Relevance of Multicolor Imaging in Type 2 Macular Telangiectasia

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Abstract

Purpose: To report the imaging characteristics of various clinical features in idiopathic macular telangiectasia (MacTel 2) on multicolor imaging (MCI) and compare its accuracy vis-à-vis color fundus photograph (CFP) and fluorescein angiography (FA).

Methods: In this retrospective observational study, 54 eyes of 27 patients with MacTel 2 were included after institutional review board approval. Multimodal imaging with CFP, optical coherence tomography (OCT), MCI, and FA was done. Images were analyzed to identify and describe the clinical findings in MacTel 2. Sensitivity, specificity, and positive and negative predictive values were computed for the various imaging modalities in MacTel 2.

Results: In this study, the MCI identified all the different clinical features of MacTel 2 in 100% of cases. The confocal blue reflectance (BR) image was more sensitive than CFP (100% vs. 96.3%) in identifying the loss of retinal transparency in MacTel 2. For other clinical features such as right-angled vessels, superficial retinal crystals, and retinal pigment epithelial hyperplasia/plaques, the sensitivity of BR, and green reflectance (GR) image, was comparable to that of CFP. Confocal infrared reflectance (IR) images showed poor sensitivity in identifying the non-proliferative features in MacTel 2 (P < 0.001). Loss of retinal transparency was not picked up on IR image. Other features such as right-angled vessels, superficial retinal crystals, and pigment plaques were seen in 20%, 4.6%, and 26.3% of cases, respectively. However, confocal IR images were superior to FA (100% vs. 47%) and CFP (100% vs. 15%) in identifying the extent and location of subretinal neovascular membrane. The confocal BR and GR images were unable to identify the choroidal neovascular membrane (P < 0.001).

Conclusion: MCI is a useful and non-invasive imaging modality to identify the clinical features in MacTel 2. MCI can be used as a complementary imaging tool to CFP, FA, and OCT.

Keywords: Choroidal neovascular membrane, Idiopathic macular telangiectasia, Imaging, Multicolor imaging

INTRODUCTION

Gass and Blodi described Type 2 macular telangiectasias (MacTel 2) as a disease entity presenting with abnormal and/or irregular dilatations of the retinal capillary network affecting only the juxtafoveal region usually of both eyes.1 The disease affects individuals between the fifth and seventh decades of life and causes progressive central visual loss due to foveal atrophy and/or subretinal neovascular (SRNV) membrane proliferation.

While the exact etiology remains unclear, initial description of the disease suggested an underlying vascular etiology; however, the neurodegenerative mechanism is a more widely accepted one.3 In fact, a number of histopathological studies have described a striking reduction of the Müller cells in the perifoveal area, leading to a decrease in the macular pigment density and subsequent structural and functional loss of the photoreceptors.3,6
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Gass and Blodi classified this progressive disease into five stages starting with the presence of occult telangiectatic vessels in Stage 1 to the development of SRNV in Stage 5. The diagnosis of MacTel 2 in its early stages can be challenging. Color fundus photographs (CFPs) in early stages of MacTel 2 show loss of retinal transparency, presence of superficial retinal crystals and pigment plaques deep in the mid-retina, and eventually the development of SRNV in the later and advanced stage. Fluorescein angiography (FA) has been used frequently for the diagnosis of early stages of MacTel 2. It shows a diffuse hyper fluorescence in the late phase predominantly temporal to the fovea. Parafoveal telangiectatic capillaries may be seen in the early angiographic phase.7,8

In recent years, confocal blue reflectance (BR) imaging using the confocal scanning laser ophthalmoscope (cSLO; HRA2, Heidelberg Engineering, Heidelberg, Germany) has proven to be a very sensitive and non-invasive method for the diagnosis of MacTel 2 as well as differentiating it from other conditions.9,10 Confocal BR imaging (488 nm) is particularly helpful in the diagnosis of early stages of MacTel 2 which are most difficult to detect clinically, demonstrating a well-defined generally oval, parafoveal area of increased reflectance that corresponds to, but is slightly larger than, the area of leakage in late-phase angiography. The activity of SRNV and presence of the photoreceptor disruption due to MacTel 2 often get missed on FA due to the mixture of leakage from both the SRNV and telangiectatic vessels.

