Macular telangiectasia (MacTel) remains a poorly understood retinal disease, but the pace of discovery regarding MacTel has recently accelerated. MacTel is likely significantly under-diagnosed and, therefore, less rare than previously reported, but still an uncommon condition.

The MacTel Project is a shining example of an international collaboration launched to study an uncommon disorder, and this has advanced our collective knowledge.

One of the most disappointing aspects of MacTel is our lack of highly effective therapies for treatment. Anti-vascular endothelial growth factor injections and laser, which have been two mainstays of therapy for retina specialists, are effective in a wide variety of disparate retinal conditions, from diabetic retinopathy to retinal vein occlusion to exudative age-related macular degeneration. Yet there is a surprising lack of efficacy for these treatments in MacTel that are so potent for many retinovascular conditions.

In this installment of Practical Retina, Panos G. Christakis, MD, and Henry E. Wiley, MD, both of the National Eye Institute, provide an update on MacTel. Classification of the various subtypes are discussed. Clinical features are outlined with an excellent summary of features observed with various imaging modalities. Theories on the etiopathogenesis behind the disease are debated, and recent genetic linkage studies are reviewed to map the disease. Probably most exciting is the authors’ review of several innovative therapies on the horizon that have shown promise in early phase clinical trials.

The macular telangiectasias are a group of diseases originally defined and categorized based on abnormalities of the macular retinal vasculature as visualized on fluorescein angiography. Three subtypes have been described. Idiopathic juxtafoveal retinal telangiectasia type 1 is a congenital, unilateral disease typically diagnosed in young men and is presumed to be a variant of Coats’ disease. Idiopathic juxtafoveal retinal telangiectasia type 2, often simply called MacTel in the recent literature, is a bilateral, slowly progressive condition affecting middle-aged and elderly individuals that is characterized by macular capillary changes, variable foveal cavitations, and loss of outer retinal structure with eventual macular atrophy. Although MacTel was originally defined by its vascular features, histopathology and recently described animal models suggest that it may be a primary neurodegeneration involving Müller cells.

Idiopathic juxtafoveal retinal telangiectasia type 3 is a rare, poorly understood disease characterized by a bilateral, severe, occlusive vasculopathy affecting the macula, often associated with systemic disease.

In this article, we discuss MacTel, which is the most common and well-studied subtype. Much of what we have learned recently about this disease is drawn from the MacTel Project, an international consortium of investigators dedicated to better understanding of the disease and development of treatment.

**EPIDEMIOLOGY**

MacTel is a bilateral disease that usually begins to affect patients between the ages of 40 and 60 years. The prevalence of MacTel is estimated to be 0.022% to 0.1%, based on assessment of fundus photographs from large population-based studies. However, diagnosis based on color photographs alone probably underestimates the true prevalence, and other kinds of imaging, as described herein, are helpful to detect early disease. In
a MacTel Project cohort of 310 affected individuals, 64% were women and 81% were Caucasian, and systemic hypertension (52%) and diabetes mellitus (28%) were common. Most patients with MacTel do not have a family history of disease, but genetic factors are suspected to play a role in at least some cases. Cases in monozygotic twins and multiple cases within families have been reported.\textsuperscript{10-13} A gene-mapping study of affected families identified a possible locus on chromosome 1, with inheritance consistent with an autosomal dominant pattern with reduced penetrance.\textsuperscript{14} A recent genome-wide association study involving 476 cases and 1,733 controls, plus a separate replication cohort, identified three additional loci,
but did not confirm the findings of the earlier linkage analysis.\textsuperscript{15} We have more to learn about genetic factors associated with MacTel, and genetic testing is not currently recommended or available.

**CLINICAL FEATURES**

The most common presenting symptom of MacTel is difficulty with reading, specifically, complaints of missing or distorted letters.\textsuperscript{16} Best-corrected visual acuity (VA) at presentation is 20/40 or better in 64% of eyes, and vision of 20/100 or worse is uncommon (10%).\textsuperscript{9} In general, VA decreases at a very slow rate of approximately 1 letter per year.\textsuperscript{17} However, although VA may test well in patients with MacTel, vision-related quality of life is reduced compared with patients with early age-related macular degeneration (AMD) and similar VA.\textsuperscript{18}

Funduscopic features present in eyes in the MacTel Project cohort at baseline, as graded on color fundus photographs, included a loss of retinal clarity / grayish perifoveal sheen (74%), telangiectatic macular vessels (51%), retinal pigment epithelial (RPE) hypertrophy (33%), blunted “right-angle” vessels (29%), and crystalline deposits (21%) (Figures 1A and 2A).\textsuperscript{9} There are no peripheral retinal abnormalities in MacTel. Depletion of macular luteal pigment, an early feature of disease, can be visualized using dual wavelength autofluorescence imaging developed for research applications.\textsuperscript{19} More relevant to clinical practice, a characteristic hyperreflective halo surrounding the fovea is often visible using blue reflectance imaging (Figure 2B), even in cases where a parafoveal gray sheen is not prominent.\textsuperscript{19} Blue reflectance imaging is distinct from the red-free capabilities on most fundus cameras, which often use green filters, and can be performed using a blue filter (480 nm or similar wavelength) on a traditional fundus camera or the blue laser of a confocal scanning laser ophthalmoscope (such as the 488 nm laser in the Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). Although traditional red-free images obtained using green or yellow filters can help highlight the subtle microvascular alterations in MacTel, they do not reliably show a hyperreflective halo.\textsuperscript{20}

