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Concurrent idiopathic macular telangiectasia type 2 and central serous chorioretinopathy

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Abstract

Purpose—To describe cases presenting with features of idiopathic macular telangiectasia (MacTel) type 2 and central serous chorioretinopathy (CSC).

Methods—Databases from 4 tertiary retina centers were searched for cases co-presenting CSC and MacTel type 2.

Results—Five cases were identified (4 men, 1 woman; mean age: 67.2 years). Four patients were referred for chronic or non-resolving CSC, and the diagnosis of MacTel type 2 was made based on multimodal imaging findings. One patient had advanced MacTel type 2, and developed acute CSC. Regarding the MacTel type 2 findings, all subjects presented perifoveal telangiectasia on fluorescein angiography, and 4 subjects showed intraretinal cavitations typical of MacTel type 2 on optical coherence tomography (OCT), in one or both eyes. Regarding the CSC findings, fluorescein angiography identified focal or extended retinal pigment epithelium alteration in all eyes, and an active leakage in 2 eyes. Indocyanine green angiography showed choroidal vascular hyperpermeability in 4 subjects. On OCT, pigment epithelial detachments were detected in 5 eyes (4 subjects), and foveal detachments were present in 5 eyes (3 subjects), which spontaneously resolved (2 eyes), responded to photodynamic therapy (2 eyes) or persisted (1 eye). Mean choroidal thickness was 402±99 µm.

Conclusion—The co-diagnosis of CSC and MacTel type 2 should be considered in atypical presentations associating features from both disorders.

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Keywords

central serous chorioretinopathy; macular telangiectasis; choroid; retinal pigment epithelium; choroidal thickness; optical coherence tomography; fluorescein angiography; indocyanine green angiography

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachments that often spontaneously resolve,^{1–4} and most commonly affects middle-aged males.⁵ This disorder is associated with choroidal vascular dilation and multifocal hyperpermeability, thickening of the choroid, alterations of the retinal pigment epithelium (RPE), and leakage into the subretinal space. It may be triggered by environmental factors such as psychological stress,^{6–9} corticosteroid intake,^{5,10,11} or circadian rhythm dysregulation.^{12,13} Predisposing factors possibly linked to genetic traits include increased choroidal thickness,^{14–16} cardiovascular risk,^{5,10,11,17} psychiatric illness,^{5,18–21} and allergy.^{10,11} Genetic variants associated with CSC have been identified in the *complement factor H*,^{22,23} *age-related maculopathy susceptibility-2*²³ and *cadherin-5* genes.²⁴

Type 2 idiopathic macular telangiectasia (MacTel type 2) is a macular disease manifesting with subtle leakage from perifoveal retinal telangiectasia,^{25–30} macular pigment loss,^{31,32} intraretinal cavitations, crystalline deposits, focal disruption of the retinal layers,^{33,34} or photoreceptor loss.^{35,36} First symptoms usually occur in the fifth and sixth decades,³⁷ and MacTel type 2 is frequently associated with diabetes mellitus, hypertension or cardiovascular disease.³⁸ Despite reports of familial cases,^{39,40} no Mendelian inheritance pattern has been evidenced.^{41,42} Recently, genome-wide analysis identified variants in the glycine/serine metabolic pathway.⁴³ Müller cell loss has been observed in MacTel type 2 eyes^{44,45} and in two proposed rodent models recapitulating part of MacTel type 2 phenotype.^{46,47} Although the role of Müller cells in MacTel type 2 is not well understood, it is considered a neurodegenerative disease with secondary vascular changes.

There is one previous report of an atypical co-presentation of CSC and MacTel type 2, but there is no study focusing on a possible overlap between both disorders, and its frequency.⁴⁸ We report herein a series of cases combining CSC and MacTel type 2 features.

METHODS

This observational, multicenter, retrospective case series involving human subjects was designed in accordance with the Tenets of the Declaration of Helsinki. It was approved by the Western Institutional Review Board (Puyallup, WA), the Combined Neuroscience Institutional Review Board at the National Institutes of Health (Bethesda, MD), the Swiss Federal Department of Health Ethics Committee (Lausanne, Switzerland, CER-VD n°19/15), and the Rotterdam Eye Hospital Review Board (Rotterdam, The Netherlands).