Multicolor imaging (MCI) is a newly introduced non-invasive imaging technique available on the Heidelberg, Spectralis spectral domain optical coherence tomography (OCT) machine, wherein a single point of laser light of a defined wavelength is scanned across the retina and thus, enables an alternative method of capturing fundus images.11,12 Light of three different spectrums, blue (488 nm), green (515 nm), and infrared (820 nm), penetrate the tissue to different depths and simultaneously capture the reflectance strengths from different retinal structures and represent the information as en-face images. The appearance of all phenotypic features of MacTel 2 on MCI has not been studied in detail. Here, we aim to evaluate the utility of MCI in identifying the different clinical features in MacTel 2.

**METHODS**

In this retrospective study, eyes with MacTel 2 identified between July 2017 and June 2018 that had undergone multimodal fundus imaging were included from the retina clinic of a tertiary eye care referral center. The participants underwent complete ophthalmologic examination. The diagnosis of MacTel 2 was based on the presence of characteristic clinical features as described by Gass and Blodi.1 The diagnosis of MacTel 2 was confirmed on FA as an area of early hyperfluorescence temporal to fovea with increased leakage and staining in the later phases of the angiogram, in the early stages, or by the presence of perifoveal hyperfluorescence in advanced stages of the disease. SRNV in MacTel 2 was suspected when lipid exudates, intra or subretinal hemorrhage, and macular edema appeared as these features are not otherwise characteristic of MacTel 2. On FA, an area of hyperfluorescence in late stages was noted, which was more intense than the area of perifoveal leakage due to MacTel 2. As the aim of the study was to describe the clinical features of MacTel 2 on MCI, we included cases with both early and advanced stages of the disease. Institutional review board and ethics committee approvals were obtained for the study. The exclusion criteria included patients with any associated, previous, or concomitant ophthalmological condition that could confound the interpretation of multimodal fundus imaging or with a history of previous treatment, including thermal laser photocoagulation, photodynamic therapy, or intravitreal administration of anti-vascular endothelial growth factor. Cases with choroidal neovascularization due to other etiologies such as central serous chorioretinopathy, age-related macular degeneration, and polypoidal choroidal vasculopathy were excluded from the study. The clinical details of each patient were collected retrospectively by review of records, including age, gender, and laterality. Each patient underwent complete ocular examination including best corrected visual acuity, slit-lamp examination, and indirect ophthalmoscopy. CFP was done using the Topcon TRC 50Dx (Topcon medical Systems, Inc. Oakland, NJ, USA) machine color fundus camera. In addition, all patients had OCT, FA, and MCI (in that order) performed by a skilled technician. MCI was done at the end after a minimum of 20 min of dark adaptation in order to avoid the fading of confocal BR hyperreflectivity seen in MacTel 2. The scanning field was 30° in all cases. No manual alterations in the imaging features such as brightness, contrast, sharpness, and pseudocolor channels were done. The MCI were analyzed by a single certified skilled retinal specialist (R.V.) who was blinded for the clinical diagnosis and the stage of the disease. The images were compared vis-à-vis CFP for loss of retinal transparency, superficial retinal crystals and pigment plaques, FA for right-angled vessels, and OCT for SRNV. OCT-angiography (OCT-A) images were not available in all cases and were not evaluated. Even in the limited number of cases which were available, SRNV could not be confirmed due to the projection artifacts from the migrated retinal pigment epithelium plaques to the superficial retinal layers. Hence, we compared the SRNV features of MacTel 2 on MCI with OCT imaging. On the confocal BR, green reflectance (GR), and infrared reflectance (IR) images, findings were described as hyper (white) or hypo (dark) or iso (normal) reflectance areas against the surrounding normal retinal reflectance, whereas on MCI, the color changes were identified and documented. Any abnormal hyper reflectance noted on IR image was cross-verified with the same area on the OCT image to confirm the presence of SRNV.

**Statistical analysis**

All the analyses were done using the GraphPad Prism statistical software version 8.0.2 (GraphPad Prism version 8.0.2 for Windows, GraphPad Software, San Diego, California USA). Continuous variables such as age were described in the form of mean and standard deviation, whereas categorical variables
such as sex and laterality were described as absolute numbers and percentages. In this study, sensitivity analysis for every clinical finding in MacTel 2 was calculated comparing different imaging modalities. Detection rate or sensitivity was calculated using the Wilson–Brown method. Chi-square tests were performed for categorical analysis. $P < 0.05$ was considered statistically significant.

