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RESEARCH

Clinical and morphologic features of macular telangiectasia type 2: natural course of the disease

Maküler telenjiektazi tip 2'nin klinik ve morfolojik özellikleri: hastalığın doğal seyri

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Abstract

Purpose: The purpose of this study is to report the clinical characteristics of macular telangiectasia type 2 (MacTel 2) in a natural disease course.

Materials and Methods: A retrospective analysis of patients diagnosed with MacTel 2 over a 4-year period. Best-corrected visual acuity (BCVA), fundus photography, and optical coherence tomography (OCT) images were reviewed. Differences in BCVA, fundoscopic findings, and OCT parameters were compared between the initial and final visits.

Results: The study included 28 eyes from 14 patients (11 women, 3 males), with a mean age of 65.5 ± 9.8 years. The mean follow-up period was 55.6 ± 32.9 months. The mean BCVA at baseline and final follow-up were 0.51 ± 0.6 and 0.7 ± 0.62 logMAR, respectively. At the first and last visits, the right-angle venules were the most common fundoscopic finding (78.6% for both). Subretinal neovascularization (NV) was initially present in two eyes and developed in one eye during follow-up. The mean temporal macular thickness decreased significantly during the follow-up period, while the central and nasal thickness did not show a significant change. At the last visit, focal ellipsoid zone (EZ) loss was found in 27 eyes (96.4%), compared to 24 eyes (85.7%) at baseline. External limiting membrane (ELM) loss was found in 23 eyes (82.1%) at the first visit and in 25 eyes (89.3%) at the final visit. The increase in mean length of the EZ and ELM loss during the follow-up was not statistically significant.

Conclusion: Despite the progressive effect of the disease on central visual acuity, it is very important to closely monitor these eyes for the development of secondary NV, which may develop due to degenerative and atrophic changes in the macula.

Keywords:. Ellipsoid zone, external limiting membrane, hyporeflective cavitation, macular telangiectasia type-2

Öz

Amaç: Bu çalışmanın amacı maküler telenjiektazi tip 2'nin (MacTel 2) doğal hastalık seyrindeki klinik özelliklerini bildirmektir.

Gereç ve Yöntem: MacTel 2 tanılı hastaların 4 yıllık bir süre boyunca en iyi düzeltilmiş görme keskinliği (EİDGK), fundus fotoğrafı ve optik koherens tomografi (OKT) görüntüleri incelenerek retrospektif analizleri yapıldı. EİDGK, fundoskopik bulgular ve OKT parametreleri ilk ve son vizitler arasında karşılaştırıldı.

Bulgular: Çalışmaya ortalama yaşı 65,5 ± 9,8 yıl olan 14 hastanın (11 kadın, 3 erkek) 28 gözü dahil edildi. Ortalama takip süresi 55,6 ± 32,9 ay idi. Başlangıç ve son vizit ortalama EİDGK sırasıyla 0,51 ± 0,6 ve 0,7 ± 0,62 logMAR idi. İlk ve son vizitlerde, dik açılı venüller en yaygın fundoskopik bulguydu (%78,6). Subretinal neovaskülarizasyon (NV) iki gözde başlangıçta mevcuttu ve takip sırasında bir gözde gelişti. Ortalama temporal makula kalınlığı takip süresi boyunca anlamlı olarak azalırken, santral ve nazal kalınlık da anlamlı bir değişiklik bulunmadı. Başlangıçta 24 gözde (%85,7) fokal ellipsoid zon (EZ) kaybı mevcutken, son vizitte 27 gözde (%96,4) saptandı. Dış limitan membran kaybı ilk vizitte 23 gözde (%82,1) saptanırken, son vizitte 25 gözde (%89,3) mevcuttu. Takip süresince ortalama EZ ve dış limitan membran uzunluğu kaybındaki artış istatistiksel olarak anlamlı bulunmadı.

