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Does size of telangiectasia on optical coherence tomography angiography influence vision in eyes with type 2 macular telangiectasia?

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Purpose: To study the influence of dimensions of macular telangiectasia (MacTel) on enface optical coherence tomography angiography (OCTA) on vision and clinical parameters in eyes with MacTel type 2. **Methods:** MacTel was classified based on OCTA location, i.e. either temporal to the fovea (grade 1), or spread nasally (grade 2), or circumferentially (grade 3), or the presence of neovascular-like tissue in the outer retina–choriocapillary complex (ORCC) (grade 4). On enface images, the maximum dimensions of the MacTel in the deep plexus were noted using calipers by a single experienced observer. **Results:** Ninety-eight eyes of 49 patients with MacTel with a mean visual acuity was 0.46 + 0.26 logMAR and mean macular thickness of 202 ± 132 μ were included. Based on OCTA, grade 3 MacTel (n = 35, 36%) was the commonest followed by grade 4 (n = 28, 29%). The mean maximum vertical diameter of the MacTel was 2019 + 753 μ, and every 500 microns increment in vertical diameter of the MacTel was associated with a half-line drop in vision (95%CI = 0.005 to 0.08 logMAR, $P = 0.03$). Vision gradually reduced with increment in OCTA grades of MacTel from grade 1 to 3; however, the trend was not maintained in grade 4 MacTel, which showed better vision and lesser degenerative cysts. **Conclusion:** Larger telangiectasias were associated with significantly lower vision in MacTel. Eyes with deeper telangiectasia involving ORCC have better vision and evidence of far lesser neurodegeneration than type 3 disease, suggesting that this may not be part of the continuum and does not represent neovascularization.

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Macular telangiectasia (MacTel) is thought to be a neurodegenerative disease of unknown etiology that causes bilateral gradually progressive vision loss in the middle-aged and elderly population.[1] The MacTel Project, an international multicentric collaboration, has helped us gain newer insights into disease characteristics and natural history;[2,3] however, no therapeutic options have shown promising results in treating MacTel.[4]

The advent of optical coherence tomography (OCT), and especially OCT angiography (OCTA), has helped understand the MacTel disease process better than before owing to the ability to segment different vascular plexus separately in a noninvasive manner.[5,6] Understandably, OCTA has been extensively used to characterize different aspects of the MacTel over the past few years.[7-10] Toto *et al*.[11] described a useful OCTA-based grading system for MacTel that has been widely adopted and is based on either temporal, nasal, or circumferential location of the MacTel. They also describe a fourth grade characterized by neovascular tissue in the otherwise silent outer retina and photoreceptor area. Other authors have approached data analysis in different ways, with some describing the qualitative aspects[10,12] of the vascular telangiectasia, while others have used quantitative metrics such as retinal vascular density,[8] size of the foveal avascular zone, acircularity index, and other morphometrics to understand the disease process.[7,9] Surprisingly, none of the previous studies have measured the dimensions of the vascular telangiectasia, which is clearly visible on the en face OCTA images. In this study, we studied the influence of the dimensions of the MacTel measured using the OCTA on various clinical and structural OCT parameters in eyes with MacTel type 2 in the Indian population.

Methods

This was a cross-sectional observational study conducted in a tertiary care hospital in western India. The study was approved by the institutional ethics committee. Informed consent was obtained from all patients before enrolment. All consecutive patients presenting to the outpatient department between April and December 2019 and diagnosed to have MacTel type 2 were invited to participate in the study. Macular telangiectasia was diagnosed based on typical clinical characteristics described previously,[1] including any combination of perifoveal retinal graying, pigment clumps, right-angled venules, telangiectatic macular vessels, crystalline deposits, and characteristic finding of foveal thinning associated with degenerative retinal cysts. All eyes with other macular pathologies such as neovascular

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age-related macular degeneration and macular edema secondary to retinal vein occlusion or diabetic retinopathy and eyes with significant cataract or other media opacities precluding OCT and OCTA were excluded.

