

Original Investigation

Retinal Vascular Layers in Macular Telangiectasia Type 2 Imaged by Optical Coherence Tomographic Angiography

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IMPORTANCE Macular telangiectasia type 2 (MacTel 2) is a rare disease in which abnormalities of the retinal vasculature play a key role. The vascular abnormalities are typically evaluated using fluorescein angiography, a modality with known defects in imaging the deeper layers of the retinal vasculature. Angiography based on optical coherence tomography can image vessels based on flow characteristics without dye injection and may provide improved information concerning the pathophysiology of MacTel 2.

OBJECTIVE To investigate MacTel 2 using optical coherence tomographic angiography.

DESIGN, SETTING, AND PARTICIPANTS Fourteen eyes of 7 patients with MacTel 2 were analyzed in a community-based retina practice. The flow imaging was based on split-spectrum amplitude decorrelation angiography, which can dissect layers of vessels in the retina. The inner retinal vascular plexus, the outer plexus, and deeper vascular invasion into the outer and subretinal spaces were optically dissected in en face images based on flow.

MAIN OUTCOMES AND MEASURES Visualization and qualitative evaluation of the vascular layers of the retina as they may be affected by MacTel 2, both in terms of depth and topographic characteristics.

RESULTS A consistent set of retinal vascular changes were seen in the eyes with MacTel 2. There was some loss of capillary density in the inner retinal vascular plexus but many more prominent alterations in the deep retinal vascular plexus. In milder forms of the disease, the deep plexus showed dilation and telangiectasis and, in more advanced cases, thinning and loss. The remaining vessels were elongated and widely spaced capillary segments. Invasion by new vessels into the outer and subretinal spaces occurred subjacent to the regions showing greatest flow imaging abnormalities in the inner and deep retinal vascular layers.

CONCLUSIONS AND RELEVANCE As evidenced by the patients in this study, important retinal vascular changes in MacTel 2 occur in the deep capillary plexus of the retina, a layer poorly visualized by fluorescein angiography and, to a lesser extent, in the inner vascular plexus. The proliferation of vessels in the outer and subretinal spaces may be in part compensatory for poor retinal perfusion by established vascular layers in the retina.

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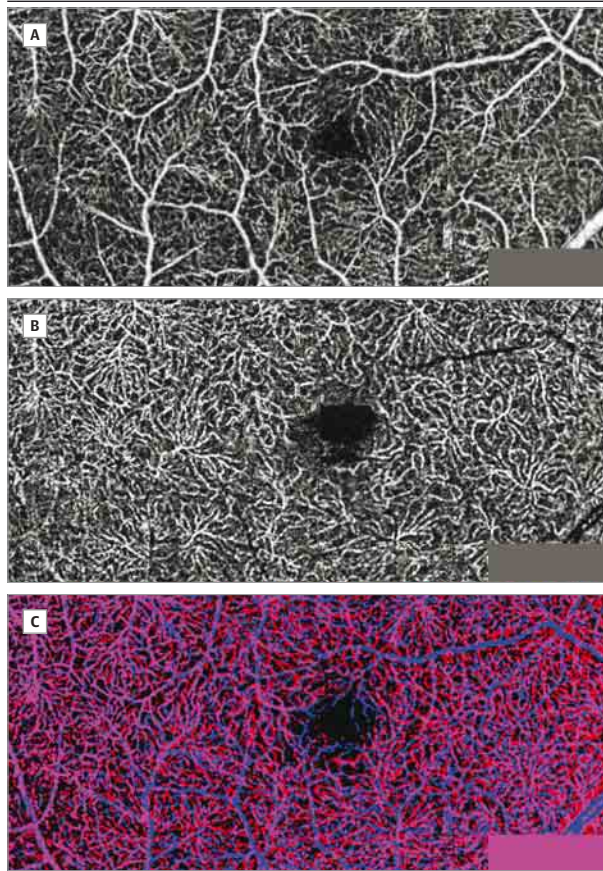
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Macular telangiectasia type 2 (MacTel 2) is a simplified term¹ that refers to idiopathic juxtafoveolar telangiectasia type 2, originally described by Gass and Oyakawa.² Patients with this condition have loss of macular transparency surrounding the fovea, crystalline deposits in the inner retina, migration of hyperplastic retinal pigment epithelium, lack of macular pigment, and progressive abnormalities of the juxtafoveolar retinal vessels.³⁻⁸ Fluorescein angiography shows ectatic vessels with hyperfluorescence in the involved regions. Additional retinal vascular abnormalities include right-angle veins, proliferation of vessels in the outer retina and subretinal space, and, in some patients, obliteration of the foveal avascular zone.^{6,7} Optical coherence tomography (OCT), developed after the original classification by Gass, shows thinning of the macula. Some eyes develop cavitation in the inner retina, outer retina, or both and a minority progress to develop full-thickness macular holes in the absence of observable vitreous traction, suggesting a depletion of intrinsic retinal tissue rather than tensile failure of the retinal structure.⁹⁻¹¹ Gass⁸ proposed the telangiectatic vessels had altered structure of the capillary walls that impeded metabolic exchange. The resultant low-grade chronic nutritional damage was posited to cause degeneration and atrophy of not only the Müller cells, but also the associated photoreceptor cells.⁸ Later investigators described additional retinal abnormalities and highlighted the potential role for Müller cell abnormalities in MacTel 2.⁹⁻¹²