Sonuç: Hastalığın merkezi görme keskinliği üzerindeki ilerleyici etkisine rağmen, bu gözlerin maküladaki dejeneratif ve atrofik değişikliklere bağlı olarak gelişebilecek ikincil NV gelişimi açısından yakından izlenmesi önemlidir.

Anahtar kelimeler: Dış limitan membran, ellipsoid zon, hiporeflektif kavitasyon, makular telanjiektazi tip-2

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INTRODUCTION

Idiopathic macular telangiectasia type 2 (MacTel 2 or perifoveal telengiectasis) is a rare bilateral, asymmetrically acquired disease of the macula. The disease tends to occur in the fifth and sixth decades, with a slightly higher incidence in women[1, 2]. Although the disease was previously thought to be a vascular pathology of the macula, current histopathological research indicates that it is a neurodegenerative process[3]. It is known that Müller cells play an important role in maintaining the blood-retinal barrier and providing trophic factors to surrounding neuronal cells. It is believed that a neurodegenerative process, which initiates Müller cell disfunction and loss, primarily causes the pathophysiology of the disease; vascular alterations and retinal layer damage follow this process[4,5]. However, the mechanisms causing damage to Müller cells remain controversial.

The parafoveal temporal area of the retina typically initiates the characteristic retinal pathology, which is characterized by loss of clarity, grayish retinal opacities, crystalline deposits in the inner retina, right-angle venules (RAVs), vascular telangiectasia, and hyperplastic retinal pigment epithelium (RPE) migration[6]. As the disease progresses, it may lead to development of macular atrophy, progressive abnormalities of juxtafoveal retinal vessels, neovascularization (NV), a lamellar hole, and a full-thickness macular hole[7,8].

Gass and Blodi classified type 2 MacTel into five stages based on clinical and angiographic findings: perifoveal greying and loss of retinal transparency (stage 1), no visible/occult telangiectasias, dilated right angled venules, retinal pigment clumps (stages 2-4), and development of subretinal neovascular membrane (SNVM) (stage 5)[9]. However, the 2005 Mactel Study Project, using different imaging techniques, has led to a more comprehensive understanding of the clinical features, natural history and underlying causes of the disease [7].

Optical coherence tomography (OCT), a non-invasive technique, is important in terms of helping to understand the pathogenesis by detecting retinal structural abnormalities in vivo during the course of the disease[10]. There are a few articles describing the OCT imaging features such as the internal limiting membrane (ILM) drape, degenerative inner and outer retinal hyporeflective cavities, disruption of the external limiting membrane, ellipsoid zone, interdigitation zone, presence of macular hole, and SNVM in type 2 MacTel[11-13]. However, there are a limited number of studies on the visual and OCT findings in the long-term follow-up of the disease.

The aim of this study was to evaluate the changes in fundoscopic and OCT findings over time and their association with visual results to reveal the clinical course of MacTel 2.

MATERIALS AND METHODS

Study design and sample

Patients who were diagnosed with MacTel type 2 and followed up in Çukurova University Department of Ophthalmology between September 2014 and October 2023 were included in this study. The institutional review board and ethics committee at Cukurova University approved the present study, adhering to the guidelines of the Declaration of Helsinki (meeting number: 142/41, March 8, 2024). All participants in the study provided informed consent to keep their identification information personal and not shared with other entities. We obtained written informed consent to guarantee the confidentiality of patient identity information and its non-disclosure to any other entities.

We retrospectively reviewed the medical records of patients with at least 6 months of follow-up. We excluded patients with other retinal diseases such as diabetic retinopathy, hypertensive retinopathy, retinal vein occlusion, and a history of previous intraocular surgery. In addition, participants who did not have regular follow-up and did not allow their medical records to be used for the study were also excluded from it. At each visit, we performed the best corrected visual acuity (BCVA) measurement (with Snellen's chart), dilated fundus examination, color fundus photography, and optical coherence tomography (OCT, Spectralis, Heidelberg, Germany). Additionally, we performed FFA on each patient during the first visit and any necessary follow-up visits.

