ADULT-ONSET FOVEOMACULAR VITELLIFORM DYSTROPHY EVALUATED BY MEANS OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

A Comparison With Dry Age-Related Macular Degeneration and Healthy Eyes

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Purpose: To investigate alterations of superficial and deep retinal vascular densities, as well as of choroidal thickness, in patients affected by adult-onset foveomacular vitelliform dystrophy (AOFVD).

Methods: A total of 22 eyes (15 patients) affected by AOFVD were recruited in the study. Furthermore, 20 eyes of 20 healthy subjects and 20 eyes of 18 patients affected by intermediate dry age-related macular degeneration (AMD) were enrolled. All patients underwent a complete ophthalmologic examination, including optical coherence tomography angiography. Outcome measures were superficial vessel density, deep vessel density, and choroidal thickness.

Results: Parafoveal superficial vessel density was increased in patients with AOFVD compared with the AMD group (50.6 ± 4.3% and 46.3 ± 4.3%, respectively, $P = 0.016$). Parafoveal deep vessel density was 57.9 ± 6.4% in patients with AOFVD, 52.2 ± 3.8% in patients with AMD, and 52.7 ± 6.0% in healthy controls ($P = 0.006$ and $P = 0.035$, respectively, after comparison with the AOFVD group).

Conclusion: We demonstrated that both superficial and deep vessel densities were significantly increased in patients with AOFVD, after the comparison with intermediate patients with AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in AMD and that optical coherence tomography angiography could be useful in differentiate early stages of these two diseases.

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Adult-onset foveomacular vitelliform dystrophy (AOFVD) is a clinically heterogeneous maculopathy first described by Gass[1] in 1974. The disease typically manifests between the fourth and sixth decades of life, showing subfoveal (SF) bilateral, asymmetric, yellowish deposits.[1] Several clinicopathologic studies in AOFVD eyes showed these deposits being composed by lipofuscin pigments derived from photoreceptor and retinal pigment epithelium (RPE) cell damage.[2,3] Nevertheless, AOFVD is clinically miscellaneous because SF lesions show heterogeneity in appearance.[4–6] Then, AOFVD may mimic other conditions, the latter aspect leading to AOFVD being often misdiagnosed as age-related macular degeneration (AMD). Moreover, AOFVD can be complicated, as well as AMD, by choroidal neovascularization and geographic atrophy.

Optical coherence tomography angiography (OCTA) has been developed to study retinal and choroidal microvasculature without needing for the dye injection and has let us to study both the superficial and the deep retinal vascular plexuses.[7,8]

In this study, we used an OCTA system based on a spectral domain optical coherence tomography (SD-OCT) device using a split-spectrum amplitude decorrelation angiography algorithm. The main aim

of this study was to investigate superficial and deep retinal vascular densities, as well as choroidal thickness, in AOFVD eyes. Moreover, we compared the latter parameters between AOFVD and AMD eyes.

METHODS

Study Participants

We prospectively enrolled 22 eyes (15 patients) affected by AOFVD who consecutively presented to the University Gabriele D'Annunzio Department of Ophthalmology, between April 2015 and February 2016. University Gabriele D'Annunzio institutional review board approved this study and all patients gave informed consent to the use of their data.

The diagnosis of AOFVD was based on 1) age ≥50 years; 2) macular yellowish deposits on fundus examination; 3) fundus autofluorescence images showing hyper-autofluorescent spots; 4) fluorescein angiography exhibiting late staining, without leakage; 5) indocianin green angiography without any sign of choroidal neovascularization. We enrolled only patients affected by either the vitelliform (characterized by hyper-reflective material located between the photoreceptor layer and the RPE) or the pseudohypopyon (in which a partial reabsorption of the vitelliform material occurred) or the vitelliruptive stage. Moreover, patients in the atrophic/fibrotic stage were not enrolled.

