Research Article

Mactel Type 2: Evaluation of Systemic Associations and Imaging Characteristics

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Abstract

Purpose: The purpose of this study was to study the clinico-demographic characteristics of Mactel patients and to correlate its clinical findings with FFA and OCT findings.

Methods: This prospective study was conducted in 30 Mactel patients at a tertiary eye care centre in south Kerala between May 2014 and May 2016. Clinical staging of the disease was done based on Gass and Blodi classification. In FFA, disease was classified into those with < 180 degrees leakage, > 180 degrees leakage and CNVM leakage. OCT findings were also noted. Routine blood investigations were carried out in all the patients. These were arbitrarily divided into convenient groups for the statistical analysis.

Results: The mean age of MacTel patients was 57 years with a female predominance in study group. Out of this, 86.71% had overt diabetes mellitus, 36.67% had hypertension and 16.7% had familial hypercholesterolemia. Most of the patients had stage 2 disease (48.33%) while none of them had Stage 1 disease. 46.67% in the study had < 180 degrees leakage on FFA while 48.33% had > 180 degrees. 3 eyes (5%) had CNVM type of leakage. Degree of leakage on FFA tended to correlate with the stage of disease. Common OCT findings were normal OCT (43.3%), Inner Lamellar Hole in 23.33%, Outer Lamellar Hole in 15%, full thickness hole in 1.67%, foveal pigmentation in 11.67% and CNVM in 5%. However central foveal thickness did not show a correlation with vision loss.

Conclusion: The coexistence of high prevalence of diabetes mellitus and hypertension was suggestive of the fact that the vascular stress in these conditions may add to the pathogenesis of Mactel. Further research is required to establish the significance of the higher prevalence of dyslipidemia in Mactel l patients as found in our study. As the disease progresses, the degree of FFA leakage seems to suggest greater disease severity. OCT characteristics, however, failed to demonstrate such a correlation. Central foveal thickness in OCT may not be a good index to correlate with visual prognosis in these patients.

Keywords: Macular Telangiectasia, Mactel; Systemic Associations; Fundus Fluorescein Angiography; *Optical Coherence Tomography*

Introduction

Macular telangiectasia (Mactel) type 2 is a slowly progressive bilateral macular disease characterised by both neurodegenerative and vascular abnormalities [1]. Based on findings from clinical and angiographic examinations, Gass and Blodi defined and categorised these entities in 1993 [2]. Secondary neovascularisations are considered to be a rare vision-threatening complication in Mactel [1,2]. Their origin still remains controversial. The clinical spectrum of these macular vasculopathies has recently been refined and enlarged based on their newly recognized manifestations. With the development of advanced imaging methods like the OCT angiography, we were able to better define the nature of these vascular anomalies and, to some extent, match the histological observations documented in the ophthalmic literature.

The aim of our study was to evaluate possible causes and associations of Mactel type 2 by studying clinico-epidemiological and metabolic parameters.

Methods

This prospective study was carried out between May 2014 and May 2016 at a tertiary eye care centre in south Kerala, following institutional ethical committee protocol approval. 30 patients who were diagnosed with Mactel type 2 were included in this study. Patients with features of concomitant retinal disease such as frank diabetic retinopathy, retinal vein occlusion, radiation retinopathy, macular degeneration, hypertensive retinopathy, vitelliform dystrophies etc were excluded. Those with media opacities significant enough to prevent clinical, angiographic or OCT imaging were also excluded. All the patient's details regarding the symptoms, systemic illnesses, similar family history etc were recorded. All the patients underwent a comprehensive eye examination including visual acuity, anterior segment examination, tonometry, fundus examination with indirect ophthalmoscopy and 90 D lens, fundus fluorescein angiography (FFA) and spectral-domain OCT (SD-OCT) on Heidelberg Spectralis platform whenever indicated.

Routine blood investigations with FBS, PPBS, ESR, Hb1Ac, GTT, total cholesterol, LDL, HDL, and VLDL were also carried out. These were arbitrarily divided into convenient groups for the statistical analysis. Clinical staging of the disease (5 stages) was done based on Gass and Blodi classification (Figure 1) [2]. In FFA, disease was classified into those with < 180 degrees leakage, > 180 degrees leakage and CNVM leakage (Figure 2). OCT findings noted in our study were normal OCT, reduced central foveal thickness, outer lamellar hole, inner lamellar hole, full thickness lamellar hole, central pigmentation, subretinal neovascular membrane (Figure 3).