Ophthalmologic examinations

Ophthalmological examination findings, BCVA, color fundus photography, OCT, and fundus angiography (FA) were evaluated at the first and last visits of all patients. The cases were classified according to the staging suggested by Gass and Blodi[9]. Central, nasal, and temporal macular

thickness (µm), ellipsoid zone (EZ) loss (µm) length, and external limiting membrane (ELM) loss length (µm) were measured manually using an OCT micrometer scale (Figure 1-2). Choroidal thickness (µm) was measured subfoveally and 1000 µm nasal and temporal to the fovea with enhanced depth imaging OCT (EDI-OCT) (Figure 3). Three experienced retina specialists (PI, EE, ND) evaluated the OCT images and measurements, and statistically compared the data from the first and last visits.

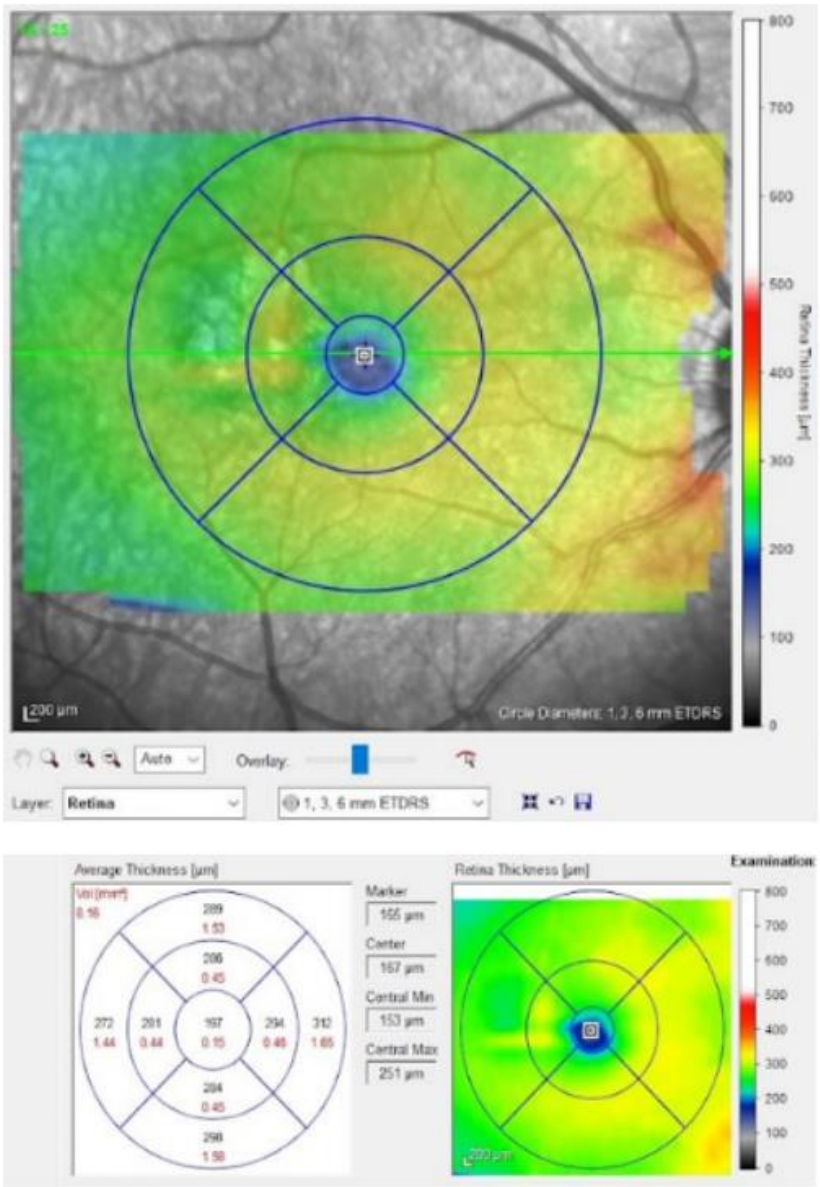

Figure 1. Automated perifoveal central, nasal, temporal macular thickness measurement by optical coherence tomography (Spectralis HRA-OCT; Heidelberg Engineering, Germany).

