CLINICAL SPECTRUM OF MACULAR-FOVEAL CAPILLARIES EVALUATED WITH OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Purpose: To describe macular-foveal capillaries (MFC) by means of optical coherence tomography angiography and to identify the clinical spectrum of this angiographic feature.

Methods: Patients with MFC presenting at the Medical Retina & Imaging Unit of the Department of Ophthalmology, University Vita-Salute San Raffaele in Milan were recruited. Patients underwent a complete ophthalmologic examination that included slit-lamp examination, fundus examination, measurement of best-corrected visual acuity, fundus autofluorescence, and spectral-domain optical coherence tomography (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography was performed in selected cases. Optical coherence tomography angiography was performed through Zeiss prototype (AngioPlex, CIRRUS HD-OCT models 5000; Carl Zeiss Meditec, Inc, Dublin, OH).

Results: Twelve eyes of 10 consecutive white patients (5 men and 5 women; 50%) presenting MFC were included. Mean age was 66.2 ± 10.2 years (range, 53–79 years); mean best-corrected visual acuity was 0.1 ± 0.13 logarithm of the minimum angle of resolution (range, 0–20/20 to 20/50). Mean central macular thickness was 348 ± 57.6 μm. Two patients were affected by macular pucker, two by postsurgical macular edema, two by age-related macular degeneration, one by diabetic retinopathy, one by dome-shaped macula, one presented with chronic serous chorioretinopathy, and one with branch artery occlusion. Six eyes disclosed a complete absence of the foveal avascular zone, whereas the six other cases showed a partial foveal avascularity. No significant difference was found between complete and incomplete MFC with regards to best-corrected visual acuity (P = 0.272) and central macular thickness (P = 0.870).

Conclusion: Cases of persistent MFC are heterogeneous in demographic characteristics, fundus appearance, and visual function. However, MFC presenting either as complete absence of the foveal avascular zone or only partial foveal avascularity, may complicate different retinal abnormalities or represents a coincident finding.

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The fovea is the highly specialized region of the human retina responsible for sharp central vision and color sensitivity, characterized by complete excavation of inner retinal neurons (creating the characteristic foveal pit), increased cone packing, and absence of rod photoreceptors. During human embryogenesis, the fovea is the last retinal area to reach maturity: its development is characterized by centrifugal displacement of inner retinal layers, centripetal migration of photoreceptors, and elongation of foveolar cones. As far as retinal vasculature is concerned, foveal vessels organize in twoplexa: a superficial net running in the nerve fiber and ganglion cell layers, and a deep more complex and denser plexus consisting of smaller caliber capillaries, running through the inner nuclear layer. The terminal
capillaries of both plexa interrupt in correspondence of
the foveola, forming a capillary-free zone, called foveal
vascular zone (FAZ), surrounded by interconnecting
vessels at its margins. This configuration of retinal
components is thought to minimize light scatter and max-
imize light sensitivity at the center of foveal pit.\textsuperscript{5}

Normal FAZ, as measured by multimodal imaging
techniques, has a diameter of 500 \( \mu \)m to 600 \( \mu \)m; how-
ever, several studies on normal population have demon-
strated individual variation in its shape and total area.\textsuperscript{6–8}

Literature reports cases in which the FAZ was absent,
or traversed by small vessels either centrally or
eccentrically, both in patients with no known abnor-
mality and normal visual acuity and in those with
macular abnormality with decreased visual acuity. Cases
of absent FAZ have been reported in aniridia, albinism,
microphthalmus, achromatopsia, vitelliform macular
degeneration, and history of prematurity with related
complications, including retinopathy of prematurity.\textsuperscript{9–13}

This condition has been referred as macular-foveal
capillaries (MFC) and has been described as intraretinal
polygonal or straight vascular nets in communication
with the surrounding retinal capillary bed.\textsuperscript{14}