Moreover, 20 eyes (18 patients) affected by intermediate AMD were recruited, to compare AOFVD and AMD eyes. The staging was based on the clinical AMD classification proposed by Ferris FL et al in 2013[9] as follows: persons with medium drusen (63–125 μm), but without pigmentary abnormalities, should be considered to have "early AMD"; persons with large drusen (>125 μm) or with pigmentary abnormalities associated with at least medium drusen should be considered to have "intermediate AMD." No patients affected by late AMD (neovascular AMD or geographic atrophy) were considered for the analysis. Staging was determined by two independent investigators in a blind manner and any discrepancies were resolved by consensus between these two observers.

Only patients with a best-corrected visual acuity of at least 0.5 logMAR (Snellen acuity of 20/63) were recruited.

Exclusion criteria for both AOFVD and AMD eyes were evidence or history of neovascularization, presence of geographic atrophy, previous ocular surgery (included anti-vascular endothelial growth factor therapy), any maculopathy secondary to causes other than both AOFVD and AMD (including the presence of an epiretinal membrane or vitreomacular traction syndrome), refractive error greater than three dioptres (because it has been known that high myopia affect choroidal thickness[10]), and significant media opacities.

All patients underwent a complete ophthalmologic examination which included measurement of best-corrected visual acuity, intraocular pressure, fundus examination, fundus autofluorescence, fluorescein angiography, and OCTA.

A healthy control group homogenous for age and sex (20 eyes of 20 patients) was also included in the current analysis. All control subjects also underwent a complete ophthalmologic examination, including best-corrected visual acuity, intraocular pressure, fundus examination, and OCTA.

Therefore, to avoid the circadian choroidal changes could influence our results,[11] all the tests were done during the morning. Finally, because it has been shown that cigarette smoking leading to a significant increase in choroidal thickness up to 1 hour after,[12] all the subjects were advised not to smoke 1 hour before the examination.

Outcome measures included: 1) foveal superficial vessel density; 2) parafoveal superficial vessel density; 3) foveal deep vessel density; 4) parafoveal deep vessel density; 5) SF choroidal thickness; 6) foveal macular thickness; and 7) parafoveal macular thickness.

Procedures

Spectral domain optical coherence tomography angiography with XR Avanti. XR Avanti AngioVue OCTA (Optovue Inc, Fremont, CA) is a device with a high-speed of 70,000 axial scans per second, using a light source of 840 nm, and an axial resolution of 5 μm. The AngioVue OCTA system based on split-spectrum amplitude decorrelation angiography algorithm (Version: 2015.100.0.35) uses blood flow as intrinsic contrast.[13] In addition, the SD-OCT tool was able to acquire the standard structural OCT

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scans typically used by commercially available devices.

Before imaging, each subject's pupil was dilated with a combination of 0.5% tropicamide and 10% phenylephrine. Study participants underwent SD-OCT imaging following a protocol that included AngioVue OCT 3D volume set of 3 mm × 3 mm, consisting of 304 pixels × 304 pixels in the transverse dimension. An internal fixation light was used to center the scanning area. The OCT signal position and quality were optimized by means of the "Auto All" function which performs in sequence with 1) the "Auto Z" function to find the best position for obtaining the retina OCT image; 2) the "Auto F" function to find the best focus for the particular subject's refraction; and 3) the "Auto P" function to find the best polarization match for the particular subject's ocular polarization.

One FastX (horizontal raster) set and one FastY (vertical raster) set were performed for each acquisition scan. Each set took approximately 3 seconds to complete. The software then performed the motion correction technology to remove saccades and minor loss of fixation. Scans with low quality (i.e., if the subject blinked or if there were many motion artifacts in the data set) were excluded and repeated until good quality was achieved. Three scans for each patient were captured, then the best one for quality (without significant motion artifacts and with a signal strength index >60) was considered for the analysis.