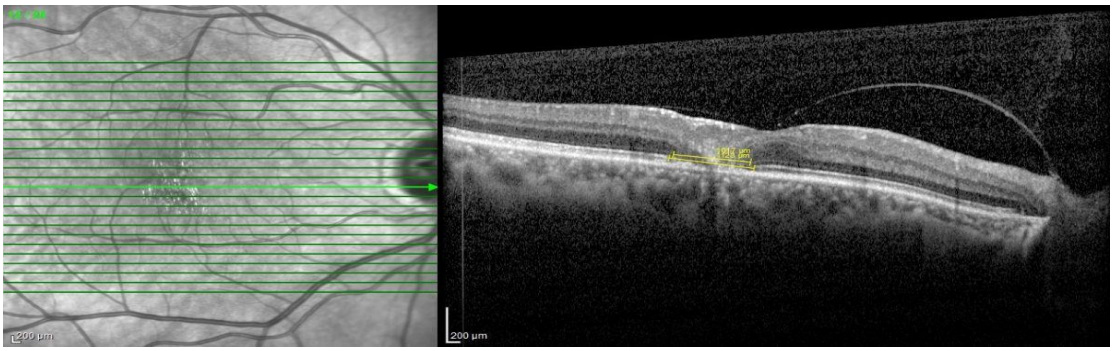

Figure 2. Ellipsoid zone (EZ) and external limiting membrane (ELM) defect length measurement using micrometer scale. (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany). The upper linner measurement line shows the length of loss of the ELM, the lower linear measurement line shows the length of loss of the EZ.

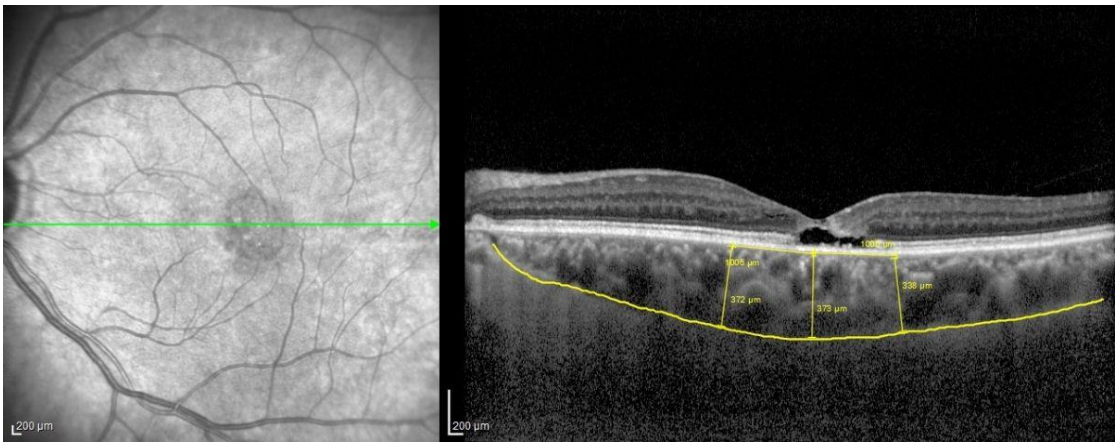

Figure 3. Choroidal thickness measurement in the central, nasal and temporal quadrants using Enhanced Depth Imaging-Optic Coherence Tomography.

Statistical analysis

All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum. Categorical variables were compared using the Mcnemar test and continuous variables using the independent t-test. Snellen visual acuity was converted to logMAR visual acuity for statistical analysis.