Histologic examination of 3 cases of fluorescein angiographically confirmed MacTel 2 have been reported. Green et al¹³ evaluated an eye removed as part of an orbital exenteration for squamous cell carcinoma of the maxillary antrum. The authors could not find telangiectasis in the histologic sections but instead found vascular narrowing secondary to proliferation of endothelial basement membrane present throughout the retina, not just the macula. There was a suggestion of loss of the normal number of pericytes in the posterior pole. No mention of Müller cells was made.¹³ Additional investigation of this case by Gass⁸ revealed focal vascular invasion to the inner border of the outer nuclear layer. Postmortem analysis of a patient with MacTel 2 by Powner and colleagues¹⁴ showed abnormally dilated vessels in the deeper plexus of the retinal vasculature in the clinically affected area. No mention of the vascular endothelial basement membrane, pericytes, or amount of vascular invasion was made. In a third eye reported separately by Powner and colleagues,¹⁵ the vessels were not mentioned. Both studies published by Powner and colleagues mentioned depletion of Müller cells in the clinically affected areas of the macula. The 2 cases with reported details about the vascular changes in MacTel 2 shared little in common in terms of what features were described or the pathologic abnormalities found.

Optical coherence tomographic angiography provides the opportunity to study retinal vasculature without the need for dye injection. Both the inner and outer retinal vascular plexus are imaged in contradistinction with fluorescein angiography,¹⁶ which does not image the outer capillary plexus well. Be-

Figure 1. Main Capillary Layers in the Normal Macular Region



A, The inner vascular plexus looks similar to the image seen with conventional fluorescein angiography. B, The deep retinal vascular plexus. Note the dense packing of these vessels. C, The inner plexus was made blue and the outer plexus, red.

cause en face OCT inherently can selectively visualize specific layers, the exact level of vascular invasion potentially can be determined. To further understand the vascular abnormalities of MacTel 2, 14 eyes of 7 patients were intensively analyzed using OCT angiography.

