When is macular edema not macular edema? An update on macular telangiectasia type 2∗

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A B S T R A C T
Macular telangiectasia type 2 (Mac Tel 2) also known as idiopathic perifoveal telangiectasia and juxtafoveal retinal telangiectasis type 2A is an enigmatic disease of unknown etiology. It manifests both neurodegenerative and vasculopathic characteristics.

It manifests itself during the fifth or sixth decades of life. Clinical characteristics include minimally dilated parafoveal capillaries with loss of the retinal transparency in the area involved, absence of lipid exudation, right-angled retinal venules, superficial retinal refractile deposits, hyperplasia of the retinal pigment epithelium (RPE), foveal atrophy and subretinal neovascularization (SRNV). Optical coherence tomography (OCT) images typically demonstrate outer retinal abnormalities and the presence of intra-retinal hyporeflective spaces that are usually not related with retinal thickening or fluorescein leakage.

The typical fluorescein angiographic finding is a deep intraretinal hyperfluorescent staining in the temporal parafoveal area. With time this fluorescein hyperfluorescence involves the whole parafoveal area but does not extend to the center of the fovea. Long-term prognosis for central vision is poor, because of the development of SRNV or macular atrophy. Its pathogenesis remains unclear but multimodality imaging with fluorescein angiography, spectral domain OCT, adaptive optics, confocal blue reflectance, short wave fundus autofluorescence, OCT angiography, and clinicopathological correlations implicate Müller cells. Currently there is no known treatment for this condition.

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1. Introduction

Retinal telangiectasis, characterized by capillary ectasia and incompetence, may occur secondary to branch retinal vein occlusion, diabetic retinopathy, X-ray irradiation, and carotid artery obstruction among several conditions.1 In 1982, Gass and Oyakawa2 described 27 patients with juxtafoveal telangiectasis with no apparent specific cause. They named this condition idiopathic juxtafoveal retinal telangiectasis (IJRT) and classified it into four groups. Group 1 represented a localized form of Coats disease that occurred predominantly in male patients. These eyes were characterized by unilateral parafoveal retinal telangiectasis associated with lipid and serous retinal exudation that was thought to be developmental in origin.2 Men with bilateral symmetric juxtafoveal telangiectasis affecting the temporal half of the juxtafoveal areas with minimal intraretinal exudation typified Group 2 eyes. Group 3 eyes comprised both female and male patients who had bilateral parafoveal telangiectasis with minimal intraretinal exudation. Group 4 eyes included individuals with familial perifoveal retinal capillary occlusion and optic disc pallor.2 By 1993, Gass and Blodi3 identified 140 patients with this condition and reassessed their classification of IJRT. IJRT was divided into three groups and each group was further subdivided into two subgroups. Eyes in Group 1A most likely represent a form fruste of Coats disease characterized by congenital telangiectasia with lipidic serous exudation that affects mostly male patients in a unilateral pattern. Laser or pharmacologic treatment appears to be effective in preserving or improving vision in these patients.2,4,5 Eyes in Group 1B share the same clinical characteristics as eyes in Group 1A except for the very limited scope of telangiectatic involvement. Group 2A is the most common form of IJRT. These eyes lack lipid exudation and most of the clinical findings...
are rather subtle. Group 2B was defined as juvenile occult familiar IJRT. This subgroup comprised only two brothers with subtle retinal juxtafoveal telangiectasia and bilateral subretinal neovascularization (SRNV). Group 3 eyes were characterized by bilateral minimal exudation and extensive occlusion of the juxtafoveal capillaries. Patients with Group 3A eyes had only ophthalmic manifestations, whereas patients in Group 3B also suffered from a central nervous system vasculopathy.3