Clinical databases of 4 retina tertiary centers were searched for co-diagnoses of MacTel type 2 and CSC, after one patient was diagnosed with both diseases at Jules-Gonin Eye Hospital,

Lausanne, Switzerland (FBC). Optical coherence tomography (OCT) was performed on Spectralis (Heidelberg Engineering, Heidelberg, Germany), Cirrus (Zeiss, Oberkochen, Germany), or OCT-HS100 system (Canon, Tokyo, Japan). Foveal enhanced-depth imaging (EDI) OCT scan was acquired (Spectralis). Fundus autofluorescence images, fluorescein (FA) and indocyanine green (ICG) angiography were acquired with the Spectralis, OCT-HS100, or TRC fundus camera (Topcon, Tokyo, Japan).

The cases were reviewed by 2 retina specialists (FBC, RFS) to identify features related to CSC or MacTel type 2. Presence of choroidal vasodilation was assessed qualitatively on the best-available OCT scans visualizing the choroidal vasculature.

Subfoveal choroidal thickness was measured on horizontal foveal EDI-OCT scans by one observer (AM). When EDI-OCT was not available, OCT image contrast was enhanced using Photoshop cc (2017.0.1, Adobe Systems Inc, San Jose, CA) to reveal the outer choroid/sclera interface.

Descriptive and contingency statistics were performed on GraphPad Prism (version 5.0f, GraphPad Software, La Jolla, CA, USA).

RESULTS

From the clinical databases of four tertiary retinal centers in the United States, the Netherlands and Switzerland, cumulating a total of 297 MacTel type 2 cases, five patients (1.7%) co-presenting features of both MacTel and CSC were detected (4 male, 1 female, mean age: 67.2 years [57–78 years]).

Clinical characteristics

The mean LogMAR visual acuity was 0.60, corresponding to ~20/33 [20/160–20/20]. Four patients (Cases 1–3,5) were referred for chronic or non-resolving CSC, and an additional diagnosis of MacTel type 2 was made at the tertiary center. One patient was followed for advanced MacTel type 2 (Case 4), and experienced acute CSC detected during a routine visit. Table 1 summarizes their medical and ocular history. Two patients had type 2 diabetes mellitus, and one had severe heart disease. One patient reported corticosteroid use.

Multimodal imaging findings diagnostic of MacTel type 2 and CSC are reported in Table 2, and Figures 1 to 5 provide a case-by-case illustration. Two patients had bilateral MacTel type 2 findings and two had bilateral CSC. All affected eyes shared manifestations of both diseases, except Case 4 who had mostly CSC features in his right eye, and MacTel type 2 features in his left eye. In total, six eyes presented features of both disorders, 2 eyes presented MacTel type 2 findings only (Case 1 and 4, left eye), and 2 eyes presented CSC findings only (Case 4 and 5, right eye). One eye showed granular changes in the pigmentation at the level of the RPE suggestive of past fluid (Case 2, left eye).

CSC features

Regarding the diagnosis of CSC, 4 patients (5 eyes) exhibited subretinal fluid, and 3 patients (5 eyes) presented one or several pigment epithelial detachments. Fundus autofluorescence

alterations from long-standing serous detachments were found in 4 patients (7 eyes). Active fluorescein leakage was detected in 2 cases (3 eyes), but focal or extended RPE alterations was present in all 5 patients (9 eyes). ICG angiography was performed in 4 patients, all showing choroidal vascular hyperpermeability (8 eyes), including 2 contralateral eyes with MacTel type 2 features but no signs of past CSC episodes (Case 1 and 4, left eye), and one eye with thick choroid (490 μ m) without CSC (Case 2, left eye). Mean subfoveal choroidal thickness of all ten eyes was 402 $\pm$ 99 μ m [210–577 μ m], and was 424 $\pm$ 87 μ m [313–577 μ m] when considering only the six eyes with combined MacTel type 2 and CSC. Of the 5 patients, 4 had a subfoveal choroidal thickness $\geq$ 395 μ m in at least one eye, a previously recognized threshold for pachychoroid.¹⁶ In all eyes, dilated large choroidal vessels could be qualitatively discerned on OCT. One patient (Case 2) presented pattern-like peripapillary yellowish subretinal deposits in both eyes, best visible on fundus autofluorescence.

