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Ⅳ. 研究成果の刊行物・別刷

CLINICAL CHARACTERISTICS OF OCCULT MACULAR DYSTROPHY IN FAMILY WITH MUTATION OF *RP1L1* GENE

KAZUSHIGE TSUNODA, MD, PhD,* TOMOAKI USUI, MD, PhD,†‡ TETSUHISA HATASE, MD, PhD,† SATOSHI YAMAI, MD,§ KAORU FUJINAMI, MD,* GEN HANAZONO, MD, PhD,* KEI SHINODA, MD, PhD,*¶ HISAO OHDE, MD, PhD,** MASAKAZU AKAHORI, PhD,* TAKESHI IWATA, PhD,* YOZO MIYAKE, MD, PhD*††

Purpose: To report the clinical characteristics of occult macular dystrophy (OMD) in members of one family with a mutation of the *RP1L1* gene.

Methods: Fourteen members with a p.Arg45Trp mutation in the *RP1L1* gene were examined. The visual acuity, visual fields, fundus photographs, fluorescein angiograms, full-field electroretinograms, multifocal electroretinograms, and optical coherence tomographic images were examined. The clinical symptoms and signs and course of the disease were documented.

Results: All the members with the *RP1L1* mutation except one woman had ocular symptoms and signs of OMD. The fundus was normal in all the patients during the entire follow-up period except in one patient with diabetic retinopathy. Optical coherence tomography detected the early morphologic abnormalities both in the photoreceptor inner/outer segment line and cone outer segment tip line. However, the multifocal electroretinograms were more reliable in detecting minimal macular dysfunction at an early stage of OMD.

Conclusion: The abnormalities in the multifocal electroretinograms and optical coherence tomography observed in the OMD patients of different durations strongly support the contribution of *RP1L1* mutation to the presence of this disease.

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Occult macular dystrophy (OMD) was first described by Miyake et al[1] to be a hereditary macular dystrophy without visible fundus abnormalities. Patients with OMD are characterized by a progressive decrease of visual acuity with normal-appearing fundus and normal fluorescein angiograms (FA). The important signs of OMD are normal full-field electroretinograms (ERGs) but abnormal focal macular ERGs and multifocal electroretinograms (mfERGs) also exist. These findings indicated that the retinal dysfunction was confined to the macula.[1–5] Optical coherence tomography (OCT) showed structural changes in the outer nuclear and photoreceptor layers.[6–11]

Recently, we found that dominant mutations in the *RP1L1* gene were responsible for OMD.[12] The *RP1L1* gene was originally cloned as a gene derived from common ancestors as a retinitis pigmentosa 1 (*RP1*) gene, which is responsible for 5–10% of autosomal dominant retinitis pigmentosa worldwide, on the same Chromosome 8.[13–17] A number of attempts have been made to identify mutations in *RP1L1* in various retinitis pigmentosa patients with no success. An immunohistochemical study on cynomolgus monkeys showed that *RP1L1* was expressed in rod and cone photoreceptors, and *RP1L1* is thought to play important roles in the morphogenesis of the photoreceptors.[13,18] Heterozygous *RP1L1* knockout mice were reported to be normal, whereas homozygous knockout mice develop subtle retinal degeneration.[18] However, the RP1L1 protein has a very low degree of overall sequence

From the *Laboratory of Visual Physiology, National Institute of Sensory Organs, Tokyo, Japan; †Division of Ophthalmology and Visual Science, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan; ‡Akiba Eye Clinic, Niigata, Japan; §Department of Ophthalmology, Sado General Hospital, Niigata, Japan; ¶Department of Ophthalmology, School of Medicine, Teikyo University, Tokyo, Japan; **Department of Ophthalmology, School of Medicine, Keio University, Tokyo, Japan; and ††Aichi Medical University, Aichi, Japan.

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Reprint requests: Kazushige Tsunoda, Laboratory of Visual Physiology, National Institute of Sensory Organs, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan; e-mail: tsunodakazushige@kankakuki.go.jp

identity (39%) between humans and mice compared with the average values of sequence similarity observed between humans and mice proteins. The results of linkage studies have strongly supported the contribution of *RP1L1* mutations to the presence of this disease,[12] but the function of *RP1L1* in the human retina has not been completely determined.