Yannuzzi and co-workers6 proposed the most recent and simplified classification of IJRT. They merged Gass Groups 1A and 1B into a single aneurysmal telangiectasia group which they called aneurysmal telangiectasia or idiopathic macular telangiectasia type 1 (Mac Tel 1). Gass and Blodi3 Group 2A was renamed as idiopathic perifoveal telangiectasia, also known as idiopathic macular telangiectasia type 2 (Mac Tel 2). Mac Tel 2 was further subdivided into a nonproliferative stage characterized by telangiectasia and foveal atrophy; and a proliferative stage characterized by the presence of SRNV.7 Gass and Blodi3 Groups 2B and 3 were discarded because of their rarity. In the accompanying editorial, Chew et al7 endorsed this new classification and encouraged its use. For the purposes of this review, we will refer to IJRT Type 2A as synonymous of idiopathic perifoveal telangiectasis or idiopathic Mac Tel 2.

2. Clinical findings

Most patients complain of nonspecific symptoms such as mild blurring of vision, positive scotoma, difficulty in reading, and metamorphopsia.5–11 Initially the visual acuities are relatively good, in the order of ≥ 20/30.12,13 Gass and Blodi3 have described the biomicroscopic findings in detail. The earliest ophthalmoscopic abnormalities seen in this disease are rather subtle and may be missed easily. Mild grayish discoloration of the retina with loss of retinal transparency temporal to the fovea is one of the earliest clinical abnormalities seen in Mac Tel 2. With disease progression, this loss of retinal transparency surrounds the perifoveal retina in an oval configuration3,6,14 (Fig. 1). This parafoveal graying becomes less intense and more difficult to visualize with continuous light exposure. Following dark adaptation of at least 15 minutes the parafoveal graying reappears.15 At this stage, the juxtafoveal capillary abnormalities will be absent or barely evident. Fluorescein angiography (FA) is often required to demonstrate them.6,12,14 With time, slightly dilated and blunted retinal venules that extend at right angles into the temporal parafoveolar retina appear. Telangiectatic vessels typically are not associated with lipid exudation or hemorrhages.3,12 Multiple, golden, tiny, crystalline, refractile deposits near the inner retinal surface are a common finding occurring in up to 45% of eyes2,3,14,16 (Fig. 2). The number of these deposits may vary from one to more than twenty. Up to 5% of eyes with Mac Tel 2 will exhibit yellow foveal lesions. These round intraretinal yellow spots measure anywhere between 100 μm and 300 μm in diameter and cause a minimal loss of the foveolar depression. They may be confused with Best disease or an adult form of vitelliform foveomacular dystrophy.3,17–19 Focal atrophy of the foveolar retina may develop and lead to a lamellar or even a full thickness macular hole (FTMH).2,3,6,20–27 These areas of foveal atrophy have a distinct circular margin with central retinal thinning. They do not extend beyond the edges of the capillary free zone.22 The surgical management of eyes with FTMH associated with Mac Tel 2 remains controversial. The findings on OCT might be of prognostic value. If the OCT demonstrates irregular moth eaten edges and there is no evidence of vitreomacular traction, the surgical results will probably be poor.23,25,28 If instead the OCT shows round, edematous edges typical of an idiopathic macular hole then the surgical outcome will be more favorable.26

Stellate foci of intraretinal pigmented black plaques composed of hyperplastic retinal pigment epithelium (RPE) cells may develop along the right angled vessels in more advanced cases (Fig. 3). SRNV may develop in the vicinity of these plaques. Once present, SRNV is characterized by a rapid loss of vision, retinochoroidal anastomosis, cystoid macular edema (CME), subretinal hemorrhage, lipid hard exudates, and disciform scarring.6,18 SRNV in Mac Tel 2 may be confused with choroidal neovascularization in age-related macular degeneration (AMD). There are certain features that may help distinguish between both conditions. SRNV in Mac Tel 2 is not usually accompanied by a pigment epithelial detachment.6 The size of SRNV on Mac Tel 2 is also smaller in comparison to AMD.3