MacTel type 2 features

Regarding MacTel type 2 features, a focal loss of transparency temporal to the fovea was visible with ophthalmoscopy in all 5 patients (9 eyes), and a perifoveal hyperfluorescence found on fundus autofluorescence was present in 4 patients (7 eyes). In 2 patients (Case 1, right eye and Case 5, both eyes), perifoveal fundus autofluorescence could not be evaluated due to a large area of RPE alteration resulting from chronic CSC. Four subjects presented pigment clumps or crystal deposits. Leaky perifoveal telangiectasia were visible in early and late-phase FA in all 5 subjects (7 eyes with patent MacTel type 2). Four cases (5 eyes) had intraretinal cavitations with typical MacTel type 2 morphology on OCT, including loss of retinal tissue without retinal thickening, and square edges. When the cavitations were located in the inner retina, their inner retinal border was the inner limiting membrane (Case 2 and 3, right eye; Case 5, left eye). Cases also showed focal or extended interruptions of the ellipsoid zone (Case 1, 2 and 5) and presence of a large hyperreflective lesion (Case 4 and 5, left eye).

Natural history and treatment

Serous retinal detachments were detected in 5 eyes (4 patients), 3 of which had a foveal detachment. The natural evolution of subretinal fluid, and response to therapy was variable. It resolved spontaneously in 2 eyes, 1 and 3 months after detection (Case 4 and 2, right eye, respectively), persisted for 6 and 8 months and then resolved after photodynamic therapy in 2 eyes (Case 3, right and left eye, respectively), and persisted despite oral mineralocorticoid-receptor antagonist therapy (spironolactone 50 mg/day) in one eye (Case 1, right eye).

DISCUSSION

This study reports the co-occurrence of clinical manifestations from both MacTel type 2 and CSC in 5 patients seen in 4 different tertiary retinal centers, supported by their multimodal imaging findings, and their spontaneous evolution or treatment response. Four of them had chronic CSC and were additionally diagnosed with MacTel type 2, while one case had MacTel type 2 and experienced an acute CSC episode.

Note, that patients with MacTel type 2 and increased choroidal thickness in the absence of subretinal fluid were not considered since the prevalence of increased choroidal thickness in the general population and its exact influence on the risk of CSC are not known. Whether MacTel type 2 patients have increased choroidal thickness is controversial. While Chhablani et al did not observe any significant difference in the choroidal thickness of 41 MacTel type 2 patients from India as compared to sex- and age-matched controls,⁴⁹ Nunes et al found the mean choroidal thickness to be 41 μm greater in a cohort of 62 MacTel type 2 patients in the United States (of which 40% were diabetic) than a group of sex- and age-matched controls.⁵⁰ However, only 15 of the MacTel type 2 eyes (24%) had a subfoveal choroidal thickness greater than 400 μm . Several underlying factors may explain the variability of choroidal thickness observed in these MacTel type 2 patients, including ethnicity^{15,16} and diabetes,⁵¹ although the exact influence of these factors on choroidal thickness is still debated.^{52–54}

Previous observations have reported foveal detachments in MacTel type 2 eyes. In 25 eyes with MacTel type 2, Gaudric et al identified 2 eyes with foveal detachment without subretinal neovascularization.⁵⁵ Recently, among 427 cases from 3 sites contributing to the international MacTel type 2 Project, 6 cases (1.4%) presented with subretinal fluid causing foveal detachment, a proportion similar to the rate of CSC observed among MacTel cases in the present study.⁵⁶ Four cases showed fluctuation in the amount of subretinal fluid, with spontaneous resolution in 3 cases, and partial resolution followed by recurrence in one case, that ultimately responded to intravitreal anti-VEGF. The last 2 cases responded to intravitreal anti-VEGF, and a neovascular lesion was suspected. Consistently, leakage from deep vascular invasion and subretinal neovascularization in MacTel type 2 does respond to anti-VEGF agents.^{57,58} ICG angiography was not systematically performed, yet authors ruled out the possibility of leakage from the choroid as observed in CSC, based on FA findings. Cases from the present series did not appear to have vascular proliferation with leakage and had findings consistent with CSC.