At the time of recruitment, patients' demographics, such as age and gender, were captured along with a duration of vision loss and history and duration of diabetes, hypertension, and any other systemic illness. All patients underwent a comprehensive ophthalmic evaluation, including assessment of the best-corrected visual acuity (BCVA) using Snellen's charts (converted to logarithm of minimum angle of resolution (logMAR) for analysis), anterior segment evaluation on the slit lamp, and a dilated fundus evaluation using the +90D lens. The clinical stage was noted during retinal examination based on classifications published previously.[13] Following this, all eyes underwent fundus photography, fundus autofluorescence, fluorescein angiography in selected cases with suspicion of Neovascularization and structural OCT (DRI OCT Triton, Topcon, Japan), as well as OCTA using a swept-source-based OCT machine (SS-OCT Angio, Topcon, Japan). From the structural OCT images, automated central macular thickness (CMT) was recorded. Additionally, the location (subfoveal, juxtrafoveal, and extrafoveal) and maximum diameter of the outer retinal hyporeflective areas (degenerative retinal cysts) in the horizontal and vertical planes were measured using the calipers provided by the manufacturer. Any discontinuity of the external limiting membrane and the ellipsoid zone was also noted. Additionally, any deposition of hyperreflective material in the outer retinal layers and macular neovascularization was also noted. Based on the structural OCT, the MacTel was classified into four grades as suggested by Toto *et al*.,[11] with grade 1 being the least and grade 4 being the most severe associated with neovascularization and subretinal and/or intraretinal fluid.

The OCTA scans were acquired by a technician well trained in obtaining OCTA. A 6 × 6 mm scan centered on the fovea was acquired, and en face retinal angiograms were created using the proprietary OCTARA image processing algorithm (Topcon, JAPAN). Automated segmentation was utilized to visualize the vascular abnormalities in the superficial and deep capillary plexus, the outer retina–choriocapillary complex (ORCC), and choroidal layers. Projection artifacts were minimized using the SMART Track eye-tracking software provided by the manufacturer. Signal strength of a minimum of 7/10 was required to register the scan for analysis without any motion artifacts. The technician checked for segmentation errors as well before admitting the scan for automated analysis. As described by Toto *et al*.,[11] the MacTel was classified into four stages [Fig. 1] depending upon the presence of vascular anomalies in the deep capillary plexus consistent, with MacTel either temporal to the fovea (grade 1), or spread nasally (grade 2), or spread circumferentially (grade 3). Grade 4 MacTel was noted when any of these features was associated with neovascular tissue in the ORCC, with or without frank choroidal neovascularization. On enface images, the maximum dimensions of the MacTel in the deep plexus, both vertical and horizontal, were noted using calipers [Fig. 2]. The primary outcome measure was to assess the association between BCVA and the dimensions of the MacTel. Secondary outcomes were to assess other determinants of BCVA in eyes with MacTel.

Statistical analysis

All continuous variables were described as means with standard deviation or median with interquartile range (IQR) while categorical variables were described as proportions (n, %). When comparing across two groups, differences in continuous variables with normal distribution were assessed using the student *t*-test or Wilcoxon's ranksum test for nonparametric variables. When comparing across more than two groups, the analysis of variance or the Kruskall Wallis test was used to find differences between continuous variables. Group differences between categorical variables were accessed using the Chi-square or Fischer's exact test. Correlation between continuous variables was assessed using Pearson's correlation coefficient, and this was expressed using scatter plots with locally weighted smoothening curves (LOWESS). Univariate and multivariable linear regression analysis was used to assess the determinants of BCVA. Variance inflation and forward and backward stepwise linear regression as well as Akaike's information criterion were used to finally establish the best-fit model.

Results

We included 98 eyes of 49 patients with MacTel with a mean age of 63.6 + 8.1 years of which 39 were women (80%). Thirty-three patients (67%) had diabetes for a mean duration of 9.9 + 7.8 years, and 32 had hypertension for a mean duration of 13.3 + 10.2 years. The mean BCVA of eyes was 0.46 ± 0.26 logMAR (20/50 Snellen's equivalent), and the mean CMT was 202 + 132 µ. Based on OCTA, grade 3 (n = 35, 36%) was the commonest grade of MacTel seen in our cohort, followed by grade 4 MacTel (n = 28, 29%). Clinically, stage 2 was the commonest type of MacTel (n = 58, 59%), followed by stage 4 (n = 31, 32%), while stage 5 MacTel with choroidal vascularization was seen in 4 eyes (4%) clinically.