3. Multimodality imaging findings

Because the clinical changes in Mac Tel 2 are rather subtle by biomicroscopy, particularly in the earlier stages, ancillary imaging studies are of paramount importance in the diagnosis of this condition.4,29
characterized by early and late leakage of fluorescein dye in the parafoveal temporal areas. Initially, the early phases of the angiogram show no evidence or barely minimal capillary dilatation. There is mild staining of the temporal outer parafoveal retina in the late phases, which spares the foveal center. As the disease progresses, the telangiectasia extends beyond the temporal parafoveal area and is manifested as a late oval shaped parafoveal hyperfluorescence (Fig. 4). The fluorescein leakage is not related to cystic spaces. There is a significant reduction in the size of the foveal avascular zone (FAZ) in eyes with Mac Tel 2 in comparison with normal eyes. There have even been two reported cases where the capillaries invaded the fovea and obliterated the FAZ. SRNV appears to originate from the deep retinal circulation and is characterized by early and late fluorescein leakage.

OCT has revolutionized our understanding of Mac Tel 2 by demonstrating that there is no correlation between retinal thickening and fluorescein leakage (Fig. 5). Furthermore intraretinal hyporeflective spaces, that have been named as internal limiting membrane drape, cyst, cystoid, or pseudocystoid spaces by different authors, are commonly seen but are usually not related to retinal thickening or fluorescein angiographic leakage (Fig. 6). Interestingly, foveal thickness is decreased in most patients with Mac Tel 2. Spectral domain OCT has also documented the presence of outer retina abnormalities (Fig. 5).

Research prototypes that integrate adaptive optics (AO) with high-resolution spectral domain OCT provide high-resolution photoreceptor imaging. AO imaging has shown that eyes with Mac Tel 2 eyes exhibit a lower cone density and disruption of the normal cone mosaic pattern. These abnormalities are even present in areas where the retinal vasculature appears normal.

One of the earliest changes reported in Mac Tel 2 is an increased short wavelength fundus autofluorescence (SW-FAF) signal in the foveal region (Fig. 7). As the disease advances the SW-FAF actually decreases, not only in the central foveal area but also in the parafoveal areas, paralleling the increasing RPE atrophy.

Confocal reflectance imaging refers to an imaging modality that images the fundus after illuminating it with either a confocal blue light of 488 nm or an infrared light of 820 nm emitted by a scanning laser ophthalmoscope (SLO). Confocal blue reflectance (CBR) imaging demonstrated increased reflectance in the majority of patients with fluorescein angiographic evidence for Mac Tel 2. The increased CBR appeared in an oval parafoveal pattern that was slightly larger than the area of late phase fluorescein angiographic hyperfluorescence.

OCT angiography demonstrates that the earliest vascular changes in Mac Tel 2 arise in the outer deep capillary plexus. As the disease progresses, the vascular changes also involve the inner superficial plexus, albeit to a lesser extent than the changes seen in the outer plexus. The vessels appear less densely packed, thinner, and in an abnormal arrangement. The normally avascular Henle layer and the outer nuclear layers become the target of a vascular invasion. Anastomosis between plexi and dragging of vessels temporally are also seen by OCT angiography.

4. Functional testing

Mac Tel 2 has been studied extensively with microperimetry. Microperimetric findings show that eyes with Mac Tel 2 despite having a relatively good visual acuity, exhibit severe localized dysfunction next to fixation early in the disease process. Fortunately these scotomata do not appear to progress rapidly. A longitudinal study showed that after 1 year of follow-up, MP1 testing with a 20° central testing grid did not show any differences beyond the normal test–retest variability.

5. Pathophysiology

The pathogenesis of Mac Tel 2 remains an enigma. Reports of familial and monozygotic twin cases suggest a genetic component despite the absence of established hereditary patterns. Multimodality imaging coupled with clinicopathological studies and the recent discovery of animal models have implicated Müller cells in the disease process. Because Müller cells span the entire retinal thickness, some have suggested that they function as optical fibers that permit light transmission with a minimum of reflection across the retina. Any pathological involvement of Müller cells would interrupt this mechanism causing limited transmission and an increase in retinal reflectance. The loss of retinal transparency and acquisition of the grayish discoloration seen clinically may be explained by Müller cell impairment. Jindal et al have hypothesized that a...
photochemical reaction caused by the release of chromophores from the impaired Müller cells is responsible for the changes in intensity in parafoveal graying seen with increasing light exposure and dark adaptation.