A large number of cases of OMD have been reported[7,10,19]; however, we did not always find the same mutations in sporadic cases or in small families, which had less than three affected members. This led us to hypothesize that several independent mutations can lead to the phenotype of OMD, that is, OMD is not a single disease caused by a specific gene mutation, but may represent different diseases with similar retinal dysfunctions.

Thus, the aim of this study was to determine the characteristics of OMD by investigating the phenotypes of patients with the *RP1L1* mutation from a single Japanese family.

Patients and Methods

We investigated 19 members from a single Japanese family. A homozygous mutation, p.Arg45Trp in the *RP1L1* gene, was confirmed in 14 members,[12] and 13 of the 14 were diagnosed with OMD. Among the 14 members with a mutation in the *RP1L1* gene, 11 were followed-up at the Niigata University in Niigata, Japan. The other three were examined at the National Institute of Sensory Organs in Tokyo, Japan. Each member had a complete ophthalmic examination including best-corrected visual acuity (BCVA), refraction, perimetry, fundus photography, FA, full-field ERGs,[20] mfERGs,[21] and OCT. The visual fields were determined by Goldmann perimetry or by Humphrey Visual Field Analyzer (Model 750i; Carl Zeiss Meditec, Inc, Dublin, CA). The SITA Standard strategy was used with the 30-2 program or the 10-2 program for the Humphrey Visual Field Analyzer.

Electroretinograms were used to assess the retinal function under both scotopic and photopic conditions.[22] Full-field ERGs were recorded using the International Society of Clinical Electrophysiology and Vision standard protocol. Multifactorial electroretinograms were recorded with the Visual Evoked Response Imaging System (VERIS science 4.1; EDI, San Mateo, CA). A Burian–Allen bipolar contact lens electrode was used to record the mfERGs. The visual stimuli consisted of 61 or 103 hexagonal elements with an overall subtense of approximately 60°. The luminance of each hexagon was independently modulated between black (3.5 cd/m^2) and white (138.0 cd/m^2) according to a binary m-sequence at 75 Hz. The surround luminance was 70.8 cd/m^2.

The OCT images were obtained with a spectral-domain OCT (HD-OCT; Carl Zeiss Meditec or a 3D-OCT-1000, Mark II; Topcon) from 21 eyes of 12 cases in the same pedigree.

The procedures used adhered to the tenets of the Declaration of Helsinki and were approved by the Medical Ethics Committee of both the Niigata University and National Institute of Sensory Organs. An informed consent was received from all the subjects for the tests.

Results

The findings of 5 generations of 1 family with OMD are shown in Figure 1. The numbered family members had the same mutation in *RP1L1* (p.Arg45Trp), and family members designated with the filled squares or filled circles were phenotypically diagnosed with OMD by routine examinations including visual field tests, FA, mfERGs, and Fourier-domain OCT. Only Patient 5 (age 60 years) had normal phenotype, although she had the *RP1L1* mutation.

The clinical characteristics and the results of ocular examinations of all the 14 family members with the *RP1L1* mutation (p.Arg45Trp) are listed in Tables 1 and 2. Family Member #5 was diagnosed as normal because she had normal mfERGs.

Among the 13 OMD patients (average age at the final examination, 57.2 ± 22.1 years), 12 complained of disturbances of central vision and 4 complained of photophobia (Table 1). Patient 1 did not report any visual disturbances in the right eye as did Patient 6 for both eyes. The visual dysfunction in these eyes was confirmed by mfERGs. For 13 patients, the age at the onset of visual difficulties varied from 6 years to 50 years with a mean of 27.3 ± 15.1 years.

All the patients were affected in both eyes, and the onset was the same in the 2 eyes except for Patients 1, 11, 12, and 14. Patient 1 first noticed a decrease in her visual acuity in her left eye at age 50 years, and she still did not have any subjective visual disturbances in her right eye 30 years later. However, a clear decrease in the mfERGs in the macular area was detected in both eyes. Patient 11 first noticed a decrease in the visual acuity in her right eye at age 47 years when the BCVA was 0.2 in the right eye and 1.2 in the left eye (Figure 2). Seven years later at age 54 years, she noticed a decrease in the vision in her left eye. Similarly, Patients 12 and 14 did not report any visual disturbances in their right eyes until 2 (Patient 12) or 8 (Patient 14) years after the onset in their left eyes.