Vascular layer segmentation and vessel density analysis. Vascular retinal layers were visualized and segmented as previously described.[14–17] To evaluate the superficial retinal plexus, we used a layer thickness of 60 μm from the inner limiting membrane, to include all the vessels of this plexus. Furthermore, to visualize the deep retinal plexus, we used a 30-μm thick layer 30 μm from the inner plexiform layer, for the purpose of visualizing the plexus in its entirely. We decided to use a fixed-thickness slab though the inner retinal layers are not anatomically damaged in our patients, as well as to increase the objectivity in the evaluation, as previously shown.[16,17] Two investigators checked the segmentation quality before testing vessel density and were able to finely adjust the slab positioning to ensure a correct visualization of both the superficial and the deep vascular plexuses.

Objective quantification of vessel density was evaluated for each eye using the split-spectrum amplitude decorrelation angiography software. Quantitative analysis was performed on the OCTA en face image using the AngioVue software. The vessel density was defined as the percentage area occupied by vessels in a circle region of interest centered on the center of the foveal avascular zone (FAZ) and with a diameter of 2.5 mm (Figures 1–3). The AngioVue software automatically split the region of interest into two fields: 1) the foveal area, a central circle with a diameter of 1 mm; and 2) the parafoveal area that constitutes the remaining part inside the region of interest.

The AngioVue software automatically outputs the vessel density percentage inside the foveal area (foveal vessel density) and the parafoveal area (parafoveal vessel density).

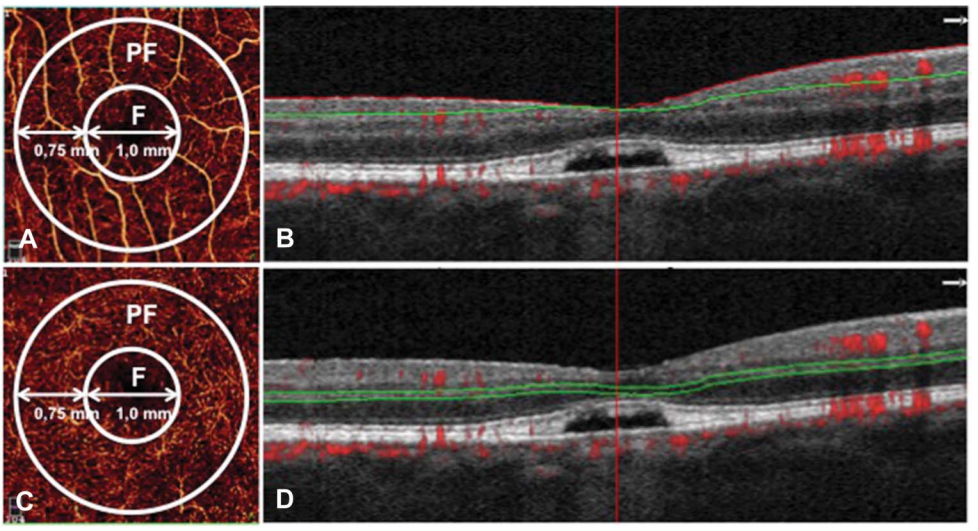

Fig. 1. Optical coherence tomography angiography (OCTA) from an enrolled adult-onset foveomacular vitelliform degeneration patient. **A.** Optical coherence tomography angiography macula 3 × 3 scan showing the superficial vascular plexus. The superficial vascular plexus flow density was defined as the percentage area occupied by vessels in a circle region of interest centered on the center of the foveal avascular zone and with a diameter of 2.5 mm. The AngioVue software automatically split the region of interest, as well as the superficial vascular plexus flow density evaluation, into two fields: 1) the foveal area (F), a central circle with a diameter of 1 mm; and 2) the parafoveal area (PF) that constitutes the remaining part inside the region of interest. The PF superficial vascular plexus vessel density data were analyzed; (**B**) OCT B-scan showing the slab set to evaluate the superficial retinal plexus; (**C**) OCTA macula 3 × 3 scan showing the deep vascular plexus; and (**D**) OCT B-scan showing the slab set to evaluate the deep retinal plexus.