To describe the association of various modality imaging findings of MacTel type 2 with visual acuity or other continuous variables, a generalised linear mixed model with generalised estimation equations was used to account for the correlation between the eyes of the same patient. The repeated measurements are used to evaluate the changes in time of the measurements. Spearman's correlation coefficient was used to examine correlations between BCVA and OCT parameters. Differences were considered statistically significant at P values < 0.05.

RESULTS

Among the 19 participants diagnosed with MacTel 2, two were excluded from the study for a short follow-up period, two for missing fundus photography at the initial examination, and one for diabetic retinopathy. The study included 28 eyes of 14 patients (11 women, 3 males), with a mean age of 65.5 ± 9.8 years (51-68). The mean follow-up period was 55.6 ± 32.9 (6-108) months. There were six patients with diabetes mellitus and hypertension, one with asthma, and one with coronary artery disease. The mean BCVA at baseline and final follow-up were 0.51 ± 0.6 and 0.7 ± 0.62 logMAR, respectively. There was no statistically significant difference between the initial and final values (p:0.276). Table 1 provides the disease stages of eyes with MacTel 2. Seventeen eyes initially classified as stages 2-4 showed no progression during the follow-up period. In all patients, the disease was bilateral, with nine eyes progressing to stage 4, and one eye progressing to stage 5 during follow-up (Table 1). In two patients, the disease was symmetrically involved, while the remaining 11 patients exhibited asymetrical manifestations. At the first and last visits, the RAV was the most common fundoscopic finding (78.6% for both). At the initial visit, funduscopic examination showed intraretinal pigmentation in 10 (35.7%) and crystalline deposits in 9 (32.1%) of the eyes. At the final visit, the number of eyes with intraretinal pigmentation 18 (64.3%) increased, whereas the number of eyes with crystalline deposits 10 (35.7%) was similar (p=0.008, p=0.92, respectively). Figure 4 shows crystalline deposits, right-angled venule, and pigment deposit in an eye with MacTel 2.

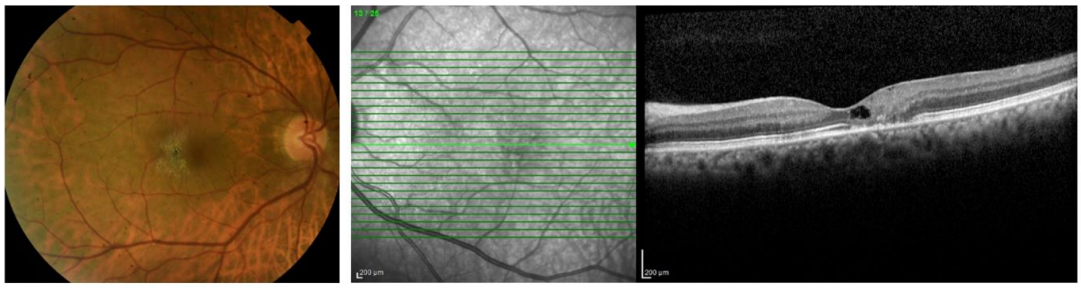

Figure 4. On the left, fundus photograph of MacTel 2 case shows crystalline deposit, right-angled venule and pigment deposit; on the right, characteristic OCT findings: ellipsoid zone and external limiting membrane loss, hyporeflective cavitation, retinal pigment epithelial atrophy.

Table 1. Stage of disease at initial and final visit

Stage	Eyes, n (%)	
	Initial visit	Final visit
1	-	-
2	5 (17.8%)	3 (10.7%)
3	13 (46.4%)	7 (25%)
4	8 (28.5%)	15 (53.5%)
5	2 (7.1%)	3 (10.7%)

Table 2. Fundoscopic and OCT findings at initial presentation and final visit

Finding	Eyes, n (%)		p value
	First visit	Last visit	
RAV	22 (78.6%)	22 (78.6%)	>0,999
Intraretinal pigmentation	10 (35.7%)	18 (64.3%)	**0,008**
Crystalin deposits	9 (32.1%)	10 (35.7%)	0.92
Hyporeflective cavitation	20 (71.4%)	18 (64.3%)	0.75
EZ defect	24 (85.7%)	27 (96.4%)	0.25
ELM defect	23 (82.1%)	25 (89.3%)	0.50