**Results**

In this retrospective study, 54 eyes of 27 patients diagnosed with MacTel 2 that met the inclusion criteria were included. All patients had bilateral involvement. The mean age of the 12 (44%) male and 15 (56%) female patients was 61 ± 9.06 years. Visual acuity was between 6/6 and 6/18 in 38 (70%) eyes and <6/18 in 16 (30%) eyes. Non-proliferative disease was identified in 35 (65%) eyes and confirmed proliferative disease (Stage 5) was seen in 19 (35%) eyes. Very early stage of the disease without clinically evident loss of retinal transparency (Stage 1) was noted in 2 (4%) eyes, while 33 (61%) eyes showed disease between Stages 2 and 4. The distribution of eyes identifying the clinical features with different imaging modalities is shown in Table 1. The detection rate of clinical features of MacTel 2 with each imaging modality is described in Table 2. The utility of MCI in identifying the various clinical features in MacTel 2 is shown in Figures 1 and 2.

**Loss of retinal transparency**

The loss of retinal transparency and small telangiectatic vessels which are almost always identifiable only on FA represents the early signs of MacTel 2. On CFP, a perifoveal grayish zone temporal to fovea was identified in 52 (96.3%) of the 54 eyes with MacTel 2. On confocal BR, loss of retinal transparency was identified as a zone of perifoveal hyper reflectance in all the 54 (100%) eyes diagnosed with MacTel 2. On the MCI, perifoveal graying was seen in 100% of eyes diagnosed with MacTel 2. The predictive ability of CFP, confocal GR, BR, and MCI to identify the initial stages of MacTel 2 was 96.3%, 96.3%, 100%, and 100%, respectively. On both BR and GR images, perifoveal graying was seen as an area of hyper reflectance (white) usually temporal to the fovea. The area of perifoveal hyper reflectance involvement on MCI appeared larger and well demarcated compared to the area of leakage identified on FA. On confocal IR images, the loss of retinal transparency was not visualized. Perifoveal leakage was seen in all eyes on FA, while the abnormal and/or irregular retinal telangiectatic vessels were not seen on either CFP or MCI.

**Right-angled vessels**

Blunting of the retinal venules with dipping into the area of retinal telangiectasia was identified in 20 (37%) eyes of MacTel 2 on FA. The sensitivities of confocal BR, GR, MCI, and CFP images were 100% in identifying the right-angled vessels in MacTel 2. However, on confocal IR images, right-angled vessels were identified in 4 (20%) eyes only.

**Retinal pigment epithelial hyperplasia/plaques**

Retinal pigment epithelial hyperplasia/plaques are seen as small focal spots of blocked fluorescence on FA corresponding to the black pigments on CFP and hyperreflective spots in the mid-retina layers, with shadowing on OCT. In this study, pigment epithelial plaques were seen in 19 (35%) eyes on

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**Table 1: Summary of clinical features in Type 2 macular telangiectasia and comparison between fluorescein angiography, color fundus photograph, optical coherence tomography, and multicolor imaging**

| Finding                              | CFP | FA | OCT | MCI | BR | GR | IR |
|--------------------------------------|-----|----|-----|-----|----|----|----|
| Loss of retinal transparency         | 52  | 2  | -   | -   | 54 | 0  | 52 |
| Right-angled vessels                 | 20  | 0  | 20  | 0   | 20 | 0  | 20 |
| Pigment plaques                      | 19  | 0  | -   | 19  | 0  | 19 | 14 |
| Retinal crystals                     | 22  | 0  | -   | 22  | 0  | 22 | 21 |
| Subretinal neovascular membrane      | 3   | 15 | 9   | 10  | 19 | 0  | 19 |

CFP: Color fundus photograph, FA: Fluorescein angiography, OCT: Optical coherence tomography, MCI: Multicolor imaging, BR: Blue reflectance, GR: Green reflectance, IR: Infrared reflectance, P: Present, A: Absent

**Table 2: Sensitivity analysis between multicolor imaging and color fundus photograph, fluorescein angiography, and optical coherence tomography in different clinical findings of Type 2 macular telangiectasia**

| Finding                              | CFP | FA | OCT | MCI | BR | GR | IR |
|--------------------------------------|-----|----|-----|-----|----|----|----|
| Loss of retinal transparency         | 96.3| 0.999| -  | -   | -  | -  | -  |
| Right-angled vessels                 | 100 | >0.999| -  | -   | -  | -  | -  |
| Pigment plaques                      | 100 | >0.999| -  | -   | -  | -  | -  |
| Retinal crystals                     | 100 | >0.999| -  | -   | -  | -  | -  |
| Subretinal neovascular membrane      | 15.8| <0.001| 47.4| 0.001| 100| <0.999| 100| <0.999|

CFP: Color fundus photograph, FA: Fluorescein angiography, OCT: Optical coherence tomography, MCI: Multicolor imaging, BR: Blue reflectance, GR: Green reflectance, IR: Infrared reflectance, DR: Detection rate in percentage, P: $P$ value $<0.05$
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CFP. The confocal BR and GR images identified the pigment epithelial plaques as jet-black spots seen in the perifoveal region. Multicolor images showed the pigment plaques as reddish-brown spots. The sensitivities of the confocal MCI, BR, GR, and IR images in identifying the pigment epithelial plaques were 100%, 100%, 100%, and 26.3%, respectively.