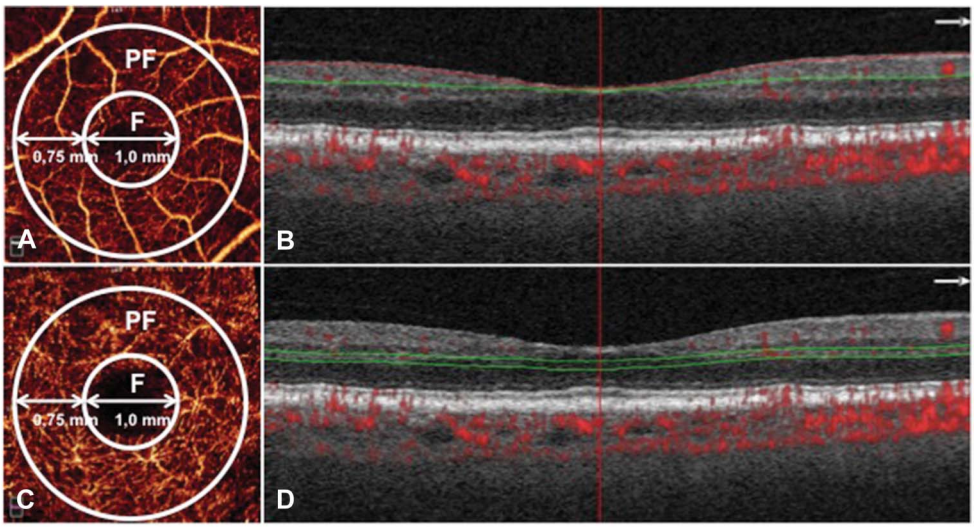

Fig. 2. Optical coherence tomography angiography (OCTA) from an enrolled age-related macular degeneration patient. **A.** Optical coherence tomography angiography macula 3 × 3 scan showing the superficial vascular plexus; (**C**) OCTA macula 3 × 3 scan showing the deep vascular plexus; and (**D**) OCT B-scan showing the slab set to evaluate the deep retinal plexus. Parafoveal area (PF).

The vessel density is calculated using the formula previously described[18] as follows:

$$\text{Vessel density} = \frac{\int V \cdot dA}{\int dA}$$

where V is one when the OCTA value is above a background threshold and zero otherwise. A is the area of interest.

Moreover, the software outputted the mean macular thickness in the foveal (foveal macular thickness) and in the parafoveal (parafoveal macular thickness) regions.

Choroidal thickness. Cross-sectional SD-OCT (10 mm scan length, 3 mm scan depth) of macular region was performed using the XR Avanti SD-OCT. The obtained scan provides visualization of structures from deep choroid well into the vitreous, in a single B-scan. The images were shown and measured with the XR Avanti software. The choroid was manually measured in the SF location by a trained investigator (E.B.) from the outer portion of the hyper-reflective line corresponding to the RPE to the inner surface of the sclera.

Statistical analysis. Statistical calculations were performed using Statistical Package for Social Sciences (version 20.0; SPSS Inc, Chicago, IL). The difference among the three groups was generated by conducting ANOVA analysis followed by Scheffe post hoc test.

The chosen level of statistical significance was $P < 0.05$.