The mean maximum vertical diameter of the MacTel as seen on the en face OCTA was 2019 ± 753 µ, while the maximum horizontal diameter was 1885 ± 553 µ. The diameter of the largest degenerative cyst in the vertical meridian was 93 ± 52 µ, while it was 403 ± 278 µ in the largest horizontal diameter. The presence of the MacTel in the deep capillary plexus was seen in 100% of eyes, while coexistent superficial capillary plexus involvement was seen in 75% of eyes (n = 73). Table 1 shows a comparison of the baseline demographics and clinical and OCT base characteristics between eyes with the four grades of MacTel. A significantly higher proportion of patients with grade 3 MacTel had diabetes. The BCVA significantly declined by 1 line each with a progressive increase in grade of MacTel from 1 to 3, but grade 4 showed better vision, comparable to grade 1. Similar trends were seen with the size of the largest horizontal and vertical degenerative cyst, being least for grade 1 MacTel on OCTA and highest for grade 3 MacTel; however, grade 4 showed a reversal trend with values comparable to grade 1 disease. Similarly, grades 1 and 4 showed juxtrafoveal degenerative cysts in the majority of eyes, with no eyes having subfoveal cysts while grade 3 eyes showed a much higher proportion of subfoveal cysts. Conversely, subfoveal cysts were exclusively seen in eyes with grade 2 (n = 4/18, 22%) and grade 3 (n = 13/18, 72%) MacTel on OCTA. There were no differences in the maximum horizontal and vertical size of the MacTel across different grades of disease on OCTA. Grade 4 MacTel showed macular