Fluorescein angiography (FA) is still considered the
gold standard for imaging retinal vascular network and
for evaluating FAZ in both healthy and pathologic
eyes. However, FA is an invasive, relatively expen-
sive, and time-consuming imaging technique, and it is
not able to focus on the deep capillary retinal layer.
Moreover, fluorescein dye poses unpredictable risks,
including nausea and allergic reactions, up to anaphy-
lexis in rare instances.\textsuperscript{15,16}

Optical coherence tomography angiography (OCT-A)
is a relatively new, dye-less, depth-resolved technique
that allows the visualization of retinal microvasculature
by detecting intravascular blood flow.\textsuperscript{17,18} Two major
motion contrast techniques, phase-based and amplitude-
based, are used to render depth imaging of retinal and
choroidal microvasculature combined with “en face”
OCT-derived technique. Optical coherence tomography
angiography may be used to noninvasively investigate
retinal capillary networks and therefore FAZ.\textsuperscript{19,20}

The aim of the present study was to describe cases of
MFC using OCT-A and to identify the clinical spectrum
of this peculiar angiographic feature along with the
associated clinical conditions.

**Methods**

Macular foveal capillaries were individuated from
a pool of patients consecutively presenting between
September and December 2015 at the Medical Retina & Imaging Unit of the Department of Ophthalmology,
University Vita-Salute San Raffaele in Milan. The study was conducted in agreement with the Declara-
tion of Helsinki for research involving human subjects
and was approved by the local Institutional Review
Board. Patients signed a written consent to participate
in the study. Inclusion criteria were the complete or
partial absence of FAZ evaluated on OCT-A, suffi-
ciently clear ocular media, adequate pupillary dilation,
and fixation to permit quality OCT-A imaging. Exclu-
sion criteria were poor cooperation, corneal and lens
opacities, macular chorioretinal atrophy, and late-stage
exudative age-related macular degeneration (AMD).

All patients underwent a clinical history collection
(including birth history), complete ophthalmologic
examination that included slit-lamp examination, fundus
examination, and measurement of best-corrected visual
acuity (BCVA) using standardized early treatment
diabetic retinopathy study charts or tumbling E chart
for unalphabetic patients and then converted to loga-
rithm of the minimum angle of resolution. Fundus auto-
fluorescence and spectral-domain (SD) OCT (Spectrals
HRA + OCT; Heidelberg Engineering, Heidelberg,
Germany) were also collected in all patients. Fluorescein
angiography was performed only in selected cases (4 of
10 patients), those who warranted a deeper diagnostic
evaluation on the bases of our clinical judgment
(because of coincident macular/retinal diseases, such as
AMD and diabetic retinopathy [DR]). Both right eye
(RE) and left eye (LE) were examined in each eye.

Mean central macular thickness (CMT) was obtained
for each patient (Spectralis SD-OCT; 19 horizontal
lines [6 mm x 6 mm area] centered on the fovea, each
with 9 averaged OCT B-scans-1024 A scans per-line at
240-\( \mu \)m intervals).

Optical coherence tomography angiography was per-
formed through a Zeiss prototype (AngioPlex,
CIRRUS HD-OCT models 5000; Carl Zeiss Meditec,
Inc, Dublin, OH). The Zeiss system relies on optical
microangiography algorithm. The OCT-A software
offers the option of 3 mm \( \times \) 3 mm OCT angiograms
and automated segmentation of full-thickness retinal
scans into the “superficial” and “deep” inner retinal
vascular plexuses, outer avascular retina, and chorioca-
pillaris. Two trained OCT-A users (M.V.C. and A.C.)
acquired the images and performed a qualitative anal-
ysis of the FAZ. A third senior (G.Q.) reader adjudicated
in case of disagreement between both readers; MFC
were arbitrarily evaluated on 3 mm \( \times \) 3 mm OCT-A
scans and on superficial plexus; deep capillary plexus
was also evaluated, but it was not as informative as the
superficial plexus. The capillaries surrounding the FAZ
in the deep plexus appear ill defined: this made it more
difficult to precisely delineate the FAZ and therefore
to evaluate the MFC in the deep plexus.
Data were analyzed with the Statistical Package for the Social Sciences version 20.0 for Mac (SPSS, Chicago, IL) and included descriptive statistics for demographics and main clinical records, comparative analysis (Student’s t-test analysis), and qualitative descriptions of the imaging findings. The chosen level of statistical significance was \( P < 0.05 \).