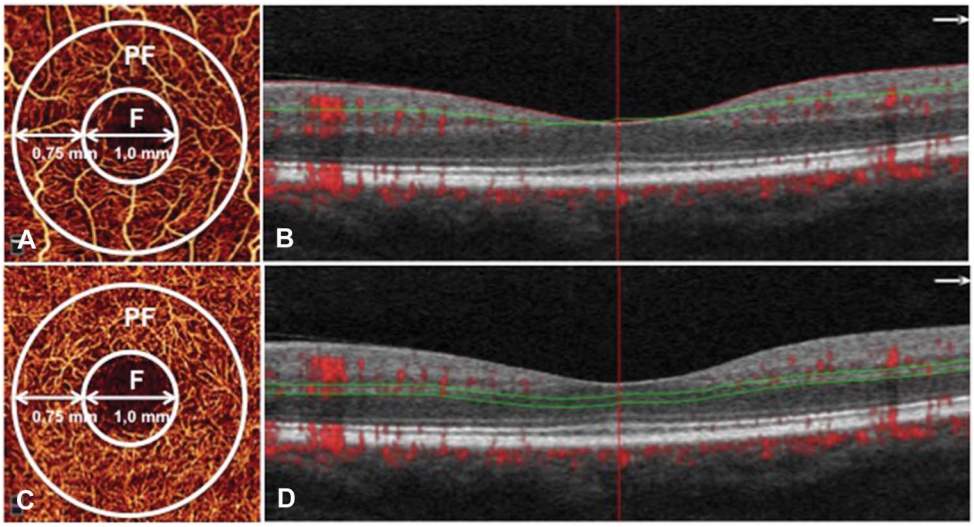

Fig. 3. Optical coherence tomography angiography (OCTA) from a healthy control. **A.** Optical coherence tomography angiography macula 3 × 3 scan showing the superficial vascular plexus; (**B**) OCT B-scan showing the slab set to evaluate the superficial retinal plexus; (**C**) OCTA macula 3 × 3 scan showing the deep vascular plexus; and (**D**) OCT B-scan showing the slab set to evaluate the deep retinal plexus. Parafoveal area (PF).

RESULTS

Demographic data of patients and healthy subjects and best-corrected visual acuity are reported in the Table 1. Two eyes of two patients with AOFVD had to be excluded from the analysis because of the software inability to perform a vessel plexus correct segmentation.

Macular Thickness Analysis

Foveal macular thickness was 282.6 ± 46.5 μm in patients with AOFVD, 233.2 ± 35.5 μm in patients with AMD, and 261.8 ± 19.2 μm in healthy controls ($P = 0.001$ and $P = 0.317$, respectively, after comparison with the AOFVD group) (Table 2).

Parafoveal macular thickness was 328.6 ± 15.4 μm in the AOFVD group and resulted significantly thicker after the comparison with the AMD group (289.5 ± 36.2 μm, $P = 0.001$). Nevertheless, no difference was found between the AOFVD and the control group (330.8 ± 22.0 μm, $P = 0.979$) (Table 2).

Vessel Density Analysis

Foveal superficial vessel density did not result different in the AOFVD group (30.7 ± 3.7%) after the comparison with both the AMD group (32.4 ± 2.7%, $P = 0.284$) and the control group (32.7 ± 4.7%, $P = 0.197$) (Table 2).

Foveal deep vessel density was 28.0 ± 2.3% in patients with AOFVD, 29.1 ± 3.3% in patients with AMD, and 29.5 ± 7.7% in healthy controls ($P = 0.142$ and $P = 0.080$, respectively, after comparison with the AOFVD group) (Table 2).

Parafoveal superficial vessel density was increased in patients with AOFVD compared with that in the AMD group (50.6 ± 4.3% and 46.3 ± 4.3%, respectively, $P = 0.016$). Moreover, parafoveal superficial vessel density was 50.4 ± 6.1% in healthy controls ($P = 0.953$ in the comparison with the AOFVD group) (Table 2).

Parafoveal deep vessel density was 57.9 ± 6.4% in patients with AOFVD, 52.2 ± 3.8% in patients with AMD, and 52.7 ± 6.0% in healthy controls ($P = 0.006$ and $P = 0.035$, respectively, after comparison with the AOFVD group) (Table 2).