The superficial retinal crystalline deposits are thought to be the footplates of degenerated Müller cells and analogous to Rosenthal fibers. Rosenthal fibers are crystalline intracytoplasmic inclusions found in astrocytes of the central nervous system associated with chronic stress conditions.18,21 Even though the fluorescein angiographic findings are similar to the ones found in retinovascular diseases such as DME, there are subtle differences that were recognized by Gass.62 In Mac Tel 2, retinal fluorescein staining occurs prior to capillary dilation. Gass62 speculated that this finding was caused by staining of the extracellular matrix and intracellular diffusion of the dye into the damaged retinal cells rather than to a breakdown of the blood retinal barrier leading to an increased retinal vascular permeability.62 He then suggested that the primary abnormality of Mac Tel 2 resides in the parafoveal neural cells or in Müller cells rather than the deep outer retinal juxtafoveal capillaries. He concluded that the retinal vascular abnormalities were a secondary rather than the primary phenomenon.62 AO imaging clearly demonstrates that neural degeneration precedes retinal vascular involvement, lending support to Gass’s hypothesis.46

OCT further differentiates Mac Tel 2 from other retinovascular diseases by documenting the presence of intraretinal hyporeflective spaces that do not correlate with an increased retinal thickness or fluorescein leakage.129 These hyporeflective spaces most likely do not represent fluid-filled spaces as seen in CME secondary to retinal vein occlusions or diabetic macular edema (DME). The density of these hyporeflective spaces can be measured and compared to the vitreous density by analyzing the light reflectivity profiles from OCT. In eyes with neurodegenerative conditions such as cone dystrophy, there is less light reflectivity as compared to eyes with exudative conditions such as DME or central serous chorioretinopathy.54 Müller cells play an important role in the structural integrity of the fovea.54 The OCT findings suggest that these hyporeflective spaces may represent cavity formation after photoreceptor and/or Müller cell loss rather than fluid accumulation caused by blood retinal barrier breakdown associated with exudation or inflammation.63

SW-FAF imaging of the normal macula is characterized by a central dark area. Absorption of the blue light by the luteal macular pigments and the RPE melanin are responsible for this finding.65 In Mac Tel 2, an increase of SW-FAF in the foveal region precedes clinical and fluorescein angiographic findings.47 Because histopathological findings show that the RPE is healthy in Mac Tel 2, the increased SW-FAF is most likely the result of macular pigment depletion from the fovea rather than an increased lipofuscin accumulation in the RPE.66,67 The increased CBR may also be explained by a decrease in macular pigment in the parafoveal area. Because the absorption maximum of macular pigment is in the range of blue light at approximately 460 nm, a decrease in macular pigment in the parafoveal area will cause an increased reflection or a decreased absorption of the blue light.27,58 Heterochromatic flicker reflectometry and subtraction autofluorescent imaging at 488 nm and 514 nm confirm the loss of macular pigment optical density (MPOD) in these eyes.47,69,70 Disease severity as documented by late FA leakage mirrors changes in the distribution of the MPOD.70