**Results**

Twelve eyes of 10 consecutive white patients (5 men and 5 women; 50%) presenting MFC were included in the study; demographic information is listed in Table 1. None of the patients reported a history of prematurity. Mean age was 66.2 ± 10.2 years (range, 53–79 years). Mean BCVA was 0.1 ± 0.13 logarithm of the minimum angle of resolution (range, 0–0.4 logarithm of the minimum angle of resolution, corresponding to 20/20 to 20/50); CMT was 348 ± 57.6 μm.

Patient 1 was a 75-year-old woman who presented for metamorphopsia in the RE; BCVA was 20/25 in the RE and 20/20 in the LE. Fundus biomicroscopy showed reduced foveolar reflex, macular wrinkling, and increased retinal reflectivity in the RE and retinal pigment epithelium (RPE) mottling in the LE. The results of SD-OCT showed increased CMT with hyperreflective epiretinal membrane and rare hyporeflective cysts in external nuclear layer in the RE and focal hyperreflective deposits under the RPE in the LE, referable to drusen; CMT was 398 μm and 251 μm in the RE and LE, respectively. Macular foveal capillaries were found in the RE (study eye) (Figure 1A).

Patient 2 was a 63-year-old woman followed for high myopia. Her BCVA was 20/20 bilaterally, and her refraction was −8.00 diopters in the RE and −7.50 diopters in the LE. Fundus biomicroscopy showed tilted optic disk insertion, peripapillary chorioretinal atrophy, diffuse retinal thinning, and abnormal macular reflex at the posterior pole in both the eyes. The results of SD-OCT showed myopic macular pucker bilaterally (CMT was 383 μm and 265 μm in the RE and LE, respectively), characterized by the loss of physiologic macular pit, and showed thin choroid; MFC were found in the RE (study eye) (Figure 1B).

Patient 3 was a 65-year-old man who had undergone pars plana vitrectomy and internal limiting membrane peeling for macular pucker in the RE 2 years before. Macular edema developed after surgery, treated with three injections of intravitreal dexamethasone implant (Ozurdex; Allergan, Inc, Irvine, CA). His BCVA was 20/25 in the RE and 20/20 in the LE. Fundus biomicroscopy disclosed abnormal macular reflex as a result of vitreoretinal surgery in the RE and was unremarkable in the LE. The results of SD-OCT showed thickened retina (CMT was 434 μm), hyperreflective internal limiting membrane, loss of foveal depression and continuity of all inner retinal layers in the RE, and normal foveal depression in the LE (CMT was 267 μm); MFC were found in the RE (study eye) (Figure 1C).

Patient 4 was a 77-year-old woman who underwent cataract surgery, pars plana vitrectomy, and internal limiting membrane peeling in the LE, complicated by macular edema and partially resolved after 5 Ozurdex injections (last treatment was 4 months before the visit). Ocular history in the RE was unremarkable. Her BCVA was 20/20 in the RE and 20/25 in the LE. Color fundus photography showed focal areas of chorioretinal atrophy at the posterior pole, confirmed by fundus autofluorescence. The results of SD-OCT showed normal retinal profile in the RE and loss of foveal depression with thickening of the innermost retinal layers in the LE (CMT was 460 μm); MFC were found in the LE (study eye) (Figure 1D).