Noise Analysis

Decorrelation can also be generated by bulk motion (causing noise). To be sure that noise did not influence the analysis, as already shown,[19,20] we tested vessel density in the FAZ area. Indeed, because there is no retinal circulation in the FAZ, this method is an assessment of background motion noise. FAZ vessel density was 0.0 ± 0.0% in patients with AMD, 0.0 ± 0.0% in patients with AOFVD, and 0.0 ± 0.0% in healthy controls. After comparisons, no difference in FAZ vessel density was found among the groups ($P > 0.05$ for all the comparisons), the latter aspect suggesting noise not influencing results.

Choroidal Thickness Analysis

Subfoveal choroidal thickness was 334.6 ± 73.9 μm in patients with AOFVD and resulted significantly thicker in comparison with both patients with AMD (215.7 ± 63.6 μm, $P = 0.001$) and healthy subjects (285.1 ± 77.8 μm, $P = 0.024$) (Table 2).

Discussion

In this prospective study, we investigated retinal and choroidal vessel changes in patients affected by AOFVD. Overall, we found that these patients show an alteration both in the retinal and in the choroidal vasculatures.

Recently, Coscas F et al[21] showed that SF choroidal thickness is thicker in AOFVD eyes, after comparison with both healthy and late stage AMD eyes. Indeed, the increased choroidal thickness has been hypothesized to contribute to the development of AOFVD and is thought to be secondary to an

Table 1. Characteristics of Analyzed Patients

	Patients With AOFVD (n = 14)	Patients With AMD (n = 18)	Healthy Subjects (n = 20)
Number of eyes	20	20	20
Age, years	64.6 ± 7.6	66.5 ± 7.5	65.4 ± 9.1
Gender, n			
Male	8	10	8
Female	6	8	12
BCVA (LogMAR) (Snellen equivalent)	0.1 ± 0.1 (~20/25)	0.1 ± 0.1 (~20/25)	0.0 ± 0.0 (20/20)

BCVA, best-corrected visual acuity (logMAR [logarithm of the minimum angle of resolution]); n, number of patients.

Table 2. Retinal Vessel Density and Choroidal Thickness in Patients and Controls

				ANOVA			
					Post hoc Test *P*		
	Patients With AOFVD	Patients With AMD	Healthy Subjects	*P*	Patients With AOFVD vs. Patients With AMD	Patients With AOFVD vs. Healthy Controls	Patients With AMD vs. Healthy Controls
Foveal macular thickness, μm	282.64 ± 46.50	233.17 ± 35.48	261.83 ± 19.21	**0.001**	**0.001**	0.317	0.077
Parafoveal macular thickness, μm	328.64 ± 15.40	289.52 ± 36.21	330.83 ± 21.99	**<0.0001**	**0.001**	0.979	**0.001**
Foveal superficial vessel density, %	30.7 ± 3.7	32.4 ± 2.7	32.7 ± 4.7	0.134	0.284	0.197	1.0
Parafoveal superficial vessel density, %	50.6 ± 4.3	46.3 ± 4.3	50.4 ± 6.1	**0.009**	**0.016**	0.953	**0.045**
Foveal deep vessel density, %	28.0 ± 2.3	29.1 ± 3.3	29.5 ± 7.7	0.080	0.142	0.080	0.926
Parafoveal deep vessel density, %	57.9 ± 6.4	52.2 ± 3.8	52.7 ± 6.0	**0.006**	**0.006**	**0.035**	0.971
Subfoveal choroidal thickness, μm	334.6 ± 73.9	215.7 ± 63.6	285.1 ± 77.8	**<0.0001**	**0.001**	**0.024**	**0.016**

Values were compared by one-way analysis of variance (ANOVA) followed by Scheffe post hoc test.
Bold values are statistically significant.

increased circulation and vascular dilatation.[21] Our results confirmed that choroidal thickness is increased in AOFVD eyes compared with both healthy and AMD eyes. Furthermore, we first showed that choroidal thickness is thicker in AOFVD than in AMD, also considering only eyes affected by intermediate AMD. The latter feature could be useful in the early differential diagnosis between the two diseases.