The co-occurrence reported in this study may be coincidental, or may result from an overlap between pathophysiological processes underlying CSC and MacTel type 2. One possible hypothesis is that similar systemic factors could increase the risk of both disorders, such as diabetes mellitus. The medical records of the 5 patients reported in Table 1 did not show common factors among all the patients. Another possibility is that MacTel type 2 may require the combination of a genetic predisposition and suitable second triggers to develop manifest disease, either systemic, such as mild diabetes or metabolic syndrome,³⁸ or local, such as irradiation⁵⁹ or changes induced by other ocular conditions.

This report had several limitations. The limited number of cases, recruited in tertiary retinal centers, reflects the rarity of the reported co-occurrence. As such this investigation seeks to gain clues to the potential implications of this co-occurrence, and not to estimate its actual frequency. The joint probability for a given individual to develop MacTel type 2 and CSC would be very difficult to determine given that MacTel type 2,⁶⁰ and forms of extramacular, asymptomatic CSC are often underdiagnosed, and that variable prevalence of MacTel type 2^{60–63} and CSC^{64–66} have been reported in the literature. The MacTel-specific incidence of CSC, or inversely the CSC-specific incidence of MacTel type 2 could be estimated by natural history studies but long-term follow-up of very large cohorts would be required.

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Summary statement

Five cases were diagnosed with idiopathic macular telangiectasia type 2 and central serous chorioretinopathy. Multimodal imaging identified specific features ascertaining each diagnosis. Five eyes showed foveal detachment, that spontaneously resolved, responded to photodynamic therapy, or persisted. This possible co-occurrence should be considered when confronted with atypical cases.

Figure 1. Case 1: 64-year-old man with MacTel type 2 in both eyes and central serous chorioretinopathy in the right eye

The patient presented with a fourth episodes of central serous chorioretinopathy (CSC) in his right eye and was co-diagnosed with MacTel type 2 in both eyes. Findings suggestive of CSC were: pigment mottling (A, yellow arrow), a descending track on fundus autofluorescence (B), diffuse fluorescein leakage (C,D), choroidal hyperpermeability on midphase ICGA (E, 3 minutes and F, 10 minutes, blue arrows), also present in the fellow eye (L, 3 minutes and M, 10 minutes, blue arrow), foveal subretinal fluid on OCT with elongated photoreceptor outer segments (G, pink arrow) and dilated choroidal vessels (G, green arrow).

The findings diagnostic of MacTel type 2 were bilateral macular pigment loss (A and H), subtle hyperautofluorescence (B and I) and fluorescein diffusion temporal to the fovea (C–D and J–K, white arrows). On OCT, the right eye showed an intraretinal cavitation merged with the subfoveal detachment, with preservation of inner layers (G, orange arrow). The left eye showed outer retinal cavitations with ellipsoid zone interruption on OCT (N, orange arrows).

Figure 2. Case 2: 78-year-old man with MacTel type 2 and central serous chorioretinopathy in the right eye

The patient had recurrent subretinal fluid and peripapillary intraretinal cystoid spaces that seemed unresponsive to intravitreal aflibercept. At presentation, crystal deposits were visible temporal to the fovea (A, white arrow), and both fundus exhibited pattern-like peripapillary yellowish subretinal deposits (A and G, yellow arrows), best visualized on green-light fundus autofluorescence (B and H, yellow arrows). Perifoveal loss of retinal transparency was visible in the right fundus (A, purple arrow). Fluorescein angiography showed subtle leakage and staining from perifoveal telangiectasia in the right eye (C, white arrow), and in both eyes a peripapillary window defect (C, I, green arrows). ICGA showed bilateral choroidal vessel dilation and hyperpermeability (D, J, blue arrows). An OCT scan superior to the fovea identified peripapillary subretinal fluid and schisis-like intraretinal cystoid spaces (E, pink and white arrows). A foveal OCT scan identified square-shaped inner atrophic cavitations typical of MacTel type 2 (F, orange arrow), and an outer retinal cavity with interrupted ellipsoid zone, fused with the subfoveal detachment (F, yellow arrow). OCT showed bilaterally a thick choroid, with enlarged vessels (E and K, blue arrows). The left eye did not show signs of MacTel type 2. Multimodal findings did not identify differential

diagnoses for peripapillary intraretinal edema, such as polypoidal choroidal vasculopathy, optic disc pit, glaucoma or hypertensive retinopathy.