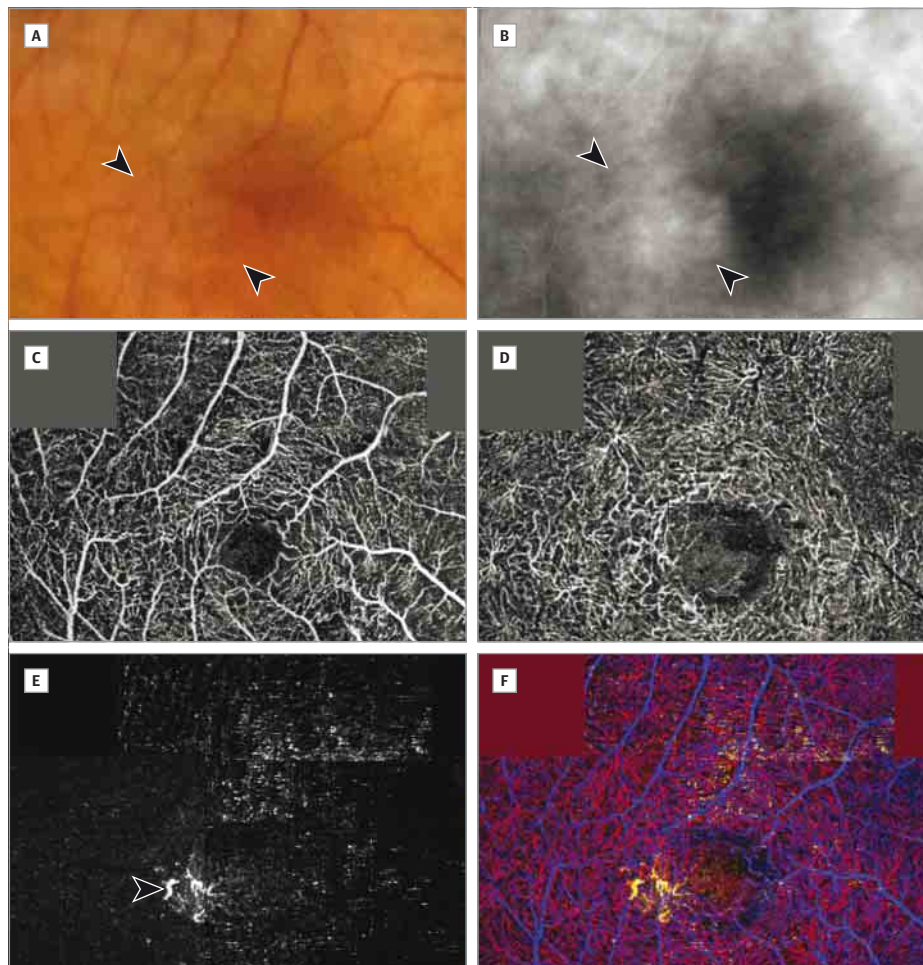
Methods

The study had approval of the Western Institutional Review Board and patients provided written informed consent. There were 7 participants with an established diagnosis of MacTel 2.

Optical Coherence Tomographic Angiography

The instrument used for the OCT images was based on the RTVue XR Avanti (Optovue Inc) and was used to obtain split-spectrum amplitude decorrelation angiography¹⁷ images. This instrument has an A-scan rate of 70 000 scans per second, using a light source centered on 840 nm and a bandwidth of 45 nm. The tissue resolution is 5 μ m axially and there is a 22- μ m beam width. Each B-scan contained 216

Figure 2. Vascular Changes in Early Macular Telangiectasia Type 2



A, Color photograph. B, Fluorescein angiogram with mild late staining. C-F, Optical coherence tomographic angiography of the inner vascular plexus (C), the deep capillary plexus (D), Henle fiber/outer nuclear layers (E), and the stacked color image (F).

A-scans. Five consecutive B-scans (M-B frames) were captured at a fixed position before proceeding to the next sampling location. The volumes were registered and the B-scan images were compared to calculate the decorrelation in the images. The decorrelation viewed as a maximal projection image imaged blood flow. Because the retina is a laminar structure with a corresponding stratification of blood supply, segmentation of the retina in specific layers allows simple en face visualization of the corresponding vascular supply in that layer.