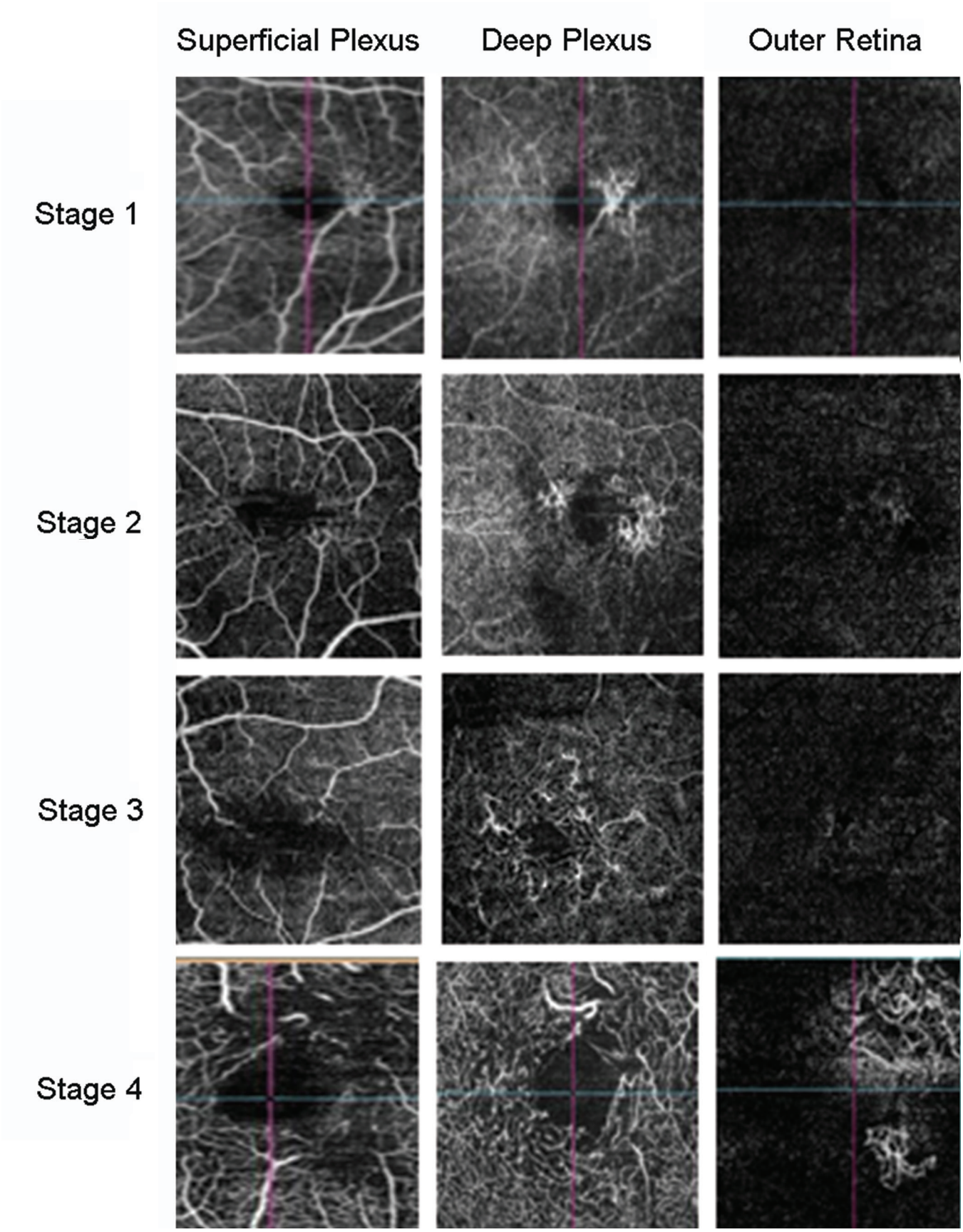

Figure 1: OCTA showing MacTel in grade 1(a), grade 2(b), grade 3 (c), and grade 4 (d) disease

neovascularization on structural OCT in 35% of eyes, while the rest did not have neovascularization

The influence of the maximum vertical diameter of the MacTel over important clinical parameters was analyzed using correlation and linear regression analysis [Table 2]. Eyes with progressively increasing vertical diameter of MacTel experienced progressively worsening vision, though this positive correlation was only modest [Fig. 3]. There was no correlation between CMT and MacTel size. Additionally, there were no differences in the vertical diameter of MacTel between different clinical stages of MacTel [Table 2]. Similarly, we found the eyes with progressively increasing horizontal diameter of the degenerative cyst also experienced progressively worsening vision [Table 3], and again, this positive correlation was only modest [Fig. 4]. Again, there was no correlation between CMT and the largest horizontal diameter of the cyst.

There was poor agreement between clinical stage and OCTA grades of MacTel (kappa = -0.03) with the same level of grading seen in only 22% of eyes. Additionally, grade 4 MacTel on OCTA associated with deep neovascularization in the ORCC slab was not picked up on clinical examination in the majority of eyes. The agreement between grades of OCTA and structural OCT was much better (kappa = 0.53), and the same grade was detected in 67% of the eyes. Multivariable linear regression analysis [Table 4] showed that every 500 µ increase in vertical diameter of the MacTel and 100 µ increment in horizontal diameter of the degenerative cyst were independently associated with more than half-line worsening of BCVA, whereas every 50 µ increment in CMT was associated with half-line improvement in BCVA. Though cyst location was associated with BCVA in univariate analysis, it was excluded from the multivariable model in view of variance inflation with horizontal cyst diameter. Other parameters such as OCTA grade, clinical stage, age, and gender did not influence BCVA significantly.

Discussion

We studied the OCTA characteristics, both qualitative and quantitative, of 98 eyes with MacTel and found that grade 3,

Table 1: Comparison of demographic, clinical, and imaging characteristics across four OCTA grades of macular telangiectasia