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Figure 3. Case 3: 58-year-old man with simultaneous MacTel type 2 and chronic central serous chorioretinopathy in both eyes

The patient presented with vision loss in his left eye lasting for several months, and was diagnosed with bilateral non-resolving CSC associated with MacTel type 2. Features diagnostic of MacTel type 2 were macular pigment loss, (A and I, yellow arrow), focal hyperautofluorescence (B and J, yellow arrow), and faint fluorescein leakage temporal to the fovea (C, D, K, L, white arrow). OCT exhibited typical cavitations with disruption of the normal retinal lamination and loss of the ellipsoid zone in the right eye (G, H, orange arrows), and one smaller cavitation in the left eye (P, orange arrow).

CSC manifested with peripapillary and macular serous detachments in the right (G) and left eye (O), associated with focal pigment epithelial detachments (G, O, pink arrow). Both eyes showed granular autofluorescence changes (B,J), and extended window defects on fluorescein angiography at 1 (C,K) and 6 minutes (D,L) (green arrows) with a leakage site in the right eye (C,D, pink arrow). ICGA demonstrated bilateral choroidal vessel dilation (E,M) and hyperpermeability (F,N). After non-resolving subretinal detachment for more than 6 months, photodynamic therapy was performed followed by reattachment in both eyes (H, P), but subretinal fluid recurred 9 months later.

Figure 4. Case 4: 65-year-old woman with central serous chorioretinopathy in the right eye and MacTel type 2 in the left eye

The diagnosis of MacTel type 2 in the left eye was made five years earlier. During routine evaluation, a subretinal detachment was detected in her right eye that resolved spontaneously over 1 month, and was attributed to central serous chorioretinopathy (CSC). The MacTel type 2 findings were: perfoveal opacification (A,H, yellow arrow) and pigment clumping (H, white arrow), focal hyperautofluorescence (B and I, yellow arrow) and fluorescein leakage temporal to the fovea (J,K, white arrow). The pigment clumping produced a masking effect on ICGA (L,M, yellow arrow), that showed no signs of neovascularization. OCT showed a hyperreflective lesion temporal to the fovea corresponding to outer retinal pigment migration (N, pink arrow) with focal disorganization of retinal layers (N, orange arrow). There were early MacTel type 2 signs in the right eye with perfoveal focal retinal opacification (A, yellow arrow), hyperautofluorescence (B, yellow arrow) and telangiectasia without leakage (C,D, white arrow). CSC manifested with a serous detachment superonasal

to the macula (G, green arrow). At the same location, fluorescein angiography showed a focal window defect (C,D, green arrow) and ICGA showed enlarged choroidal vessels and hyperpermeability at 1 and 10 minutes (E,F, blue arrow). Similar findings on ICGA were visible in the unaffected left eye (L,M, blue arrow).

Figure 5. Case 5: 69-year-old man with bilateral chronic central serous chorioretinopathy and MacTel type 2 in the left eye

The patient had a history of bilateral chronic central serous chorioretinopathy (CSC) with diffuse retinal pigment epitheliopathy. The diagnosis was strongly indicated by widespread, multifocal areas of autofluorescence alterations (C and magnified inlet, B; I and magnified inlet, H), with corresponding window defects on fluorescein angiography (D,E and K,L), due to advanced photoreceptor and retinal pigment epithelium atrophy, visible on OCT (F, yellow arrow).

During a 3-year follow-up, progressive bilateral pigment clumping and macular pigment loss (A and G, yellow arrow) and crystal deposits (A, green arrow) were noticed. The diagnosis of MacTel type 2 was made, also supported by perifoveal diffusing telangiectasia on 1- and

5-minute fluorescein angiograms (K, L and magnified inlet, J, white arrow), a hyperreflective outer retinal lesion (M, pink arrow), with loss of retinal architecture, ellipsoid zone interruption and an inner retinal cavitation (M, orange arrow). Left-eye pigment clumping (A) and outer retinal atrophy was also compatible with MacTel type 2 (F).