RAV; right angled vessels, EZ; ellipsoid zone, ELM; external limiting membrane

Table 3. OCT findings at initial presentation and last visit

Finding	Mean±SD		p value
	First visit	Last visit	
EZ loss length (µm)	997.1±595.7	1323.5±717.3	0.07
ELM loss length (µm)	936.2±694	1158.7±818.2	0.277
CMT (µm)	235.7±36.8	220.5±45.5	0.176
NMT (µm)	315.8±46.9	297.8±39.1	0.124
TMT (µm)	303.2 ± 25.3	286.5±38.1	**0.04**
CCT (µm)	292.6±57.1	282±64.3	0.522
NCT (µm)	290.6±64.5	272.2±72.2	0.319
TCT (µm)	292.3±68.1	271.2±58.8	0.221

SD; standard deviation, EZ; ellipsoid zone, ELM; external limiting membrane, CMT; Central macular thickness, NMT; Nasal macular thickness, TMT; Temporal macular thickness, CCT; Central choroidal thickness, NCT; Nasal choroidal thickness, TCT; Temporal choroidal thickness

Table 4. Correlation analysis between visual acuity and OCT findings at baseline and last visit

OCT findings	Visual Acuity	
	Baseline	**Last visit**
EZ length loss (µm)	**r=0.349**, **p=0.04**	r=0.324, p=0.09
ELM length loss (µm)	**r=0.444**, **p=0.018**	r=0.256, p=0.188
CMT (µm)	r=0.102, p=0.600	r=-0.068, p=0.729
NMT (µm)	r=0.346, p=0.710	r=-0.122, p=0.536
TMT (µm)	r=0.003, p=0.980	r=0.041, p=0.834
CCT (µm)	r=-0.112, p=0.572	r=0.076, p=0.700
NCT (µm)	r=-0.035, p=0.862	r=0.105, p=0.595
TCT (µm)	r=-0.186, p=0.344	r=-0.081, p=0.681

EZ; ellipsoid zone, ELM; external limiting membrane, CMT; Central macular thickness, NMT; Nasal macular thickness, TMT; Temporal macular thickness, CCT; Central choroidal thickness, NCT; Nasal choroidal thickness, TCT; Temporal choroidal thickness; r = Pearson's correlation coefficient.

Subretinal NV was initially present in 2 eyes and developed in 1 eye during follow-up. Four eyes had subfoveal vitelliform material accumulation, and one eye had central serous chorioretinopathy. Lamellar or full-thickness macular holes were not present in any eyes during the follow-up.

At the initial visit, there was lamellar hyporeflective cavitation in 20 eyes (71.4%); at the final visit, 18 eyes (64.3%) had lamellar hyporeflective cavitation (p=0.75) (Table 2).

Table 3 shows the mean central, nasal, and temporal macular thickness values obtained during the initial and last visits. The mean temporal macular thickness decreased significantly during the follow-up period, while the central and nasal thickness did not show a significant change (p=0.04, p= 0.176, p= 0.124, respectively).

At baseline, focal EZ loss was found in 24 eyes (85.7%), compared to 27 eyes (96.4%) at the final visit (p=0.25). External limiting membrane loss was found in 23 eyes (82.1%) at the first visit and in 25 eyes (89.3%) at the final visit (p = 0.50). The increase in mean length of the EZ and ELM loss during the follow-up was not statistically significant (p=0.07, p=0.277, respectively). Figure 4 shows EZ and ELM loss, hyporeflective cavitation, and RPEl atrophy on OCT imaging of an eye with MacTel 2.

The central, nasal, and temporal choroidal thickness measurements obtained at the first and last visits were similar (p>0.05, for all measurements) (Table 3).