Variable	Grade 1 (*n*=12)	Grade 2 (*n*=23)	Grade 3 (*n*=35)	Grade 4 (*n*=28)	*P*
Age	65.3±4.3	64.1±7.9	62.1±7.6	64.5±9.6	0.58
Gender (% women, n=39)	6 (60%)	8 (100%)	15 (88%)	10 (71%)	0.12
% with diabetes	8 (80%)	2 (25%)	16 (94%)	7 (50%)	0.02
% with hypertension	7 (70%)	5 (62%)	11 (65%)	9 (64%)	0.98
BCVA (logMAR)	0.35±0.12	0.43±0.3	0.57±0.28	0.37±0.15	0.02
Lens (% phakic)	9 (75%)	13 (56%)	21 (60%)	16 (57%)	0.72
Clinical Stage: 2	6 (50%)	13 (57%)	26 (74%)	13 (46%)	0.03
Stage 3	2 (17%)	1 (4%)	0	2 (7%)	
Stage 4	4 (33%)	9 (39%)	9 (26%)	9 (32%)	
Stage 5	0	0	0	4 (14%)	
Central macular thickness (µ)	194.3±26.1	196.3±43.8	183.77±35.3	187.3±37.8	0.60
Superficial plexus involvement (%)	6 (50%)	16 (70%)	28 (80%)	23 (82%)	0.14
Max vertical diameter of MacTel	2049±984	2059±786	2090±698	1887±705	0.55
Max horizontal diameter of MacTel	1765±445	1963±665	1904±475	1849±601	0.89
Vertical diameter of Largest cyst	73.8±23.6	93.1±52.7	117.1±64.1	71.7±32.1	0.05
Horizontal diameter of Largest cyst	279.4±87.5	352.5±201	511.8±367	365.1±220	0.06
Macular neovascularization	0	0	0	10 (35%)	<0.001
Cyst location: No cyst	2 (17%)	4 (18%)	8 (23%)	8 (29%)	0.009
Subfoveal	0	4 (18%)	13 (37%)	1 (3%)	
Juxtrafoveal	10 (83%)	15 (64%)	14 (40%)	19 (68%)	

Table 2: Influence of the maximum vertical diameter of the macular telangiectasia on vision, macular thickness and clinical stage of disease

Variable	Mean	Correlations		Univariate linear regression		
		r	*P*	β coefficient	95% CI	*P*
BCVA	0.46±0.26	0.26	0.01	0.05*	0.005 to 0.08	0.03
CMT	202±132	-0.07	0.48	–5.21*	–22 to 12.5	0.56
Clinical stage 2 (*n*=58)	1874±532	-0.11	0.25		Comparison group	
Clinical stage 3 (*n*=5)	1654±595			–120	–134 to 150	0.25
Clinical stage 4 (*n*=31)	1908±616			–210	–537 to 116	0.20
Clinical stage 5 (*n*=4)	2169±208			–59	–818 to 699	0.87

*Change per 500 micron increment in vertical diameter of MacTel

i.e. markedly diffuse circumferential vascular anomalies in the deep and superficial plexus were the commonest observation. The vertical diameter of the MacTel as measured on OCTA and the horizontal diameter of the degenerative cyst measured on structural OCT moderately correlated with the BCVA, and increment in these metrics was associated with gradually diminishing BCVA. The clinical staging did not agree well with structural OCT and OCTA; hence, it is prudent to image all patients with OCT and OCTA if available. Grade 4 MacTel on OCTA is associated with better vision and smaller degenerative cysts most of which are juxtrafoveally located as compared to grade 3, which have 2 lines worse vision, much larger cysts located predominantly in the subfoveal area. The BCVA, maximum cyst size, and cyst location follow the expected pattern from grades 1 to 3 but this is reversed in grade 4, which does not follow the expected pattern.

We found that the vertical diameter of the MacTel influenced the BCVA with larger telangiectasia having lower vision. We offer two postulations to explain this relationship, the first one being that greater neurodegeneration with disintegrating Muller cells offers greater space for the expansion of the telangiectasia. This would explain both the lower vision as well as the larger vascular telangiectasia, and if this were true, the larger size of the telangiectasia may be occurring concurrently with poor vision instead of being a cause for it. Increasing size of the degenerative cyst possibly secondary to greater neurodegeneration and resulting in reduced vision, as seen in our study, adds further credence to this theory. The other explanation we offer is that a larger telangiectasia exerts greater pressure on surrounding structures and causes pressure atrophy over many years. If