Vascular Diameter in Images

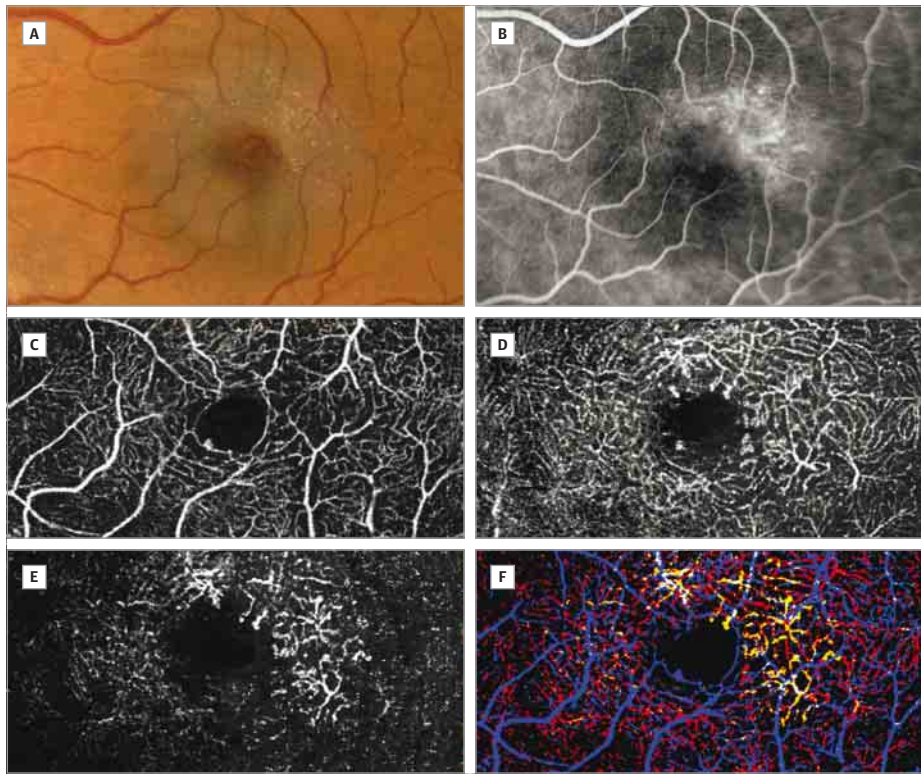
In structural OCT, the diameter of an imaged object is a function of the object size and the lateral point-spread function of the instrument. In motion contrast imaging, the interaction between the object imaged and its image size is a bit more complicated. Because some decorrelation occurs if the illuminating beam only partially covers the vessel, the lateral distance in which the beam position provides flow information is slightly larger than the vessel itself. The amount of flow-based decorrelation varies with the quantity of flow to a certain extent. This has the potential to cause

the apparent diameter of the vessels to vary somewhat with the amount of flow; higher flow vessels will appear slightly wider.

Segmentation of the Optical Coherence Tomographic Angiography Image

The retinal areas were scanned in 2×2 -mm sections. For the purposes of this study, the multiple retinal vascular planes as described by Weinhaus et al¹⁸ were simplified into 2 main layers per Snodderly et al.¹⁹ This reduced the difficulty of independently segmenting and imaging the planes of vessels (which actually course in 3 dimensions) because they were contained in retinal neural layers that were readily segmented. The inner capillary layers were imaged starting with the internal limiting membrane and by selecting sufficient thickness to include the ganglion cell layer in the central macular region. To image the outer plexus, the inner segmentation line was placed at the outer border of the inner plexiform layer and the outer boundary was the midpoint of the outer plexiform layer. This section captured both layers of the outer capillary plexus, which sandwiched the inner nuclear layer.^{18,19} The capillaries bounding the

Figure 3. Outer Retinal Vascular Invasion in the Left Eye of a Patient With Macular Telangiectasia Type 2



A, Color photograph. B, Fluorescein angiogram showing staining. C-F, Optical coherence tomographic angiography of the inner vascular plexus (C), deep plexus (D), outer retina (E), and color stack image (F).

foveal avascular zone were included in the inner layer. Also, MacTel 2 can have subretinal neovascularization, which lies within tissue under the retina. This was segmented by taking a slab thickness to include any hyperreflective material mounding above the level of the retinal pigment epithelium to the plane of the inner retinal pigment epithelium, as seen in surrounding uninvolved regions.