Figure 2: FFA in Mactel patients showing A) < 180 degrees leakage, B) > 180 degrees leakage leakage C) CNVM leakage in early phases.

Figure 3: SD-OCT images showing A) early MacTel changes with temporal flattening of fovea B) typical 'ILM drape sign' with inner lamellar hole formation C) outer and inner lamellar holes D) retinal thinning with 'collapse sign' E) full thickness macular formation.

Results

60 eyes of 30 patients were involved in the study. The age group of the study population ranged from 41 years to 74 years with a mean age of 57 years. The study had a female predominance with

Figure 1: Showing different clinical stages of macular telangiectasia type 2.

23 females (76.67%) and 7 males (23.33%) enrolled (M: F -1: 3). All the patients in our study were symptomatic. 25 patients (83.33%) had blurring of distance vision, 6 patients (20%) complained of metamorphopsia and 1 patient (3.33%) had difficulty in near vision especially reading.

14 patients (46.67%) had history of diabetes, 11 patients (36.67%) had hypertension, 5 patients had familial hypercholesterolemia (16.7%) and 4 patients (13.3%) had ischemic heart disease. However on investigating 26 patients (86.71%) had overt diabetes mellitus, an additional of 40% patients over those who had an already known history of diabetes. Out of these, 3 patients (11.53%) had high HbA1c levels indicating poor diabetic control. In addition 1 patient had abnormal GTT but no overt DM. 23 patients (76.67%) had evidence of dyslipidemia, an addition of 60% over those who had a known history of hyperlipidemia. Of these, 21 patients (91.34%) had high total cholesterol and high LDL, 7 patients (30.34%) had low LDL and 5 patients (21.74%) had high TGL. 4 patients had evidence of IHD. Raised ESR was seen in 4 patients (13.33%).

Best corrected visual acuity (BCVA) ranged from 0 (6/6) to 1 log units (6/60). The mean BCVA was 0.52 (6/18). Most of the patients - 29 eyes (48.33%) had stage 2 disease, 10 eyes (16.67%) had stage 3 disease, 18 eyes (30%) had stage 4 disease and 3 eyes (5%) had stage 5 disease. No eyes had Stage 1 disease. Stage 2 eyes had a mean VA of 0.36 (6/12), Stage 3 eyes had a mean VA of 0.12 (6/12), Stage 4 eyes had a mean VA of 0.372 (6/12 - 6/18) and Stage 5 eyes had a mean VA of 0.5 (6/18). Stage 3 eyes had the best visual acuity and Stage 5 eyes had the worst vision.

25 eyes (43.33%) had normal OCT features. Though the foveal contour appeared normal, these eyes had a reduced central foveal thickness suggestive of retinal thinning (mean CFT 130 microns). The other common OCT findings were Inner Lamellar Hole (ILH) in 14 eyes (23.33%), Outer Lamellar Hole (OLH) in 10 eyes (15%), full thickness hole in 1 eye (1.67%), foveal pigmentation in 7 eyes (11.67%) and CNVM in 3 eyes (5%). The mean central foveal thickness in this series was 153.30 μm. The mean central foveal thickness in eyes with normal OCT was 136.03 μm, outer lamellar hole 180 μm, inner lamellar hole 159 μm, CNVM 246.33 μm, and foveal pigmentation 175.43 μm.

The mean VA of eyes with normal OCT finding was 0.253 (6/12), outer lamellar hole was 0.422 (6/18), inner lamellar hole 0.371 (6/12 - 6/18), full thickness hole was 0.8 (6/36), central pigmentation was 0.442 (6/18), CNVM on OCT was 0.5 (6/18). Eyes with normal OCT had the best visual acuity and eyes with full thickness macular hole had the worst vision.

28 eyes (46.67%) in the study had < 180 degrees leakage/staining on FFA while 29 eyes (48.33%) had > 180 degrees. 3 eyes (5%) had CNVM type of leakage. Eyes with < 180 degrees leakage/staining on FFA had a mean VA of 0.242 (6/9) and eyes with > 180 degrees leakage/staining had a mean VA of 0.39 (6/12 - 6/18).