TABLE 1

Ocular and medical history in 5 patients with a combined diagnosis of idiopathic macular telangiectasia type 2 and central serous chorioretinopathy.

Case	Sex	Age, years	Ethnicity	Ocular history	Ocular diagnosis	Medical history	Medication (route, if other than oral)
1	Male	64	Caucasian	Recurrent CSC OD	MacTel2 OU + CSC OD	Benign prostatic hyperplasia, chronic bronchitis, cutaneous angiodoma, appendicitis	Hydrocortisone (nasal spray), Dutasteride, Fluticasone/Salmeterol inhalation
2	Male	78	Caucasian	Recurrent CSC OD	MacTel2 + CSC OD	Coronary heart disease, cardiac dysrhythmia, cardiac insufficiency, hypertension, dyslipidemia, Lyme disease, skin cancer, benign prostatic hyperplasia, seizures, hepatitis, gout	Amiodarone, Candesartan, Dutasteride, Warfarin, Furosemide, Keppra, Atorvastatin, Metoprolol, Spirinolactone, Terazosin, Omeprazole, Levohydroxine, Saccharomyces boulardii probiotic capsules
3	Male	57	Caucasian	Non-resolving CSC OU, PDT OU	MacTel2 + CSC OU	Healthy	none
4	Female	65	Indian	MacTel2 OS	MacTel2 OS + acute CSC OD	Diabetes mellitus (onset: 48 yo), hypertension	Insulin (subcutaneous), Metformin, Simvastatin, Enalapril
5	Male	72	Caucasian	Recurrent CSC OU	MacTel2 + CSC OU	Diabetes mellitus (onset: 71 yo), coronary heart disease, coronary angioplasty (41 yo)	Metformin, Statin, Niacin

MacTel2= Idiopathic macular telangiectasia type 2; CSC= central serous chorioretinopathy; OD= right eye; OS= left eye; OU= both eyes; PDT= photodynamic therapy; yo= year-old

TABLE 2

Clinical and multimodal imaging features diagnostic of idiopathic macular telangiectasia type 2 and central serous chorioretinopathy in 5 patients diagnosed with both conditions.

MacTel2 features														CSC features									
Case	Eye	Diagnosis	BCVA, Snellen	MP loss	Pigment clumps/ Cristal deposits	FAF	FA	SD-OCT			Fundus			FAF	ICG	SD-OCT							
								Perifoveal hyper-AF	Diffusing perifoveal telangiectasis	Cavitations	Retinal layers disruption	Pigment mottling	RPE yellow spots			Hyper/ hypo-AF tracks	Peripapillary reticulations	Leakage site (Single+ Multiple++)	RPE window defect	SRD	PED	SFCT, µm	Dilated choroidal vessels
1	OD	MacTel2 + CSC	20/25	+			+		+		+			+	++		+	+	313	+			
	OS	MacTel2	20/20	+		+	+		+						+			210	+				
2	OD	MacTel2 + CSC	20/60	+	c	+	+		+		+		+	+	++	+	+	577	+				
	OS		20/20	+		+					+		+		+			490	+				
3	OD	MacTel2 + CSC	20/25	+	c	+	+		+		+		+	+	++	+	+	437	+				
	OS	MacTel2 + CSC	20/32	+	c	+	+		+		+		+		++	+	+	426	+				
4	OD	CSC	20/20			+									++	+	+	424	+				
	OS	MacTel2	20/32	+	p	+	+		+		+				++	+	+	353	+				
5	OD	CSC	20/32	+	p				+		+		+		NA		+	398	+				
	OS	MacTel2 + CSC	20/160	+	p/c		+		+		+		+		NA		+	392	+				

MacTel2= idiopathic macular telangiectasia type 2; CSC= central serous chorioretinopathy; BCVA= best-corrected visual acuity; FAF=Fundus auto-fluorescence, FA=fluorescein angiography; SD-OCT=spectral-domain optical coherence tomography; ICG= indocyanine-green angiography; SRD= serous retinal detachment; PED= pigment epithelial detachment; RPE= retinal pigment epithelium; SFCT= subfoveal choroidal thickness; p= pigment clumps; c= cristal deposits