Image Preparation

With retinal thinning, as is commonly seen in MacTel 2, it was difficult to cleanly separate the inner from the outer vascular plexus in advanced cases. The inner retinal plexus was imaged as described but because the retina can be very thin, in some cases, the inner retinal vessels were also seen in the image of the outer retinal vascular plexus. To more accurately show only the outer retinal plexus, the inner retinal vessels were marked using a deep blue color. This was accomplished by thresholding the inner and outer retinal plexus images. These binary images were then used in the image calculator of ImageJ (National Institutes of Health) by performing a Boolean AND function to obtain a third image showing the common elements in the 2 vascular layers.²⁰ This third image was colored blue and then overlaid on the outer retinal image to highlight the inner retinal vessels that appeared in the outer retinal plexus image.

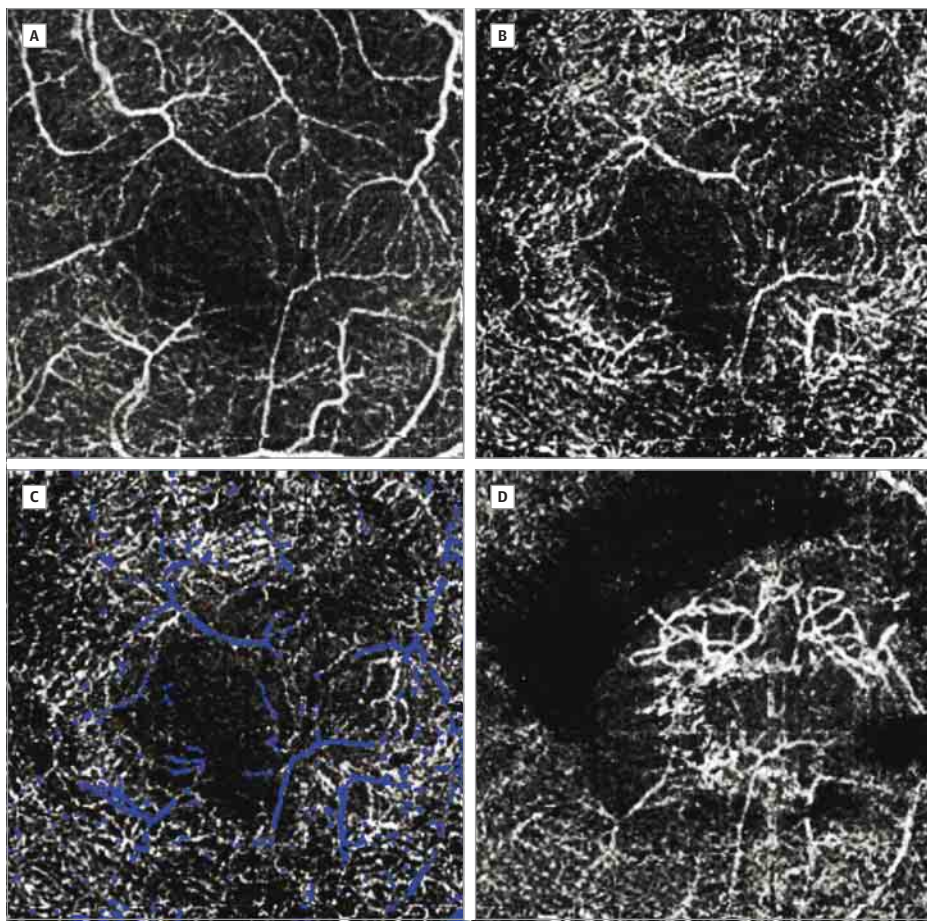
To improve the ability to simultaneously visualize different vascular layers, layers were color coded and stacked. The inner retinal vessels were made blue and the outer retinal plexus, red. Vessels in the Henle fiber layer/outer nuclear layer were made yellow. Subretinal vessels were assigned a green color. A normal eye