The human body cannot produce macular pigment; therefore, the macular pigment is entirely of dietary origin. Our bodies can convert lutein into zeaxanthin but not zeaxanthin into lutein.71 Upon ingestion, high-density lipoprotein transports both zeaxanthin and lutein into the bloodstream.72 The specific molecular mechanisms that mediate the selective uptake, concentration, and stabilization of the macular pigment are currently unknown.8 Macular pigment binding proteins have been immunolocalized to the cone and rod inner segments.73-75 Quantification of macular pigment has shown a greater reduction in zeaxanthin compared to lutein in Mac Tel 2 eyes. It is currently unknown if the main problem is retinal failure to convert lutein into zeaxanthin or zeaxanthin accumulation.90 These findings can be attributed to a primary loss of macular pigment secondary to defective transport or storage of macular pigment or a progressive pathological process that damages the anatomic structures that affect macular pigment accumulation.69,70,76 Oral supplementation with 12 mg of lutein and 0.6 mg of zeaxanthin daily for 9 months increased macular pigment in areas where the macular pigment was present at baseline, but did not produce an increase in macular pigment in areas where the macular pigment was previously absent.69

Clinicopathological correlations of eyes with Mac Tel 2 confirm these findings of depleted macular pigment.58,59 Luteal pigment was characteristically absent in these eyes. Immunohistochemical analysis demonstrated the loss of perifoveal Müller cells. Interestingly there was a topographical correlation between areas of macular pigment absence and areas of Müller cell depletion.58 Müller cells may serve as a retinal reservoir for macular pigment but the exact details of how Müller cells affect trafficking, deposition, and storage of the macular pigment are currently unknown.64
Müller cells also help provide nutrition to the surrounding retinal neurons and also play a role in inducing and maintaining the integrity of the blood-retinal barrier. Their processes are intimately related to the retinal blood vessels in the deep outer plexus. By contrast, the retinal blood vessels in the superficial inner plexus are closely related with retinal astrocytes. OCT angiography demonstrates prominent vascular abnormalities in the outer deep capillary plexus. Vascular invasion of normally avascular retinal areas such as the subretinal space or the outer nuclear layer may represent a compensatory mechanism for the ischemic insult caused by the vascular abnormalities.

Recently a transgenic mouse model with conditional ablation of Müller cells has been described. These animals exhibit photoreceptor apoptosis, retinal telangiectasis, breakdown of the blood retinal barrier and intraretinal neovascularization. It is hoped that with this model further advancements in our understanding of MacTel 2 can be made.

6. Treatment

The main limitation in the treatment of MacTel 2 is the lack of knowledge of the basic pathophysiologic mechanisms underlying this condition. FA was the earliest imaging modality used to study this disease. Because the typical angiographic findings suggested the presence of macular edema, it was thought that MacTel 2 was a primary retinovascular disease. Therefore, the same treatment modalities used to treat retinovascular diseases, such as macular laser photocoagulation, intravitreal triamcinolone, photodynamic therapy, and intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, were used to treat MacTel 2. None of these were particularly beneficial in eyes with nonproliferative MacTel 2. In some eyes with MacTel 2, SRNV will develop. These eyes may benefit from anti-VEGF treatment.

Several animal models of retinal degenerative diseases have shown that multiple cytokines, neurotrophins, and growth factors
such as ciliary neurotrophic factor (CNTF) can rescue photoreceptors.\textsuperscript{84–86} Based on the premise that Mac Tel 2 has a neurodegenerative component, neuroprotective agents such as CNTF are currently undergoing testing. Delivery of CNTF via encapsulated cell technology (ECT) into the vitreous cavity has overcome a major challenge in retinal CNTF delivery. In ECT, genetically engineered live cells are placed within a semipermeable polymer capsule that is implanted surgically at the pars plana. These cells secrete the therapeutic protein of interest in a continuous fashion directly into the vitreous cavity.\textsuperscript{87} ECT containing CNTF appears to be safe and well tolerated in eyes with Mac Tel 2 as evidenced by the results of a recently concluded phase 1 trial.\textsuperscript{88}

In summary, Mac Tel 2 is an enigmatic condition characterized by dual neurodegenerative and vasculopathic pathways secondary to Müller cell dysfunction. The exact cause of this dysfunction remains unclear. Currently there is no treatment available to halt or alter the progression of this disease. Although anti-VEGF treatment seems to limit SRNV in the final proliferative stage of the disease, previous stages currently are not treatable.\textsuperscript{1}

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