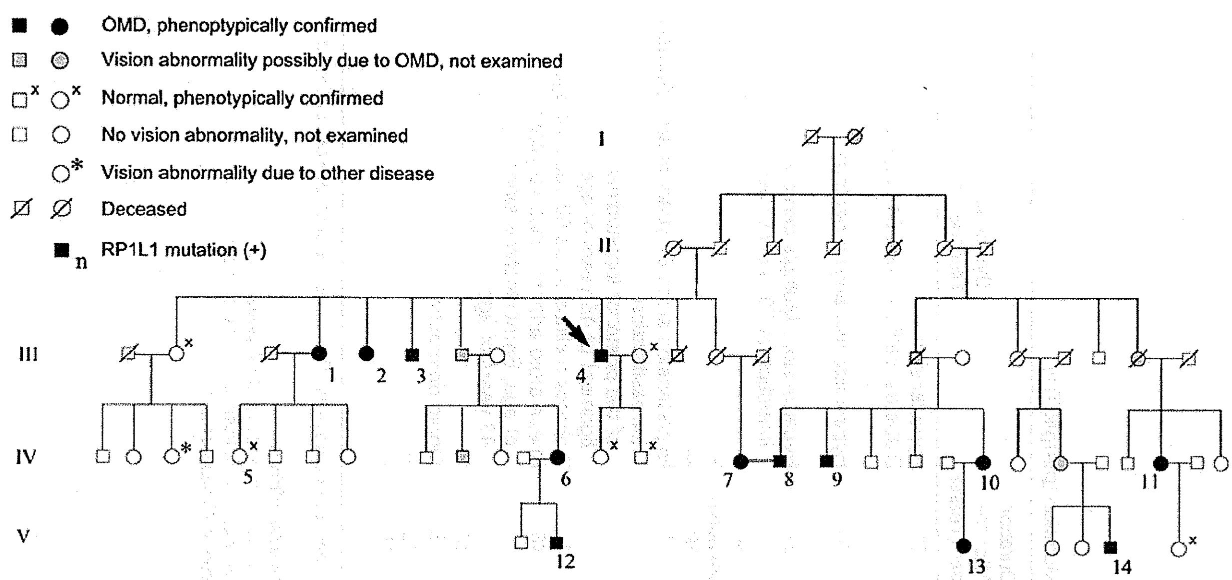

Fig. 1. Pedigree of a family with OMD. The identification number of the patients is marked beside the symbols The proband is indicated by an arrow. The open squares and circles with crosses are the relatives whose visual function was confirmed to be normal by routine examinations including Humphrey visual field tests, mfERGs, and Fourier-domain OCT Those designated by hatched squares or circles were reported to have poor vision with similar severity and onset as the other genetically confirmed OMD patients. One relative marked by an asterisk had unilateral optic atrophy because of retrobulbar neuritis

The duration of the continuous decrease in the BCVA varied from 10 years to 30 years (mean, 15.6 ± 7.7 years) in 16 eyes of 9 adult patients. After this period, these patients reported that their vision did not decrease. Patients 2, 3, 8, and 14 complained of photophobia, and the degree of photophobia remained unchanged after the visual acuity stopped decreasing. Patients 1, 2, 4, 7, and 9 had additional disturbances of vision because of senile cataracts, and Patients 2 and 4 had bilateral cataract surgery. The visual disturbances because of the OMD were still progressing at the last examination in the left eye of Patient 11 (age 57 years), and both eyes of Patient 12 (age 20 years), Patient 13 (age 18 years), and Patient 14 (age 28 years).

Different systemic disorders were found in some of the patients; however, there did not seem to be a specific disorder, which was common to all of them (Table 1).

In the 16 eyes of 9 patients whose BCVA had stopped decreasing, the BCVA varied from 0.07 to 0.5 (Table 2). The BCVA of the left eye of Patient 6 was 0.07 because of an untreated senile cataract. If this eye is excluded, the final BCVAs of all the stationary eyes range from 0.1 to 0.5. Patient 2 had photophobia, and her BCVA measured by manually presenting Landolt rings on separate cards under room light was 0.4 in the right eye and 0.5 in the left eye, which was better than that measured by a Landolt chart of 0.3 in the right eye and 0.3 in the left eye with background illumination.

