

Table 2 Correlation between autofluorescence patterns, OCT findings and patient data

	Age (Years)	Comorbidities	FAF patterns		OCT Findings		Hospitalization	IOT	Anticoagulation	Antibiotic	D-dimer
			Right eye	Left eye	Right eye	Left eye					
1	51	None	HypoFAF	HypoFAF	RPE irregularity	RPE elevation	N	N	N	N	N
2	82	None	Hypo-hyper-FAF	Isolated areas of HypoFAF and HyperFAF	Choroidal irregularity with area of RPE disruption and subretinal fluid	Area of cellular loss at the level of the ellipsoid zone	Y	N	–	–	–
3	51	None	HypoFAF	None	Cystoid spaces in the interdigitation zone	None	N	N	N	N	N
4	63	High blood pressure and diabetes	None	HypoFAF	None	Cellular loss at ellipsoid zone	Y	Y	Y	N	1.20 ng/mL
5	53	None	Isolated areas of HyperFAF and isolated areas of HypoFAF	Isolated areas of HyperFAF and isolated areas of HypoFAF	Disruption of the interdigitation zone	Disruption of the interdigitation zone with local retinal thinning	Y	N	N	Y	0.45 ng/mL
6	86	None	Hypo-hyper-FAF	Hypo-hyper-FAF	Disruption of the interdigitation zone, outer segment layer and ellipsoid zone	Disruption of the interdigitation zone, outer segment layer and ellipsoid zone	Y	N	N	Y	1.63 ng/mL
7	51	High blood pressure and diabetes	HypoFAF	HyperFAF	RPE irregularity with subretinal liquid and disruption of the ellipsoid zone	RPE irregularity with adjacent cell loss at the ellipsoid zone	Y	N	N	N	0.53ng/mL
8	69	None	Hypo-hyper-FAF	HypoFAF	RPE elevation	RPE irregularity	Y	N	N	Y	N
9	66	High blood pressure	HypoFAF	None	External limiting membrane irregularity	None	Y	N	Y	Y	0.61 ng/mL
10	49	None	Hypo-hyper-FAF	HypoFAF	Retinal thinning and loss of external retina and outer nuclear layers	RPE elevation and outer retinal layer loss	No	No	No	No	–
11	57	High blood pressure	None	Hypo-hyper-FAF	None	Retinal thinning due to loss of external retinal and outer nuclear layers	Y	N	N	Y	0.71 ng/mL
12	62	High blood pressure	HypoFAF	None	Retinal Pigmented Epithelial Detachment and adjacent loss of ellipsoid zone	None	Y	N	Y	N	–
13	48	None	Isolated areas of HyperFAF and HypoFAF	None	RPE elevation	None	Y	N	–	–	0.85 ng/mL

Table 2 (continued)

	Age (Years)	Comorbidities	FAF patterns		OCT Findings		Hospitalization	IOT	Anticoagulation	Antibiotic	D-dimer
			Right eye	Left eye	Right eye	Left eye					
14	31	None	None	HypoFAF	None	Disruption of the interdigitation and outer segment layers and adjacent scarring	--	--	N	N	N
15	35	None	HypoFAF	None	None	None	N	N	N	Y	N
16	58	High blood pressure	HypoFAF, with surrounding area of HyperFAF	None	Disruption of external retina with adjacent scarring	None	Y	N	Y	Y	0.93 ng/mL
17	34	None	HypoFAF	HypoFAF	RPE and ellipsoid irregularity	RPE irregularity and elevation	Y	N	N	N	1.80 ng/mL
18	41	None	Hypo-hyper-FAF	None	Choroidal elevetaion	None	N	N	N	N	N

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Authors' contributions
PMM, AAAM, AMCB wrote the manuscript. PM, AM, AB, WMM, VS were responsible for data collection. PMM, ACR, RBR, MF analyzed and interpreted the data. PS, MF, PA, HS and RBJ were major contributors in writing and reviewing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional and national ethics research committees under the following parameters: CAAE: 30725020.8.0000.5505, approval number 4.100.149, available at https://plataformabrasil.saude.gov.br.

Consent for publication
All patients or their representatives agreed to participate through written agreement according to the consent included as supplementary material.

Competing interests
Marinho, Marcos, Branco, Mourad, Sakamoto, Romano, Farah, Rosen, Schor, Abraao, Nascimento, Belfort Jr declare no competing interests.

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