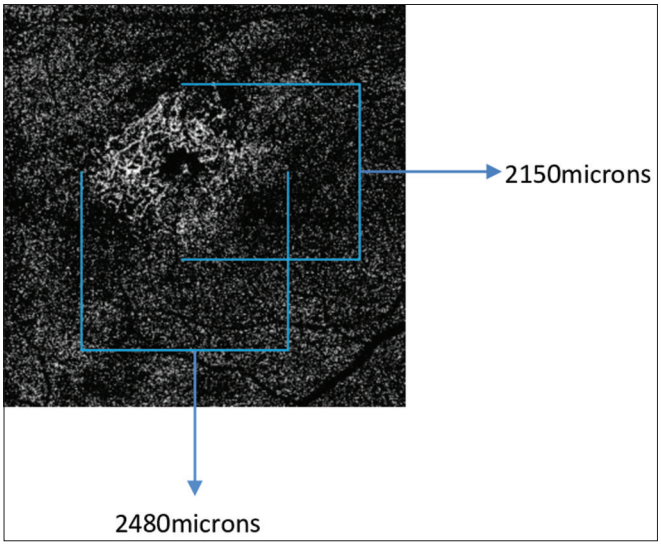

Figure 2: En face OCTA image of MacTel showing measurement of the vertical diameter using calipers

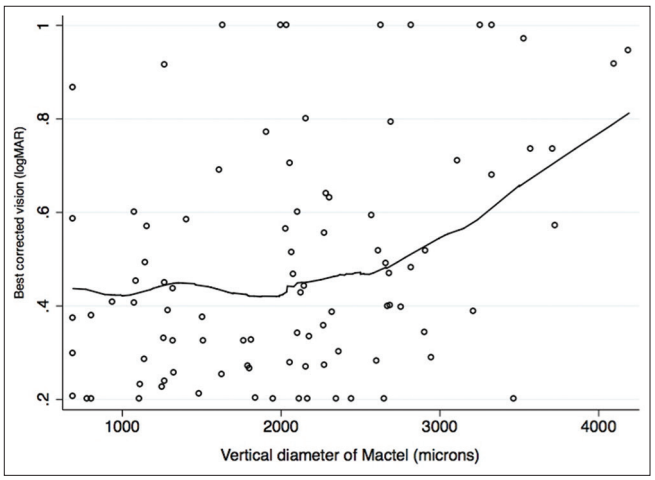

Figure 3: Eyes with progressively increasing vertical diameter of MacTel experienced. progressively worsening vision

Table 3: Influence of the largest horizontal diameter of the macular telangiectasia on vision and macular thickness

Variable	Mean	Correlations		Univariate linear regression		
		r	*P*	β coefficient	95% CI	*P*
BCVA	0.46+0.26	0.35	0.002	0.047*	0.03 to 0.07	<0.001
CMT	202+132	0.06	0.60	0.83*	−2.03 to 3.69	0.56

*Change per 500 micron increment in vertical diameter of MacTel

Table 4: Univariate and multivariable linear regression analysis showing factors predicting best-corrected vision

Variable	Interval	Univariate analysis		Multivariable analysis	
		β coefficient	95% CI	β coefficient	95% CI
Age	1 year increment	−0.005	−0.012 to 0.0001	-	-
Gender	Female vs. Male	0.04	−0.09 to 0.17	-	-
Clinical stage	Vs. Stage 2 disease	0.016	−0.04 to 0.07	-	-
OCTA grade	Vs. Grade 1 disease	0.013	−0.04 to0.06	-	-
CMT	50 μ increment	0.02	−0.004 to 0.03	−0.07*	−0.013-−0.01
Vertical diameter of MacTel	500 μ increment	0.05*	0.005 to 0.08	0.055**	0.03 to 0.08
Horizontal cyst diameter	100 μ increment	0.046**	0.03 to 0.06	0.044**	0.03 to 0.06
Cyst location	Juxtrafoveal vs. Subfoveal	−0.11**	−0.17-−0.04	-	-

*P<0.05, **P<0.001

this were true, the telangiectasia may be a cause of poor vision. A longitudinal study showing a progressive increment in the vertical dimension of the MacTel and a corresponding drop in BCVA periodically will be required to further characterize this moderate yet significant relationship.