is shown for comparison in **Figure 1**. Note the vascular density and patterns of the vessels seen in the inner (**Figure 1A**) and outer (**Figure 1B**) vascular layers. There were no vessels in the outer or subretinal spaces. Therefore, the color stack image shows only the inner and outer retinal vascular layers (**Figure 1C**). It is estimated that 45% of the perifoveal retinal area is occupied by blood vessels in the inner and outer vascular plexus.¹⁹

Results

There were 14 eyes of 7 patients (3 women and 4 men) and the patients ranged in age from 45 to 79 years, with a mean age of 61.9 years. Of the 14 eyes, cavitation was present in the macula in 8 eyes, full-thickness macular holes in 3 eyes, and 9 eyes had evidence of either outer retinal vascular invasion or subretinal neovascularization. The severity of MacTel 2 disease affected the appearance of the vessels in all levels. In a patient with early stage 3 disease in the Gass classification, there was slight retinal opacification in the color photograph (**Figure 2A**), with mild retinal staining during fluorescein angiography (**Figure 2B**). The vessels in the inner (**Figure 2C**) and outer (**Figure 2D**) vascular layers as seen by OCT angiography showed minimal enlargement and slightly larger intervascular spaces than were seen elsewhere. There was vascular invasion into the outer retina (**Figure 2E**). The black arrowhead shows a repeating noise pattern. The color stack image succinctly showed the vascular changes (**Figure 2F**). A case with more advanced disease is illustrated in **Figure 3**; this patient had a more fully developed Gass stage 3 appearance. There were some small

Figure 4. Vascular Layers in Subretinal Neovascularization Secondary to Macular Telangiectasia Type 2



A-D, Optical coherence tomographic angiography of the inner vascular plexus (A), from the level of the outer plexus (B), after highlighting images of the inner plexus in blue (C), and image of the subretinal neovascularization (D).

flecks of pigmentary migration into the perifoveal macula (Figure 3A). The fluorescein angiogram showed telangiectasis and staining around approximately two-thirds of the circumference of the fovea (Figure 3B). The inner layer of vessels visualized by split-spectrum amplitude decorrelation angiography (Figure 3C) had decreased vascular density with a coarse branching pattern. The deep capillary network (Figure 3D) had a dilated, widely spaced dendritic appearance in the region affected in the fluorescein angiogram. The small bright circular figures (some appearing on vessels, some not) seemed to colocalize with intraretinal pigment seen in the color photograph. The vascular pattern in the deeper layer outside of this region was manifested by thin vessels. Sectioning the retina at the Henle fiber/outer nuclear layer, a region that would be ordinarily dark in OCT angiographic evaluation if avascular, showed invasion by gnarly telangiectatic vessels (Figure 3E). The topographic extent of the invading vessels was adjacent to the area of rarified, dilated outer retinal vascular plexus, as seen in the color stack image (Figure 3F).

Advanced disease is shown in Figures 4 and 5; this patient had Gass stage 5 disease with subretinal neovascularization. In Figure 4A, the superior macula in the OCT angiographic image showed a loss of the perifoveal capillaries, with the remaining longer segments separated from fellow capillaries by open spaces. In Figure 4B, the outer vascular plexus

image showed a loose pattern of vessels in the more superior portion of the OCT angiographic image while the areas closer to the fovea looked like the same vessels seen in the inner layer image. This is because the perifoveal retina in this eye had the characteristic thinning that patients with MacTel 2 develop; there was almost no apparent outer retinal plexus present in the perifoveal region. To isolate vessels solely in the outer retinal plexus, the inner and outer plexus images were thresholded and, by use of a Boolean AND operation, the common elements of both were isolated and made blue in color. This focused attention on vessels only in the outer vascular plexus (Figure 4C). There was a loss of flow information originating from the plane of the outer retinal vascular plexus. Optical sectioning immediately above the level of the retinal pigment epithelium showed the extent of subretinal neovascularization (Figure 4D). In a color stack overlay (Figure 5), the strata of vessels was more evident. The region of subretinal neovascularization shown in green was adjacent to areas of poor or absent flow in the inner and deeper layers of the retina.