FFA v/s OCT

Out of the 25 eyes with normal OCT findings, 15 eyes (60%) had < 180 degrees FFA leakage/staining and 10 eyes (40%) had > 180 degrees leakage/staining. Out of the 10 eyes with outer lamellar hole, 8 eyes (80%) had > 180 degrees leakage compared to 2 eyes (20%) with < 180 degrees leakage and this was statistically significant. Out of the 14 eyes with inner lamellar hole, 10 eyes (71.43%) had < 180 degrees leakage compared to 4 eyes (38.57%) with > 180 degrees leakage and this was also statistically significant. One eye had full thickness hole and had > 180 degrees leakage/staining. All the 3 eyes with CNVM and Mactel showed corresponding characteristic leakage on FFA. 7 eyes had foveal pigmentation of which 6 eyes (85.71%) had > 180 degrees leakage compared to 1 eye (14.29%) with < 180 degrees leakage/staining and this difference was statistically significant (Table 1).

FFA Leakage	Normal	OLH	ILH	FTMH	CNVM	Foveal Pigmentation	Total
< 180 deg	15	2	10	0	0	1	28
> 180 deg	10	8	4	1	0	6	29
CNVM	0	0	0	0	3	0	3

Table 1: Comparison of FFA and OCT features of Mactel patients.

FFA v/s Stage of disease

Out of the 28 eyes with < 180 degrees leakage on FFA, 21 eyes (75%) had stage 2 disease, 6 eyes (13.79%) had Stage 3 disease and one eye had stage 4 disease (3.57%). Out of the 29 eyes with > 180 degrees leakage/staining on FFA, 8 eyes (58.62%) had stage 2 disease, 4 eyes predominantly had early stages (stage 1, 2) of the disease and eyes with > 180 degrees leakage/staining had late stages (stage 3,4 5) of the disease (Table 2). Thus the degree of leakage on FFA tended to correlate with the stage of disease.

FFA Leakage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
< 180 deg	0	21	6	1	0
> 180 deg	0	8	4	17	0
CNVM	0	0	0	0	3

Table 2: Comparison of FFA features and stage of the disease in Mactel patients.

CNVM with Mactel

Patients with Mactel and CNVM (Stage 5 disease) were a decade older than the rest of patients, with a male preponderance. These eyes had VA in the range of 0.2 to 1. 2 of these patients (66.67%) each had associated overt diabetes mellitus; hyperlipidemia and hypertension. 1 (33.33%) patient also had increased ESR. None of these eyes had any other OCT feature other than the evidence of CNVM leakage with retinal thickening.

Stage of disease v/s OCT

None of the patients in this series had stage 1 disease. Out of the 30 eyes with stage 2 disease, 16 eyes (53.33%) had normal OCT pattern but with decreased central foveal thickness, 10 eyes (33.33%) had inner lamellar hole in OCT, 3 eyes (10%) had outer lamellar hole in OCT and 1 eye had (3.33%) central foveal pigmentation. Out of the 10 eyes with stage 3 disease, 5 eyes (50%) had normal OCT pattern but with decreased central foveal thickness, 3 eyes (30%) had inner lamellar hole, 1 eye (10%) had outer lamellar hole and full thickness macular hole. Out of the 17 eyes with stage 4 disease, 5 eyes (29.41%) each had normal OCT pattern and outer lamellar hole, 6 eyes (35.29%) had central foveal pigmentation and 1 eye (5.88%) had inner lamellar hole (Table 3). All the 3 eyes with CNVM showed evidence of CNVM with RPE-choriocapillary complex thickening.

OCT Features	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Normal	0	16	5	5	0
ILH	0	10	3	1	0
OLH	0	3	1	5	0
FTMH	0	0	1	0	0
CNVM	0	0	0	0	3
Foveal pigmentation	0	1	0	6	0

Table 3: Comparison of OCT features and stage of the disease in Mactel patients.

There seemed no preponderance of any of these systemic diseases in any stage of the disease, angiographic leakage/staining or OCT finding except for the group with overt DM and poor HbA1c. 66.67% of patients with overt DM and poor HbA1c had stage 3 disease. These groups of patients also were younger with a mean age of 47 years compared to the mean age of 57 years of the study population. 75% of these eyes also had inner lamellar hole in OCT. 14 eyes (23.33%) had none of the systemic disease studied which was associated.