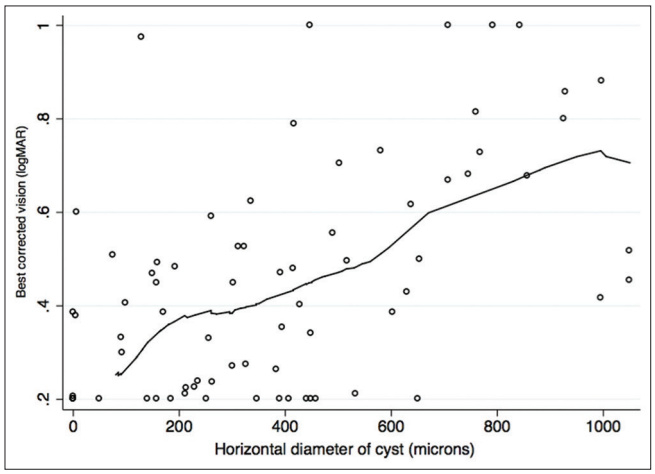

Figure 4: Eyes with progressively increasing horizontal diameter of the degenerative cyst also experienced progressively worsening of vision

Our results showed that, compared to grade 3 MacTel on OCTA, eyes with grade 4 MacTel, i.e. with a neovascular component in the ORCC slab, had significantly better vision and smaller size of degenerative cysts which were predominantly juxtrafoveal indicative of lesser neurodegeneration. Hence, we believe that grade 4 disease on OCTA might not be part of the continuum from grades 1 to 3. Even though Toto *et al.* labeled these changes as neovascularization involving the outer retina, our findings, i.e. 65% of eyes with neovascular tissue in ORCC did not have neovascularization on structural OCT [Fig. 5], show that these may actually be part of the telangiectasia in the deep plexus which spreads both superficially and into deeper structures including the ORCC slab, and not really be neovascular tissue.

Deeper telangiectasia may also not be a precursor to choroidal neovascularization as we might believe. Spaide and associates have further characterized grade 4 MacTel with abnormal deeper vessels in the ORCC and coined a new term called "retinal subsidence" to designate the descent of the outer retinal vessels toward the retinal pigment epithelium.[14] Grade 0 had deep vessels involving less than 1/3rd of the hyporeflective outer retina, commonly attributed to the outer nuclear layer (ONL)/Henle nerve; grade 1 was used to designate extension from one-third to two-thirds of