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<th>Patient Number</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Study Eye</th>
<th>Diagnosis</th>
<th>BCVA</th>
<th>Macular Thickness, μm</th>
<th>MFC Type</th>
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<td>M</td>
<td>RE</td>
<td>Postsurgical inflammatory edema</td>
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<td>F</td>
<td>LE</td>
<td>Postsurgical inflammatory edema</td>
<td>20/25</td>
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<td>RE</td>
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<td>LE</td>
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<td>20/20</td>
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BRAO, branch retinal artery occlusion; CSC, central serous chorioretinopathy; DR, diabetic retinopathy; F, female; M, male.
Patient 5 was a 53-year-old woman with a history of untreated chronic central serous chorioretinopathy with good BCVA (20/20 in both eyes). Fundus autofluorescence did not show the typical foveal darkening in correspondence of posterior pole (suggestive of absence of macular pigments), with focal areas of hyperfluorescence/hypoautofluorescence within the vascular arcades bilaterally. The results of SD-OCT showed bilaterally reduced foveal depression with continuity of innermost retinal layers (inner plexiform and inner nuclear layers), with CMT of 314 μm and 312 μm in the RE and in the LE, respectively (Figure 1, E and F). Fluorescein angiography revealed multiple areas of patchy hyperfluorescence/hypofluorescence referable to RPE atrophy in early frames and late fluorescein pooling in correspondence of serous retinal detachment bilaterally; MFC were found in both eyes (both were considered as study eyes).

Patient 6 was a 73-year-old man followed for nonproliferative DR and untreated exudative AMD in the RE. His BCVA was 20/40 in the RE and 20/20 in the LE. Fundus biomicroscopy showed rare microaneurysms and focal spots of laser photocoagulation at the posterior pole bilaterally, while a fibrotic plaque involving the macular area and RPE atrophy were detectable only in the RE. The results of SD-OCT showed a subfoveal hyperreflective thickening above the RPE with intraretinal cysts in the RE and reduced foveal pit, continuity of innermost retinal layers, with no evidence of macular edema in the LE; CMT was 319 μm in the RE and 289 μm in the LE (Figure 1G). Fluorescein angiography revealed early focal hyperfluorescence in correspondence of microaneurysms and absence of retinal ischemia bilaterally, early hyperfluorescence as a result of window defect with late dye leakage from the neovascular lesion in the RE, and a reduction of the hypofluorescent FAZ in the LE were detected on FA; MFC were found in the LE (study eye).

Patient 7 was a 60-year-old woman with BCVA of 20/32 in the RE and 20/20 in the LE, with emmetropic refraction. Fundus biomicroscopy did not show any relevant pathologic feature in either eye; however, the results of SD-OCT revealed a dome-shaped macular appearance bilaterally, complicated with serous retinal detachment in the RE; CMT was 368 μm in the RE and 300 μm in the LE (Figure 1H), and MFC were found in the LE (study eye).
Patient 8 was a 79-year-old man experiencing early AMD in the RE and neovascular AMD in the LE, treated with 5 intravitreal injections of aflibercept. His BCVA was 20/40 in the RE and 20/50 in the LE. The results of SD-OCT disclosed hyperreflective sub-RPE material suggestive of drusen and hyperreflective lesions above the RPE, referable to reticular pseudodrusen in the RE; a hyperreflective RPE parafoveal elevation in correspondence of the choroidal neovascularization was recognizable in the LE, then confirmed on FA; CMT was within normal limits in both eyes (301 μm in the RE and 304 μm in the LE) (Figure 1, I–L), and MFC were found in both the RE and LE (study eyes).

Patient 9 was a 64-year-old man followed for neovascular AMD in the RE, treated with 3 anti–vascular endothelial growth factor injections, and nonexudative AMD in the LE. His BCVA was 20/50 in the RE and 20/32 in the LE. Fundus ophthalmoscopy showed subretinal blood and fluid, surrounding central macular fibrosis in the RE, and RPE dystrophy with numerous small drusen at the posterior pole in the LE. Fluorescein angiography confirmed the diagnosis of active choroidal neovascularization in the RE and absence of neovascular network in the LE, where early and late dye-staining was observed (Figure 2). The results of SD-OCT showed retinal thickening, intraretinal and subretinal fluid accumulation in the RE, and a flat hyperreflective elevation of the RPE, with normal macular thickness and conserved foveal depression in the LE; however, a slight subfoveal thickening of the outer nuclear layer, with a thin centripetal displacement of the inner plexiform and the inner nuclear layers, was also noted in the LE (Figure 1M). Also, MFC were identified in the LE (study eye).