Discussion

The mean age of our study population was 57 years (range 41 - 77 years). This disease often manifests its symptoms around the sixth decade of life. According to previous research works, presenting age ranged from 39 to 86 years [3,4]. There was a female preponderance in our series (M:F - 1:3) which was similar to previous studies [5-8]. Commonest symptoms of presentation in our study were near vision difficulty (83%), metamorphopsia (20%) and distant blurring of vision (3%). Gass and Blodi also found metamorphopsia to be a common presenting problem in this patients [2].

Regarding systemic associations, 87% patients in our series had overt diabetes. Though 20% of the native population have diabetes, this high prevalence of diabetes in mactel patients is indeed significant. Many series of mactel have not included diabetic patients, as diabetes by itself could be a cause of retinal vessel telangiectasia in early stages. Chew., *et al.* however had reported that diabetes mellitus is a risk factor in patients with mactel [9]. Similar to Gass and Blodi, Yannuzzi., *et al.* reported

higher incidence of diabetes mellitus (19%) in his study but he attributed this findings to the mixed racial group his study population [6]. Among the 77% patients with dyslipidemia, 60% were newly detected during the period of the study. Thus there seemed a higher preponderance of dyslipidemia in patients with mactel compared to the normal population. There are no reports of such an occurrence in the literature and the significance of this association needs more scrutiny.

The mean best corrected visual acuity was 0.5 log units (6/18) and the visual acuity of the study population ranged from 6/6 to 6/60. Most of the reported series have also reported a wide range with better vision in early stage of the disease and poorer vision towards late phases of the disease. Chokshi., *et al.* had studied the correlation between vision and stage of the disease [10]. Stage 1 eyes in our series had a mean visual acuity of 6/6, stage 2 eyes 6/15, stage 3 eyes 6/9, stage 4 eyes 6/15 and stage 5 eyes 6/18. This was comparable to the series by Chokshi., *et al.* who had reported a mean visual acuity of 6/6 in stage 1 disease, 6/9 in stage 2 disease, 6/15 in stage 3 disease, 6/18 in stage 4 disease and 6/60 in stage 5 disease.

In FFA, 47% of eyes had < 180 degrees leakage, 48% had > 180 degrees leakage and 5% had leakage typical of classic CNVM on FFA. This was in contrast to the report by Alan Gaudric., *et al.* who reported 72% eyes with < 180 degrees leakage compared to 28% eyes with > 180 degrees leakage [5]. However, the significance of this occurrence in this series appears to be a coincidental finding.

The earliest sign noted on OCT is temporal flattening of the foveal pit, due to thinning of the temporal juxtafoveal retina [11]. OCT features in this series included normal OCT findings in 43%, inner lamellar holes in 23%, outer lamellar holes in 15%, full thickness hole in 2%, central foveal pigmentation in 12% and CNVM in 5%. Yannuzzi., *et al.* had observed the occurrence of defects intra-retinally and discussed to call them cysts or holes. Paunescu., *et al.* had reported the occurrence of these cysts in the inner nuclear layer and ganglion cell layer as seen in ultra high resolution OCT images [12]. Foveal plaque pigmentation has been reported to be seen in 29 - 36% of eyes in various series compared to 12% in our series. The other features described in literature include disruption of photoreceptor layer seen in as high as 76% with disruption of outer plexiform - inner nuclear layer interface, subfoveal

detachment in 8%, intra-retinal new vessels, intra-retinal deposits in 11% of eyes and an unique "ILM drape sign" over underlying loss of tissue. Alan Gaudric., *et al.* had reported the progressive enlargement of cysts both in inner and outer retinal layers during follow up [5]. Olson., *et al.* had also reported the occurrence of full thickness macular hole during follow up of a patient with mactel [13]. Eyes with disorganized inner retinal layers, collapsed outer retinal layers and disrupted outer retinal hyper-reflective bands have significantly worse visual acuity [14]. However the eye with full thickness macular hole in our series had 6/36 vision. Eyes with inner lamellar hole and outer lamellar hole had moderate visual loss. It is evident that central foveal thickness may not be a good index to correlate with vision changes in these patients. A more reliable index will be the anatomic characterization of the macula rather than focal thickness. The area of ellipsoid zone loss in SD-OCT can be employed as a diagnostic feature as well as for outcome measure. The extent of photoreceptor loss correlates with visual impairment, and limiting photoreceptor loss looks to be the most viable therapeutic method for sustaining vision.