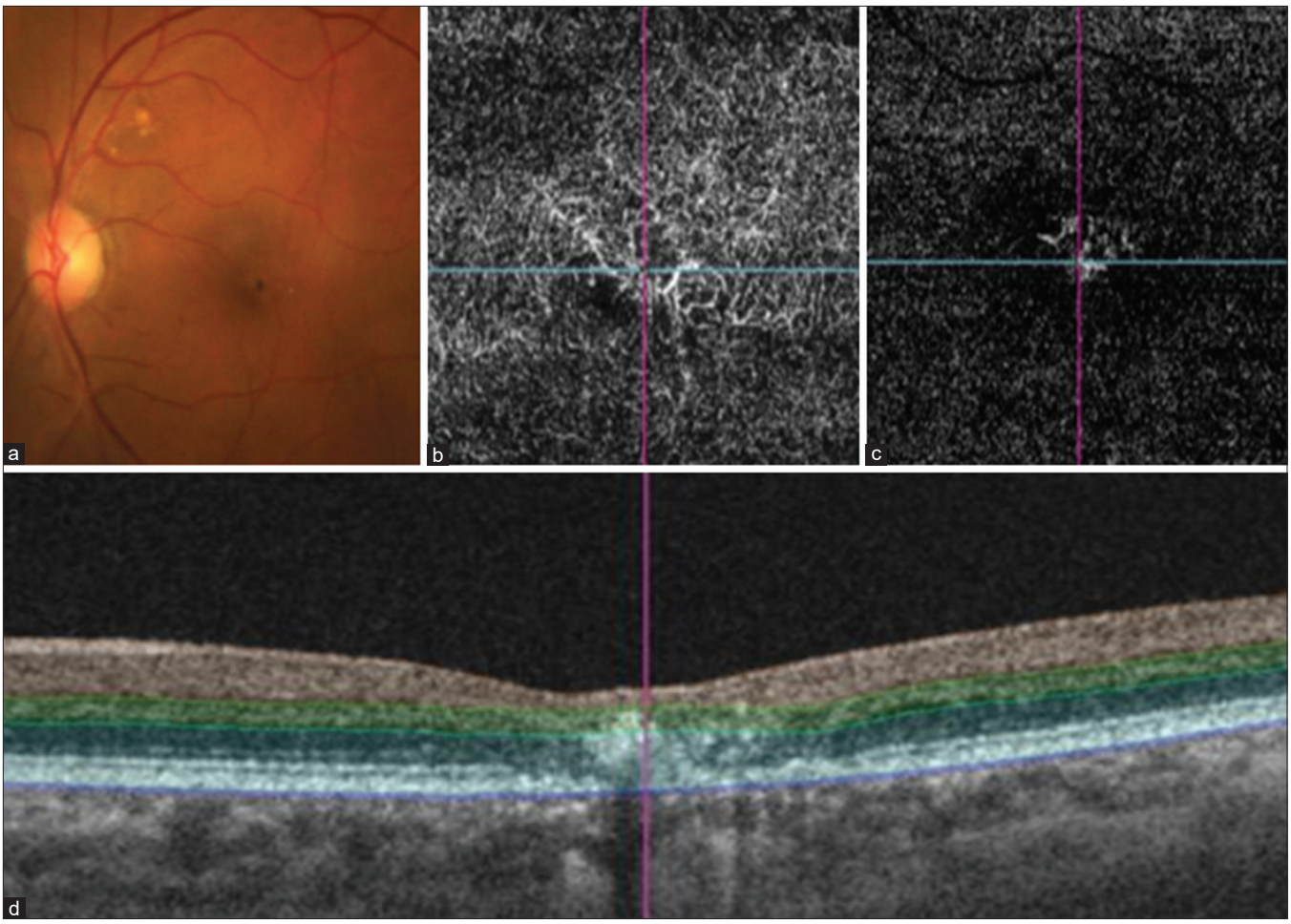

Figure 5: MacTel with pigment clump on fundus photograph (a), deep vascular plexus showing telangiectasia (b), ORCC showing neovascular-like tissue (c) likely to be a deeper extension of MacTel and structural OCT showing pigment clump (d) with back shadowing without any choroidal neovascularization, degenerative cysts or macular thinning

the thickness, and grade 2 greater than two-thirds of the entire thickness of the outer retina. They also showed clear evidence for retino-choroidal anastomosis (RCA) as the next stage of evolution of the MacTel vessels after grade 2 subsidence, without any evidence of choroidal neovascularization. Though a smaller sample than ours (n = 43 eyes), Breazzano *et al*.[15] showed that eyes with deeper MacTel in the ORCC without RCA had much better vision compared to those with RCA. Additionally, they also showed that right-angled venules were a sine qua nonfeature associated with RCA in MacTel. It is possible that our patients with grade 4 MacTel had lower grades of retinal subsidence and did not have RCA, thereby explaining the good vision in these eyes. However, we were unable to evaluate these details from our images. Given these findings, it will be prudent to follow up eyes with grade 4 MacTel longitudinally using OCTA to see whether neovascular tissue or deeper telangiectasia, as we believe, in the outer retina indeed leads to RCA or choroidal neovascularization in the majority of the eyes.

The merits of this study are the relatively large sample size and use of both qualitative metrics of MacTel, i.e. size of the MacTel seen on enface OCTA imaging to better understand the disease process. We believe that ours is perhaps the first study showing the influence of the vertical diameter of MacTel on the vision. The demerits of the study are image interpretation by only one examiner and lack of longitudinal data to show changes in the MacTel, retinal architecture, and vision over time.

Conclusion

In conclusion, larger MacTel lesions are associated with lower vision and may represent advanced stages of neurodegeneration. Eyes with deeper telangiectasia involving the outer retina have better vision and evidence of far lesser neurodegeneration than type 3 disease, suggesting that this may not be part of the continuum and that newer classifications of MacTel based on OCTA are required for better understanding the disease and have a more uniform medium of communication between researchers.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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