Discussion

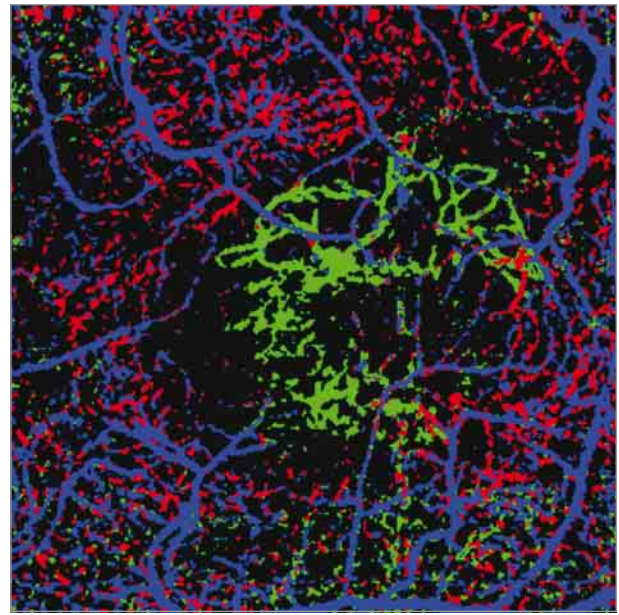
This OCT angiographic study of eyes with MacTel 2 showed there was loss of capillaries in both the inner and outer

plexus in the macular region (seemingly more so in the outer plexus). The vessels in the outer plexus showed a more widespread thinning in caliber and density in advanced disease. Even in areas well outside of the clinically visualized MacTel 2 abnormalities, the outer retinal plexus showed absent or decreased flow information. Vascular invasion into the normally avascular Henle fiber/outer nuclear layers was visualized and principally happened beneath areas of prominent retinal vascular change of the inner and outer vascular layers related to the MacTel 2. More advanced cases of MacTel 2 had increased loss of the perifoveal capillaries of the inner plexus, more prominent decrease in the imaged outer plexus, and invasion of deeper layers and the subretinal space with new vessels.

The pathophysiology of MacTel 2 is befuddling in part because of the lack of detailed information as to what happens in the disease. Gass⁸ proposed that Müller cell abnormalities could be at the core of MacTel 2 and subsequent reports have extended this line of reasoning. The histopathologic correlation of 2 patients with MacTel 2 showed depletion of Müller cells. Müller cells provide numerous functions in the retina.^{21,22} They manage fluid and electrolyte concentrations in the retina,²³⁻²⁵ mediate some of the effects seen with cytokines and growth factors,^{26,27} and produce a wide variety of growth factors themselves^{28,29} including proangiogenic and antiangiogenic factors.²⁹⁻³⁵ Müller cells participate in inflammatory and proliferative processes,³⁶ the removal and metabolization of neurotransmitters^{37,38}; play roles in synaptogenesis, neuroprotection,³⁹ and survival of photoreceptors; and simultaneously act as light guides in the retina.⁴⁰ Müller cell ablation causes both neuronal and vascular pathologies including photoreceptor apoptosis, vascular telangiectasis, and eventual intraretinal neovascularization.⁴¹ Younger patients with MacTel 2 may not have clinically detectable manifestations; therefore, for the histologic examination to show depletion, Müller cells must die. Loss of Müller cells is the extreme end of the spectrum but prior to death, it is possible that the Müller cells may not function properly. The retinal vascular and other abnormalities seen in MacTel 2 may be the result not only of Müller cell depletion, but abnormal Müller cell function prior to death. A main result of the present study was that eyes with MacTel 2 appeared to have broad areas of abnormalities in the outer retinal vascular plexus around the macula, as determined by OCT angiography. These vessels appeared to be thinner, less densely packed, and, in more advanced disease, had an abnormal arrangement. These retinal vascular abnormalities may in turn affect the health and vitality of the remaining retinal tissue.