48% of eyes had stage 2 disease, 17% had stage 3 disease, 30% had stage 4 disease and 5% stage 5 disease in our series. Though 5% of eyes have been reported to have stage 1 disease in previous studies, our study did not identify any patient who had stage 1 disease. 5% of eyes in our series had stage 5 disease which may be higher than those reported in literature. In the 2 series of Cohen., *et al.* and Alan Gaudric., *et al.* none of the eyes had stage 5 disease included [5,15]. Charbel Issa., *et al.* had reported that 26% of eyes in his series had late disease which included stage 4 and stage 5 eyes, which is less than what was observed in this series (35%) [16].

There was a statistically significant correlation between FFA leakage and stage of disease especially in stage 2 and stage 4 disease. Stage 2 eyes had significantly more eyes with < 180 degrees leakage and stage 4 eyes had significantly more eyes with > 180 degrees leakage. However such a correlation could not be seen in Stage 3 eyes. Thus the degree of leakage ended to correlate with the stage of the disease. Hypothetically this means that as the stage of the disease increases, the degree of leakage and more specifically the area of the perifoveal macular involvement also increases.

There seemed no statistically significant correlation between stage of disease and OCT findings. Though it was expected that

as the stage of disease worsens, the occurrence of cysts and their location within the retinal layers would increase, such a change was not observed in this series. Lamellar holes or cysts were involved in 45% of Stage 2 eyes, 50% of Stage 3 eyes, 33% of stage 4 eyes and none in stage 5 eyes. Moreover the one case of full thickness macular hole had stage 3 disease. However Cohen., *et al*. had reported that majority of Stage 2 eyes with mactel had normal OCT with rare occurrence of cysts/holes and 100% of Stage 3 eyes demonstrating lamellar holes/ cysts in his series which is different from that of our observation [15]. Other OCT studies on mactel also have not reported such an association. But this may be irrelevant as it is possible that disparity may exist between the clinical staging of the disease on retinal examination and SD-OCT features as reported by Venkatesh., *et al*. [17].

As expected there appeared no correlation between the degrees of FFA leakage and OCT findings. It was expected that eyes with normal OCT would have less FFA leakage and eyes with lamellar hole/cysts have more leakage, such a correlation was seen in former group. Moreover, the latter group showed an inverse relationship in at least some eyes. Eyes with outer lamellar holes did not show a significant correlation with FFA leakage but eyes with inner lamellar holes had significantly less leakage contrary to what was expected. The pathologic explanation for such an association is however difficult.

Patients with mactel and CNVM (Stage 5 disease) were a decade older than the rest of patients with a male preponderance. Wet form of age related macular degeneration is also prevalent in the same age group and hence this association would have been an affect of age related mechanisms like oxidative stress etc. which are implicated in ARMD. CNVM of ageing also is more common in males than females which probably simply reflecting the gender difference in the population itself. However in this series with a female preponderance the occurrence of Stage 5 disease in males predominantly cannot be a chance occurrence.

Anti-VEGF treatment does not seem to affect the long-term results in non-proliferative Mactel [18,19]. Photoreceptor degeneration may also result from anti-VEGF therapy. Thus, the utility of anti-VEGF medications during the non-proliferative stage is still debatable. However, anti-VEGF therapy plays a significant role in the management of the proliferative stage due to improvements in visual acuity and reduction in central macular thickness [20,21]. The role of carotenoid supplementation is still unclear and requires more research.

Conclusion

The coexistence of high prevalence of diabetes mellitus and hypertension was suggestive of the fact that the vascular stress in these conditions may add to the pathogenesis of Mactel. Higher preponderance of dyslipidemia in patients with Mactel compared to the normal population needs further studies to prove its significance. Mactel patients have generally better vision in early stage of the disease and poorer vision towards late phases. The degree of FFA leakage seemed to indicate increased severity of the disease as the disease progress. However OCT features did not show such a correlation. Central foveal thickness (CFT) in OCT may not be a good index to correlate with vision changes in these patients. The area of ellipsoid zone loss in subfoveal region as evident from SD-OCT is rather a better biomarker than CFT in predicting visual prognosis in Mactel patients.

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Conflicts of Interest

Nil.

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