**Superficial retinal crystals**

The presence of yellow-white refractile crystals in the superficial layers of the parafoveal retina is a characteristic and frequent feature of MacTel 2. Small retinal crystals were identifiable in 22 (41%) eyes on CFP in our study. MCI identified the retinal crystals as bright yellow deposits at the parafoveal region. On confocal BR and GR images, the retinal crystals were identified as bright white spots/clumps against a dark background. Retinal crystals were identified on confocal MCI, BR, GR, and IR images in 22 (100%), 22 (100%), 22 (100%), and 1 (4.6%) eyes, respectively.

**Subretinal neovascularization**

On FA, the SRNV has angiographic features similar to classic neovascularization demonstrating early hyperfluorescence, which increases and leaks in the late phases of the angiogram. However, the leakage from the SRNV often gets mixed with the hyperfluorescence from the telangiectatic vessels. In this study, the presence, location, and extent of SRNV were confirmed on OCT as a small irregular elevation noted often above the retinal pigment epithelium with associated intraretinal/subretinal fluid. In 19 (35%) eyes, SRNV was identified on OCT in our study. The confocal IR image identified the SRNV.
as a well-defined area of hyper reflectance within the area of retinal telangiectasia. On the MCI, the SRNV was seen as a bright orange speckled lesion corresponding to the hyper reflectance on the IR image. The exact extent and the location of SRNV was identified in 9 (47%), 3 (16%), 0 (0%), 0 (0%), 19 (100%), and 19 (100%) eyes with FA, CFP, confocal BR, GR, IR, and MC images, respectively.

**DISCUSSION**

This study analyzed the macular images obtained from MCI technique to describe the various clinical features in MacTel 2 and compared them with the CFP and/or OCT and computed their predictive abilities. The results suggest that MCI could be a useful and non-invasive modality that may be beneficial in the diagnosis of MacTel 2.

One of the earliest signs and also the sole criterion of Stage 2 MacTel is the “graying of the foveal area” or “loss of retinal transparency.” Charbel Issa et al. showed that an area of abnormally increased hyper reflectance could be visualized with short wavelength blue (488 nm) light using a cSLO, which corresponded to this loss of retinal transparency. The intensity appears to fade with continuous light exposure and is restored following dark adaptation as noted by Jindal et al. This study found increased parafoveal reflectance on confocal BR images in all eyes of MacTel 2, which corresponded to the area of reduced retinal transparency (when visible on fundus photography) and to the area of diffuse hyperfluorescence in late-phase FA. In two eyes, increased parafoveal confocal BR was also present in parafoveal areas with normal retinal transparency. Thus, the confocal BR seems to be a good, non-invasive screening modality to identify the earliest sign in MacTel 2, when done after a period of dark adaptation. Interestingly, the area of increased reflectance on confocal BR was noted to be larger than the area of diffuse hyperfluorescence in late-stage FA, suggesting that the disease process might go beyond the margins of the angiographically apparent leakage. Furthermore, the angiographically visible alterations in MacTel 2 are due to secondary vascular phenomenon. This fact has been well demonstrated by other studies as well. The exact nature of the phenomenon of increased reflectance in the parafoveal area with foveal sparing on confocal BR is not well understood. One possibility could be the lack of macular pigment in the parafoveal area and absence of the retinal nerve fibers in the foveal area which could be responsible for this phenomenon.

Dilated right-angled vessels are seen as paracentral, vertically oriented vessels with blunted tips, dipping and draining the telangiectatic area, evident clinically on biomicroscopic examination. In this study, right-angled vessels were identified with equal sensitivity on CFP, confocal BR, and GR images. The vessels were seen as dark structures on the BR and GR images. This is due to the increased absorption of the low wavelength light by the retinal vessels. The dark appearing right-angled vessels were more easily visible against the increased reflectance due to the loss of retinal transparency on the confocal BR and GR images.