Optical coherence tomography (OCT) is helpful for diagnosing MacTel in early and later stages. Initially, subtle splaying of the foveal depression and focal areas of hyporeflectivity in the normally hyperreflective ellipsoid zone layer may be seen (Figure 3A). Over time, enlargement of regions of ellipsoid zone loss, most common temporal to the fovea, may be accompanied by more general disruption of the layers of the outer retina (Figure 3B). Foveal hyporeflective spaces, which must be distinguished from typical cystoid cavities (as seen with macular edema) and from pseudohole formation (as seen with epiretinal membrane), may be present early or late in disease (Figures 3A and 3B). In more advanced cases, presence of hyperreflective intraretinal migration and hypertrophy. OCT angiography offers a noninvasive means to assess alterations in the macular capillary network

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**Figure 2.** (A) A color fundus photograph shows a prominent perifoveal gray sheen, a variable feature of MacTel. (B) A corresponding blue reflectance image obtained using a 488-nm laser (blue reflectance mode) on the Spectralis HRA+OCT shows a prominent bright halo.
Figure 3. Optical coherence tomography line scans of the eye shown in Figure 2 showing progression over time. (A) A small region of only focal attenuation (relative hyporeflectivity) of the ellipsoid zone band is visible subfoveally at the time of imaging shown in Figure 2. Hyporeflective cavitation, which can be present early or late in disease, is present in the inner retina at the fovea, with still-intact internal limiting membrane. (B) Four years later, the area of ellipsoid zone disruption is much more extensive. Inner retinal cavitation is more prominent. Worsening in this case is rapid compared with most eyes with the disease.

(Figure 1B). Finally, fluorescein angiography allows visualization of the telangiectatic vessels that represent the traditional defining feature of the disease. Abnormal capillaries may be present sectorally, most typically temporal to the fovea, or may surround the fovea, and are associated with leakage in the late phase (Figures 1C and 1D). Lipid exudates, intra- or subretinal hemorrhage, and macular edema are not characteristic of MacTel in the absence of complicating neovascularization (see below), and any of these features should prompt reconsideration of the diagnosis or stage of disease. Features of tamoxifen-induced retinopathy, including presence of crystals and foveal cavitations, can simulate MacTel, and a history of exposure to this medication should be solicited.21

The natural history of MacTel usually involves a slow decline in central vision secondary to the changes described above. Retinal neovascularization, accompanied by exudation, hemorrhage, and / or fibrosis is uncommon (2% to 14%).1,9 and is thought to arise from the deep capillary plexus in a process similar to retinal angiomatosus proliferation seen in AMD. Retinal neovascularization is often aggressive and may result in abrupt vision loss from hemorrhage or exudation, with progression to scarring in the absence of treatment.

MANAGEMENT

Treatment for MacTel in the absence of retinal neovascularization is supportive, as there is currently no proven therapy. Macular grid laser photocoagulation,22 photodynamic therapy,23 and intravitreal injections of vascular endothelial growth factor (VEGF) antagonists24-26 have been tried in small series without success. Anti-VEGF agents seem able to reduce angiographic leakage during the short-term, but do not improve VA or prevent vision loss, and there is even question about whether they might make progression more likely during the long-term.27 In patients with MacTel who develop neovascularization, anti-VEGF agents have been shown to help limit scarring and vision loss.28 Full-thickness macular holes (MHs) occasionally develop in the setting of MacTel and must be distinguished from more common hyporeflective foveal cavitation with still-intact ILM.
(Figure 3B). MHs that show more typical features of vitreous traction may close with vitrectomy and gas tamponade, but those that seem to arise from disintegration of foveal tissue may not respond to surgery, and closure rates in small series are lower than those achieved for traditional MHs. 29

There is great interest in finding treatments for MacTel, spurred recently by MacTel Project efforts. Recognition of MacTel as a neurovascular degeneration and insights from animal models have led to interest in therapy using neuroprotective or neurotrophic factors. A phase 2 clinical trial evaluating an intraocular implant secreting ciliary neurotrophic factor (CNTF) (Renexus; Neurotech Pharmaceuticals, Cumberland, RI), the same device previously tested for advanced dry AMD and retinitis pigmentosa, showed positive results in patients with MacTel. 30 Ninety-nine eyes among 67 adults were randomized to receive either a CNTF implant or sham surgery with masking of participants. At 2 years, eyes that received the CNTF implant showed a 31% reduced rate of ellipsoid-zone loss measured using en face OCT analysis, compared with eyes that received sham (P = .039). This lesser rate of progression in CNTF-treated eyes correlated functionally with microperimetry testing and resulted in a stabilization of reading speed in CNTF-receiving eyes compared with sham eyes. Phase 3 trials evaluating the CNTF implant are underway. 31 Another promising lead is suggested by work that builds on findings from the recent genome-wide association study, which suggested that serine and glycine metabolism might be relevant to disease pathogenesis. 15 Comparison of 50 cases and 50 matched controls revealed that serum levels of serine and glycine were both significantly lower in patients with MacTel, a provocative finding that is being further studied.

CONCLUSIONS

MacTel is a bilateral neurodegeneration affecting middle-aged adults originally classified according to its vascular features. Making the diagnosis enables counseling about prognosis, helps to spare patients unnecessary treatment, and identifies the need for surveillance for treatable neovascular complications. Early clinical trial results of CNTF therapy appear promising, and further research on this and other potential therapies is underway.

REFERENCES


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