For the 13 patients whose original refractions were confirmed, 11 of 26 eyes were essentially emmetropic (<± 0.5 diopters). Both eyes of Patients 1, 3, 4, 6, and 8 and the left eye of Patient 5 were hyperopic (+0.675 to +4.625 diopters). The right eye of Patient 7, the left eye of Patient 12, and both eyes of Patient 13 were moderately myopic (−0.625 to −2.75 diopters). These results indicate that there is no specific refraction associated with OMD patients in this family.

The visual fields were determined by Goldmann perimetry or Humphrey Visual Field Analyzer. All the patients had a relative central scotoma in both eyes except for Patient 1 whose right eye was normal by Goldmann perimetry. In all cases, no other visual field abnormalities were detected during the entire course of the disease. In the patients examined shortly after the onset, a relative central scotoma was not detected by Goldman perimetry and was confirmed by static perimetry.

The fundus of all except one eye was normal. The left eye of Patient 9 had background diabetic retinopathy. At the first consultation at age 46 years, Patient 9 did not have diabetes, and the funduscopic examination and FA revealed no macular abnormalities. At the age 66 years, there were few microaneurysms in the left macula away from the fovea; however, OCT did not show any diabetic changes such as macular edema. The OMD was still the main cause of visual acuity reduction in this patient.

Six patients consented to FA, and no abnormality was detected in the entire posterior pole of the eye. It is noteworthy that both the fundus and FA of Patient 4 were normal at the age 73 years, which was >50 years

Table 1. Clinical Characteristics of the Family Members With RP1L1 Mutation (p.Arg45Trp)

Case	Age and Gender	Chief Complaint	Affected Eye	Age at Onset (Years)	Duration of Continuous Decrease in BCVA (Years)	Duration After the Onset (Years)	Systemic Disorders
1	81, F	Decreased visual acuity	Bilateral*	50	20	31	Hypertension
2	71, F	Decreased visual acuity and photophobia	Bilateral	25	25	46	Diabetes mellitus since 64 years of age
3	74, M	Decreased visual acuity and photophobia	Bilateral	30	10	44	Hyperlipidemia, angina pectoris
4	83, M	Decreased visual acuity	Bilateral	20	10	63	Hypertension, Multiple cerebral infarction at 73 years of age
5	60, F	None	—†	—	—	—	—
6	50, F	None	Bilateral*	Unknown	Unknown	Unknown	—
7	69, F	Decreased visual acuity	Bilateral	50	10	19	—
8	69, M	Decreased visual acuity and photophobia	Bilateral	28	10	41	Hypertension since 67 years of age, Surgery for ossification of the posterior longitudinal ligament at 45 years of age
9	66, M	Decreased visual acuity	Bilateral	30	15	36	Diabetes mellitus since 63 years of age
10	58, F	Decreased visual acuity	Bilateral	10	30	48	Rheumatoid arthritis since 46 years of age, Bronchiectasis since 43 years of age
11	57, F	Decreased visual acuity	Bilateral ‡	47	OD, 10, OS, still progressing	10	—
12	20, M	Decreased visual acuity	Bilateral§	14	Still progressing	6	Atopic dermatitis
13	18, F	Decreased visual acuity	Bilateral	6	Still progressing	12	—
14	28, M	Decreased visual acuity and photophobia	Bilateral¶	18	Still progressing	10	—

*Patient 1 has subjective visual disturbance only in the left eye, and Patient 6 does not have any subjective visual disturbances in both eyes. The visual dysfunction was confirmed by mfERG.

†This woman has a mutation in RP1L1, but her visual function was confirmed normal after routine examinations including mfERG.

‡This patient noticed visual disturbance only in the right eye at 47 years of age. The visual disturbance in the left eye was first noticed at 54 years of age.

§This patient noticed visual disturbance only in the left eye at 14 years of age. The visual disturbance in the right eye was first noticed at 16 years of age.

¶This patient noticed visual disturbance only in the left eye at 18 years of age. The visual disturbance in OD was first noticed at 26 years of age.