Pigment epithelial plaques occur in later stages of MacTel 2 as a result of retinal pigment epithelial migration along the course of the right-angled vessels into the retina. Anatomically, on OCT, they are seen as hyperreflective foci with back shadowing located in the middle retinal layers. The confocal BR and GR images identified the pigment epithelial plaques with comparable sensitivity compared to CFP as dark spots in the area of retinal telangiectasias in this study. The location of the retinal pigment epithelial plaques in the superficial middle retinal layers allows the confocal BR and GR images to visualize them better than the IR image. The presence and increase in plaque size may correlate with the development of SRNV later.

Yellow-white refractile crystals are noted in the superficial layers of the parafoveal retina in eyes with MacTel 2. They can be seen all along the Stages 2–5. They represent the remnants of degenerated Müller cells because of their location near the internal limiting membrane (ILM). In a study by Sallo et al., the amount of the retinal crystals showed a direct correlation with the amount of loss of retinal transparency, loss of macular pigment, and fluorescein leakage. In this study, the retinal crystals appeared as highly reflective dots in all the three reflectance images. All eyes with retinal crystals on CFP were identified on BR and GR images. In IR images, typically only a subset of crystals seen in confocal BR or GR images were detectable. The high reflectivity of the retinal crystals is mainly due to the Müller cells having a higher refractive index than the surrounding tissue and the vertical orientation of the cells along the direction of light propagation. Disruption in the Müller cells leads to loss of retinal transparency and its remnants being identified as retinal crystals on the ILM surface. In our study, we found equal sensitivity between CFP and MCI in identifying pigment plaques and retinal crystals in MacTel 2. However, we believe that in eyes having small plaques or minimal retinal crystals, the MCI may more readily identify these lesions in the BR and GR images against a dark background.

The presence of SRNV marks the onset of the proliferative stage of MacTel 2. SRNV occurs as a result of retinal capillary modeling, proliferation, and invasion of the outer retina, leading to the formation of retino-retinal anastomosis and later to retino-choroidal anastomosis. Rapid visual decline occurs as the SRNV causes exudation, neurosensory elevation, intra- and subretinal hemorrhage, and fibrovascular proliferation.

SRNV on OCT was identified in 19 of the 54 eyes in this study. CFP and FA were able to pick the SRNV in 3 and 9 of the 19 eyes, respectively, in the study. The confocal BR and GR images did not show the SRNV in any of the cases; however, IR images detected SRNV in all 19 eyes as a focal area of hyper reflectance within the retinal telangiectasia. The confocal infrared light penetrates deeper toward the outer retina, retinal pigment epithelium, and choroid, and hence,
the IR image visualizes structures at this level better. Hyper reflectance on IR image can also be seen in other macular diseases such as age-related macular degeneration, chronic central serous chorioretinopathy, choroidal nevus, polypoidal choroidal vasculopathy, and in inherited retinal diseases such as Stargardt disease. The presence of hyper reflectance on the IR image does not necessarily signify the presence of SRNV but must be correlated with clinical and other imaging features to arrive at a correct diagnosis.

MCI has some additional advantages as well: (1) it is non-invasive, (2) non-dye-based imaging, (3) less photophobic to the patient, (4) can be used in undilated pupil, (5) 55° images give a larger view of the retinal periphery, (6) can be combined along with OCT to allow simultaneous fundus and cross-sectional imaging, and (7) provides high-contrast images, thus allowing to image through hazy media-like cataract.

In this study, we included eyes with both non-proliferative and proliferative stages of the disease. This helped us to better understand the role of MCI in MacTel 2 in its different stages. Our study had several limitations as well. Absent follow-up images meant inability to describe MCI changes over time and following treatment. In this study, the image grading was done by a single examiner. This was another important limitation of this study. In addition, we did not look at the OCT-A images in identifying the neovascular lesions in MacTel 2. Although we did not study the reasons for poor visual acuity secondary to MacTel 2, the presence of areas of retinal pigment epithelial atrophy and photoreceptor loss located underneath the fovea and also the exudation by SRNV could have been responsible for the poor vision. This would have been picked up as bright orange areas on the composite multicolor image and white areas on IR image at the subfoveal region. Thus, MCI can also be considered a useful tool in disease prognostication. More studies with larger sample size and longitudinal follow-ups will be required for reproducing these results and for better understanding the utility of MCI in MacTel 2.

In conclusion, MCI has the ability to identify the clinical features ranging from the earliest sign—before the development of perifoveal graying to the late stage—presence of SRNV in MacTel 2. Currently, MCI can be used as an important complementary imaging tool to FA, CFP, and OCT in identifying the early as well as advanced stages of MacTel 2.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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