The absence of flow imaging in these eyes does not necessarily mean the vessels are not present. However, the lack of flow would have undesirable tissue effects whether the vessel was physically present or not. Loss of vessels with development of telangiectasis may limit the delivery of oxygen and metabolites to the retina. This idea is consistent with what Gass⁸ proposed many years ago, although not by the same exact mechanism. The vascular density in this disease is difficult to evaluate by ophthalmoscopy or fluorescein angiography. The consistent finding in the present study

Figure 5. Color Stack Image of the Patient Shown in Figure 4



The inner plexus is blue; the outer plexus, red; and the subretinal neovascularization, green. The area occupied by the subretinal neovascularization is under the region of the macula with the most affected flow abnormalities in the overlying retinal vascular layers.

using OCT angiography was the apparent loss of functional vessels in MacTel 2, particularly in the deep vascular plexus. The vascular invasion, which seemed to happen under the areas of more prominent retinal capillary loss, may be a logical and expected consequence. The oxygen tension in a normal retina is quite low in the region extending from the ellipsoid portion of the photoreceptors to the middle of the retina.⁴² Ordinarily, the Müller cell is an important manager of vascular endothelial growth factor in the midretina and loss or defective function of Müller cells may alter growth patterns of intraretinal neovascularization.^{27,28,30,33,40} One basic goal of neovascularization is to ameliorate hypoxia. Thus, posterior invasion of the newly growing vessels into areas of extremely low-oxygen tension would be expected. One looming question is why the vessels do not grow in normal eyes, but Müller cells are known to produce antiangiogenic substances and, therefore, may modulate vascular expression in various layers of the retina in both health and disease.

Conclusions

This study has potential for error given that the interpretation of images provided by new technology had no gold-standard comparison imaging to gauge the effects of MacTel 2 on the retinal vessels. There were a limited number of eyes imaged in this study. Imaging with the OCT angiography technique used in this study is time consuming and each image has a relatively small field of view. For many of the figures shown, montages of several images were required to

obtain a good field of view. With technical improvements, it is likely imaging will be progressively easier over time, similar to what has been the case for OCT in general. We had previously shown that the fluorescein angiographic image in humans is highly dominated by the inner vascular plexus, as seen by OCT angiography.¹⁶ Previous investigators have shown the same thing by using animal models and

histologic examination. The OCT angiographic evaluation in this study provided interesting and novel information about vascular abnormalities in MacTel 2 that complement hypotheses concerning Müller cell anomalies. The vascular changes may be the result of and accentuate the Müller cell abnormalities. The findings of this study raise several questions that can direct future histologic evaluations.

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Study concept and design: Spaide, Klancnik.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Spaide.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Spaide.

Study supervision: Spaide, Cooney.

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OPHTHALMIC IMAGES

Leukemic Retinopathy

Johnathan D. Warminski, MD; Eduardo Uchiyama, MD



A 17-year-old adolescent boy presented with blurred vision for several weeks. Indirect ophthalmoscopy revealed dilated and tortuous vessels with diffuse retinal infiltrates and intraretinal hemorrhages as well as a macular leukemic infiltrate. Visual acuity was 20/400 OD and 20/20 OS, the white blood cell count was 521 400 cells/ μL (to convert to $\times 10^9/\text{L}$, multiply by 0.001), and a bone marrow biopsy supported a diagnosis of chronic myelogenous leukemia. In this composite fundus image of the right eye with decreased visual acuity, peripheral intraretinal hemorrhages with cotton-wool spots are apparent in addition to a large leukemic infiltrate in the macula.