In the correlation analysis of OCT findings and BCVA, the presence of hyporeflective cavities was associated with a higher BCVA at baseline (logMAR, p=0.03).

The baseline BCVA showed a positive correlation with the ellipsoid zone and ELM length loss (logMAR; p=0.04, r=0.349, p=0.018, r=0.444). However, there was no significant correlation between the last BCVA and any OCT findings (p>0.05, for all parameters).

DISCUSSION

In this study, we evaluated the pathological course and visual outcome of MacTel type 2 over an average follow-up period of approximately four years. Our results was consistent with earlier data in terms of age of diagnosis, bilateral involvement, female predominance, and coexistence of systemic vascular disease[14,15]. Research reveals that up to 45% of MacTel 2 patients had systemic diseases such as diabetes, obesity, hypertension, or cardiovascular disease.

Consistent with previous studies, 50% of patients had diabetes, hypertension, or coronary artery disease in our cohort. However, the low incidence of MacTel 2 in patients with systemic vascular disease suggests that these secondary factors may actually only increase susceptibility to the disease[16, 17].

The typical MacTel 2 macular changes begin in the parafoveal temporal region, and the first finding detectable on OCT is thinning of the temporal juxtafoveal retina[4]. Although the exact cause of this mechanism remains unclear, it is proposed that the growth of retinal vessels in the temporal perimacular region during development occurs by connecting the superior and inferior vessels with anastomosis rather than by elongation in other retinal veins. This may lead to structural abnormalities and the decompensation of these vessels in adult life[15,16]. This study showed a significant decrease in mean temporal macular thickness during follow-up, consistent with the pathogenesis of the disease.

Retinal cavitations are hyporeflective cystoid formations in the foveola, typically found in the inner and outer layers of the retina. This may be a result of cystic macular degeneration near the fovea caused by Müller cell degeneration[20,21]. The cavitation volumes were found to be associated with visual acuity (VA) decreases, and it seems that these cavitations occur before the loss of the ellipsoid zone (EZ), especially as it approaches the foveal center[22].

Venkatesh et al. showed that the volume of hyporeflective inner retinal spaces decreases and disappears due to the loss of supporting structures as the disease progresses.

This causes the inner retinal layers to bend outward and the outer retinal layers to collapse, resulting in atrophy. They reported that eyes with disorganized inner retinal layers, collapsed outer retinal layers, and disrupted outer retinal hyperreflective bands have significantly worse visual acuity [23]. Our cohort shows that the majority of patients who had hyporeflective cavitation at the initial examination also had concurrent EZ-ELM defects. Although the volume, localization and depth of hyporeflective cysts were not evaluated in this study, the presence of hyporeflective cavities was associated with low visual acuity at baseline. However, since most of the eyes in our cohort also had EZ and ELM defects at the first visit, it may not be correct to directly associate hyporeflective cavities with low initial visual acuity. In this cohort, a slight decrease in the presence of hyporeflective cavitation and a modest rise in the rate of ELM-EZ loss over time may support the hypothesis that hyporeflective cavities are a precursor to degeneration in the outer retina.

According to Gass and Blodi's clinical staging system, the presence of RAVs in funduscopy indicates a rather later stage of the disease.These vessels frequently occur in solitary or multiple forms, and they are associated with ectatic capillaries[9,24].

These vessels frequently occur in solitary or multiple forms and are associated with ectatic capillaries [24]. Recent studies on optical coherence tomography-angiography revealed that early disease stages (stages 1-2) could detect vessels reflecting the morphological characteristics of RAVs, even before they became visible in funduscopy. Although it has been known so far that RAVs are mainly composed of dilated venules, recent studies have shown that some of these vessels are arteriolar in nature, and form retinal-retinal or retinal-choroidal anastomoses in the outer retinal layers[17, 25]. Studies have also demonstrated a potential association between these vessels and secondary NV as the disease progresses[23,25]. In our patient group, the most common fundoscopic finding at both visits was a RAV. Although we detected subretinal NVs in a small number of eyes due to the relatively short follow-up period, all eyes with subretinal NV had RAVs. Considering the aforementioned studies, eyes with RAVs should be closely followed for the long-term development of NV.