Patient 10 was a highly hypertensive 53-year-old man followed for Coats disease since infancy in the RE and branch retinal artery occlusion in the LE, diagnosed after an episode of sudden visual loss. Visual field examination in the LE showed residual paracentral relative scotoma. The patient had undergone several laser photocoagulative treatments in the RE, whereas the LE had not been ever treated. His visual acuity was 20/200 in the RE and 20/20 in the LE. Indirect ophthalmic examination showed a flat retina, massive preretinal fibrosis, and focal areas of pigmented chorioretinal atrophy, referable to cicatrized laser spots in mid and extreme periphery in the RE; LE fundus examination revealed a translucent macular reflex, with an artery-to-artery anastomosis with a dilated vascular loop temporally to the fovea (Figure 1N), which did not show any dye leakage on FA; MFC were identified in the LE (study eye).

In all study eyes, OCT-A disclosed absence of the normal interruption of superficial capillary plexus in correspondence of the physiologic FAZ, with either polygonal or straight linear MFC crossing through the macular area centrally or eccentrically. In particular, 6 of 12 eyes (Cases 3, 5-right, 5-left, 6, 7, 10; 50%) disclosed a complete absence of the FAZ, whereas the other 6 eyes showed only a partial foveal avascularity (Cases 1, 2, 4, 8-right, 8-left, 9; 50%) (Figure 3). No significant difference was found between complete and incomplete forms of MFC with regards to BCVA ($P = 0.272$) and retinal thickness ($P = 0.870$) using Student’s $t$-test.

Optical coherence tomography angiography of fellow eyes disclosed normal representation of FAZ in Patients 1, 2, 3, and 4. Optical coherence tomography angiography was abnormal in both eyes of Patients 5 and 8, who disclosed absence of FAZ bilaterally. Patient 6 showed an incomplete FAZ in the LE, but the examination was excluded for the presence of motion artifacts because of poor target fixation; OCT-A in Patients 8 and 9 disclosed a poorly defined choroidal
neovascular network at the choriocapillary level within the macular area, consistent with the diagnosis of neovascular AMD. Moreover, Patient 6 showed focal areas of RPE atrophy with the underlying choroidal vasculature, as a result of the previous laser treatment. The OCT-A signal was not recordable in the RE of Patient 10, possibly because of the macular fibrosis.

**Discussion**

It is commonly accepted that FAZ size reflects the health condition of the microcapillary circulation in the human retina, and FAZ measuring could serve an important role in the diagnosis and management of various retinal vascular diseases, such as DR or retinal vein occlusions. Moreover, FAZ location has been used as an anatomic landmark for the identification of foveal point of fixation. Several articles have been addressed to the assessment of FAZ dimension and its morphofunctional state by means of various imaging methods, including histologic feature, immunohistochemistry, FA, and indocyanine green angiography. Purpose of our study was to investigate cases of absent or reduced FAZ by means of OCT-A.

We have identified 12 cases of persistence of MFC, heterogeneous in demographic characteristics, associated conditions (i.e., primary ophthalmic diagnosis), fundus appearance on ophthalmoscopy, and functional outcome. In detail, two patients were affected by macular pucker, two by postsurgical macular edema, two patients by AMD, one by DR, one by dome-shaped macula, one presented with chronic central serous chorioretinopathy, and one with branch artery occlusion. Clinical association between MFC and congenital or inherited ocular conditions are well represented in the literature, including aniridia, albinism, microphthalmus, achromatopsia, and retinopathy of prematurity. Furthermore, Yeung et al have described cases of MFC both in healthy subjects and in acquired ocular conditions, such as DR, branch vein occlusion, and malignant uveal melanoma.