Introduction of OCTA has allowed to image accurately two layers of the retinal vasculature without the needing of the dye injection.[7,8] We used this new useful imaging tool to study both the superficial and the deep vascular layers in patients with AOFVD.

Our group recently showed that the superficial vascular plexus is damaged among patients affected by intermediate AMD.[20] Inasmuch as systemic hypertension,[22] dietary fat intake,[23,24] and history of coronary, carotid, and peripheral vascular disease[25] are risk factors as for vascular damage as for AMD, we hypothesized that a retinal and choroidal vessel damage could contribute to the AMD pathogenesis.

In this current, study we demonstrated that both superficial and deep vessel densities are significantly increased in patients with AOFVD, after the comparison with patients with AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in AMD and that OCTA could be useful to differentiate early stages of these two diseases.

Recently, Querques et al[26] evaluated patients affected by AOFVD by means of OCTA. In the latter study, 22 AOFVD eyes were enrolled and a comparison with healthy eyes was performed: the authors concluded that a general vascular rarefaction characterized AOFVD eyes. Nevertheless, our results are in contrast with those of Querques et al.[26] Indeed, we showed that 1) there is no difference in superficial vessel density between AOFVD and healthy eyes; and 2) the deep vessel density was higher in AOFVD eyes. Possible explanations for these differences could be: 1) the different patients' selection (indeed Querques et al considered also AOFVD eyes affected by vitelliruptive stage or complicated by choroidal neovascularization); 2) our assessment concerned the vessel density rather than the morphologic vessel features.

Histology and electron microscopy revealed that photoreceptors seem to be the first cells affected in AOFVD.[27,28] The photoreceptor damage, followed by an excessive outer segment shedding, leads to the formation of subretinal deposits of photoreceptor debris. The debris accumulation initially over-activates and finally harms the RPE.[29] Indeed, several authors demonstrated vitelliform deposits are composed primarily of extracellular photoreceptor debris and RPE-derived material.[27] Furthermore, progression of AOFVD is characterized by reabsorption of this vitelliform material followed by fluid accumulation and RPE disruption.[30,31] The migration of inflammatory cells, associated with vasodilatation, was also observed by Kaur et al[32] in retinas of adults rats: an activation of retinal microglial cells and a vasodilatation were aimed to remove debris. Then, we speculated that an increasing in deep vessel density, in eyes affected by early stages of AOFVD, could be part of an inflammatory response aimed to reabsorb vitelliform material. Another possible explanation is that the vitelliform material could lead to a vessels' displacement toward the parafoveal area. Querques et al[26] have speculated that this displacement could follow the progressive accumulation of vitelliform material forcing the blood vessels away.

Our study has several limitations. The series presented here is relatively small. However, one should look at the current series in consideration of: 1) the rarity of the AOFVD disease; and 2) the strict inclusion criteria for patients and control group, as well as similarity of groups about the meaningful characteristics such as age (which is known to affect the choroid measurements). Furthermore, another major limitation is that we used two different methods to study retinal and choroidal vessels. However, the OCTA choriocapillaris loss seen in patients with AOFVD and AMD should be interpreted with caution because as vitelliform lesion as drusen could lead to an attenuation artifact deceiving the evaluation. Finally, the vitelliform lesion could affect the vessel density test by influencing the segmentation. In order to reduce the latter limitation and not analyze images with segmentation errors, in the current paper two investigators checked the segmentation. Moreover, we finely adjust the slab position, although we did not change the slab shape on the OCT B-scan.

In conclusion, we provide the first fully integrated study of retinal and choroidal blood supply in patients with AOFVD, and we showed that both choroid and retinal vessels were modified in these patients, after comparison with both patients with AMD and healthy subjects. This study raises many questions and prompts further investigation including the evaluation of a possible prognostic role of OCTA in predicting evolution of AOFVD to the atrophic stage.

Key words: adult-onset foveomacular vitelliform dystrophy, age-related macular degeneration, vessel density, choroidal thickness, optical coherence tomography angiography.

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