Intraretinal pigment plaques and crystalline deposits are recognized as disease-specific changes; however, their impact on visual impairment may differ significantly[9, 26]. Gass and Oyakawa revealed that the loss of photoreceptors caused hyperplastic RPE cells to move along RAVs, leading to the formation of intraretinal hyperpigmented black plaques[9]. Intraretinal pigments are associated with disease

progression, but the relationship between plaques and visual loss remains controversial [4,27].

Although the origin of the crystalline deposits remains unclear, they may be observed in the early stages of the disease, and they do not exhibit a relationship with the disease's severity[9,28]. In our cohort, the incidence of intraretinal pigmentation increased over time, while the rate of eyes with crystal deposits at baseline was similar at the last visit. Based on this result, it can be concluded that crystalline deposits are found in a smaller proportion of eyes with MacTel-2 regardless of disease stage; on the other hand, intraretinal pigmentation can increase as the disease stage progresses over time.

Optic coherence tomography provides cross-sectional imaging that enables us to observe the morphological changes occurring as the disease progresses and evaluate the relationship between these findings and visual outcomes. Certain features of the disease, such as hyporeflective degenerative inner and outer retinal spaces, disruption of the hyperreflective layer known as ELM and EZ, macular hole, and subretinal neovascular membrane, can be detected by OCT [24, 29].

Although slowly progressive, type 2 MacTel may lead to significant loss of central visual acuity during the long-term course [9,14,18]. In this study, although there was a decrease in mean BCVA during follow-up, this change was not statistically significant. Recent studies have shown that some parameters may be associated with visual acuity and functional outcomes regardless of the clinical stage of the disease.

Research shows that regardless of the involvement of the foveal center, the eyes with ELM and EZ disruptions, indicating photoreceptor damage, had worse visual acuity [14,26,30]. However, Peto et al. demonstrated that while EZ and ELM disruptions showed modest visual loss, the defect only progressed to the foveal center, causing clinically significant central visual loss [26]. In this study, EZ and ELM loss were present in 85.7% and 82.1% of eyes at baseline and 96.4% and 86.3% of eyes at the last visit, respectively.

However, we found that EZ and ELM length loss was associated with lower baseline BCVA, and there was no correlation between the loss of EZ and ELM length and final VA. This may be explained by the fact that as the disease progresses, many factors, such as the localization of the EZ and ELM defects, neovascular membrane development, outer retinal layer collapse, and atrophy may affect the final visual acuity.

The study has several limitations. It was a retrospective nonrandomized design, and the numbers of cases were relatively small, however, this is expected due to the rarity of the disease. Moreover, the fact that we evaluated the visual results only with central visual acuity and did not perform microperimetric testing can be considered another limitation of the study. As a result, we may not have fully assessed the impact of the disease's changing morphological features on functional outcomes. On the other hand, our study's strength is in its long-term analysis of morphological and functional alterations in MacTel 2, a rare macular disease whose etiology remains unknown. Here, the pathophysiology of the disease can be better understood with the help of future prospective multi-center trials with a larger cohort.

In conclusion, we conducted a study to observe the change in clinical findings of MacTel 2 over time, the pathophysiology of which is still being debated. Study results showed that central visual loss was not progressive despite changes in macular findings over a period of approximately four years. However, it is important to follow these patients in the long term for secondary NV that may develop due to degenerative and atrophic changes in the macula.

Author Contributions: Concept/Design : PI, EE; Data acquisition: IK; Data analysis and interpretation: PI, IK, HB; Drafting manuscript: PI, HB; Critical revision of manuscript: ND, EE; Final approval and accountability: PI, IK, EE, ND, HB; Technical or material support: -; Supervision: ND; Securing funding (if available): n/a.
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