In our series, all patients disclosed different macular SD-OCT features, as far as it regarded morphologic profile or central thickness. However, 5 of 12 eyes (Cases 1, 2, 3, 4, 10; 41; 7%) presented loss of physiologic foveal pit along with relatively increase in CMT, caused by tractional/cystoid retinal edema. These findings are in agreement with previous reports that have correlated FAZ area with central foveal thickness measured on SD-OCT. In fact, according to Dubis et al, FAZ area inversely relates with central foveal thickness, suggesting that thicker retinas are characterized by smaller FAZ area, whereas thinner ones present larger FAZ area. The fact that thicker retina requires a smaller FAZ has been explained as a need to satisfy a major metabolic demand, compared with thinner neuroepithelial sheet, less energy demanding.
Dimensions of FAZ seem also to depend on foveal pit morphologic profile: a steep less pronounced foveal depression is significantly associated with smaller FAZ and MFC. These findings are explained by current models of foveal development, which suggest that a well-represented FAZ is required for complete foveal excavation. Absence of foveolar depression, along with the lack of the physiologic displacement of inner retinal layers above Henle fibers and normal development of cone photoreceptors has been generally referred to as fovea plana (FP). Other terms, including fovea hypoplasia, foveal dysgenesia, and foveal aplasia have been introduced to describe cases of FP associated with poorer visual outcome, in fact, a surprisingly broad range of clinical expression with visual acuities ranging from 20/20 (as the 2 patients included in our study) to 20/400 in conjunction with FP have been described in the literature. We found 1 patient with bilateral OCT features of FP (Case 5) and 2 cases of unilateral FP (Cases 6 and 9): in agreement with our findings, histologic, angiographic, and dye-less imaging techniques have demonstrated the persistence of MFC in cases of FP.

Recently, the introduction of OCT-A has provided new insights in noninvasive imaging of retinal vasculature and choriocapillaris at the macular level. This has led to the finding that MFC may happen not only in complex rare cases but also complicate more common retinal abnormalities, such as central serous chorioretinopathy and macular pucker. In fact, we speculate that these conditions structurally subvert normal macular cytoarchitecture, with tangential forces causing vascular displacement toward the FAZ; this displacement seems to persist after the resolution of the ocular condition (either surgically or medically). Alternatively, the presence of MFC may simple represent a coincident finding and is not causally linked to the primary retinal condition.

This study sought to characterize the clinical spectrum of MFC: absence of FAZ is not a sign of macular abnormality and does not seem to contribute to final visual acuity. It can be a bystander of a primary ocular condition, or in other cases, it can be a consequence of a causative primary disease that alters normal macular structures, as it happens in macular pucker or cystoid edema.

Limitations of this study are mainly related to the small sample size and the lack of follow-up. Increasing the dimension of the included sample could help in enlarging the clinical spectrum of MFC. The inclusion of only white patients may represent a potential bias to our study. Variations in the measurements of the FAZ in the literature suggest that its dimensions may be affected by the ethnicity. Therefore, the evaluation of MFC in different ethnicities would be an interesting field of research to understand if race may play a significant role in the incidence of MFC.

Moreover, the heterogeneity of the sample precludes a reliable evaluation of the effects of MFC on functional outcome. In turn, we are not able to state if absent FAZ is definitely associated with any specific abnormality. Finally, this study lacks of histologic confirmation that corroborates our findings in vivo.

In conclusion, we described persistent MFC as heterogeneous in demographic characteristics, ophthalmic diagnosis, fundus appearance, and visual function. However, MFC, presenting either as complete absence of the FAZ or as only partial foveal avascularity, may complicate different common retinal conditions or, alternatively, may represent a coincident finding not causally linked to primary retinal diagnosis. Further studies should be addressed toward deeper morphologic and functional evaluation of patients with MFC; microperimetry and multifocal electroretinogram along with macular oxygen extraction rate could help in further knowledge of metabolic state of retina with absent FAZ and abnormal macular vascularization.

Key words: fovea plana, foveal avascular zone, macular-foveal capillaries, optical coherence tomography angiography.

References