Table 2. Results of Ocular Examinations of the Family Members With RP1L1 Mutation

Case	Age and Gender	BCVA at Final Visit		Refraction (D)*		Visual Field	Fundus Appearance	FA	Full-Field ERG	Relative Amplitude in mfERG at Fovea (Ring 1/Ring 5 or Ring 6)†	Other Ocular Disorders
		OD	OS	OD	OS						
1	81, F	1.2	0.1	+4.25	+4.625	Relative central scotoma, OS	Normal, OU	Normal, OU	NE	2.34, OD, 0.60, OS	Senile cataract, OU
2	71, F	0.4	0.5	Unknown‡	Unknown‡	Relative central scotoma, OU	Normal, OU	NE	NE	Not measurable, OU	Cataract surgery, OS at 58 years of age, OD at 69 years of age, Ptosis, OU
3	74, M	0.2	0.3	+2.875	+3.375	Relative central scotoma, OU	Normal, OU	NE	NE	Not measurable, OU	Laser peripheral iridotomy, OU at 73 years of age
4	83, M	0.2	0.2	+1.0	+1.625	Relative central scotoma, OU	Normal, OU	Normal, OU	Normal ISCEV standard protocol ERG, OU	Not measurable, OU	Cataract surgery, OU at 80 years of age
5	60, F	1.2	1.2	−0.25	+0.875	Normal, OU	Normal, OU	NE	NE	4.24, OD, NE, OS	—
6	50, F	1.2	1.2	+1.0	+1.0	Relative central scotoma, OU	Normal, OU	NE	NE	2.74, OD, 2.23, OS	—
7	69, F	0.1§	0.07§	−0.625	+0.25	Relative central scotoma, OU	Normal, OU	NE	Normal ISCEV standard protocol ERG, OU	Not measurable, OU	Senile cataract, OU
8	69, M	0.1	0.1	+1.125	+0.675	Relative central scotoma, OU	Normal, OU	NE	Normal ISCEV standard protocol ERG, OU	1.01, OD, 1.30, OS	—

Table 2. (Continued)

Case	Age and Gender	BCVA at Final Visit		Refraction (D)*		Visual Field	Fundus Appearance	FA	Full-Field ERG	Relative Amplitude in mfERG at Fovea (Ring 1/Ring 5 or Ring 6)†	Other Ocular Disorders
		OD	OS	OD	OS						
9	66, M	0.2	0.3	+0.125	+0.125	Relative central scotoma, OU	Normal, OD Background diabetic retinopathy with microaneurysm, OS	Normal, OU	Normal mixed rod–cone responses, OU	1.21, OD1.59, OS	Senile cataract, OU
10	58, F	0.1	0.1	+0.5	+0.375	Relative central scotoma, OU	Normal, OU	NE	Normal cone responses, OU	Not measurable, OU	—
11	57, F	0.1	0.4	+0.5	0.0	Relative central scotoma, OU	Normal, OU	Normal, OU	Normal ISCEV standard protocol ERG, OU	Not measurable, OU	—
12	20, M	0.3	0.3	−0.375	−0.75	Relative central scotoma, OU	Normal, OU	Normal, OU	Normal ISCEV standard protocol ERG, OU	0.98, OD1.03, OS	—
13	18, F	0.2	0.15	−1.625¶	−2.75¶	Relative central scotoma, OU	Normal, OU	Normal, OU	Normal ISCEV standard protocol ERG, OU	Not measurable, OU	—
14	28, M	1.0	0.6	−0.25	−0.25	Relative central scotoma, OU	Normal, OU	NE	Normal ISCEV standard protocol ERG, OU	1.63, OD, 0.66, OS	—

D, diopter; ISCEV, International Society of Clinical Electrophysiology and Vision; NE, not examined.
*Spherical equivalents at the initial visit.
†The responses of Ring 1 were extinguished and the N1–P1 amplitudes were not measurable in Cases 2, 3, 4, 7, 10, 11, and 13.
‡This patient had already undergone cataract surgeries for both eyes at the initial visit, and no data could be obtained about the original refraction.
§This patient's visual acuity was reduced also by senile cataract.
¶The refraction of this patient was measured after instillation of cycloplegics.

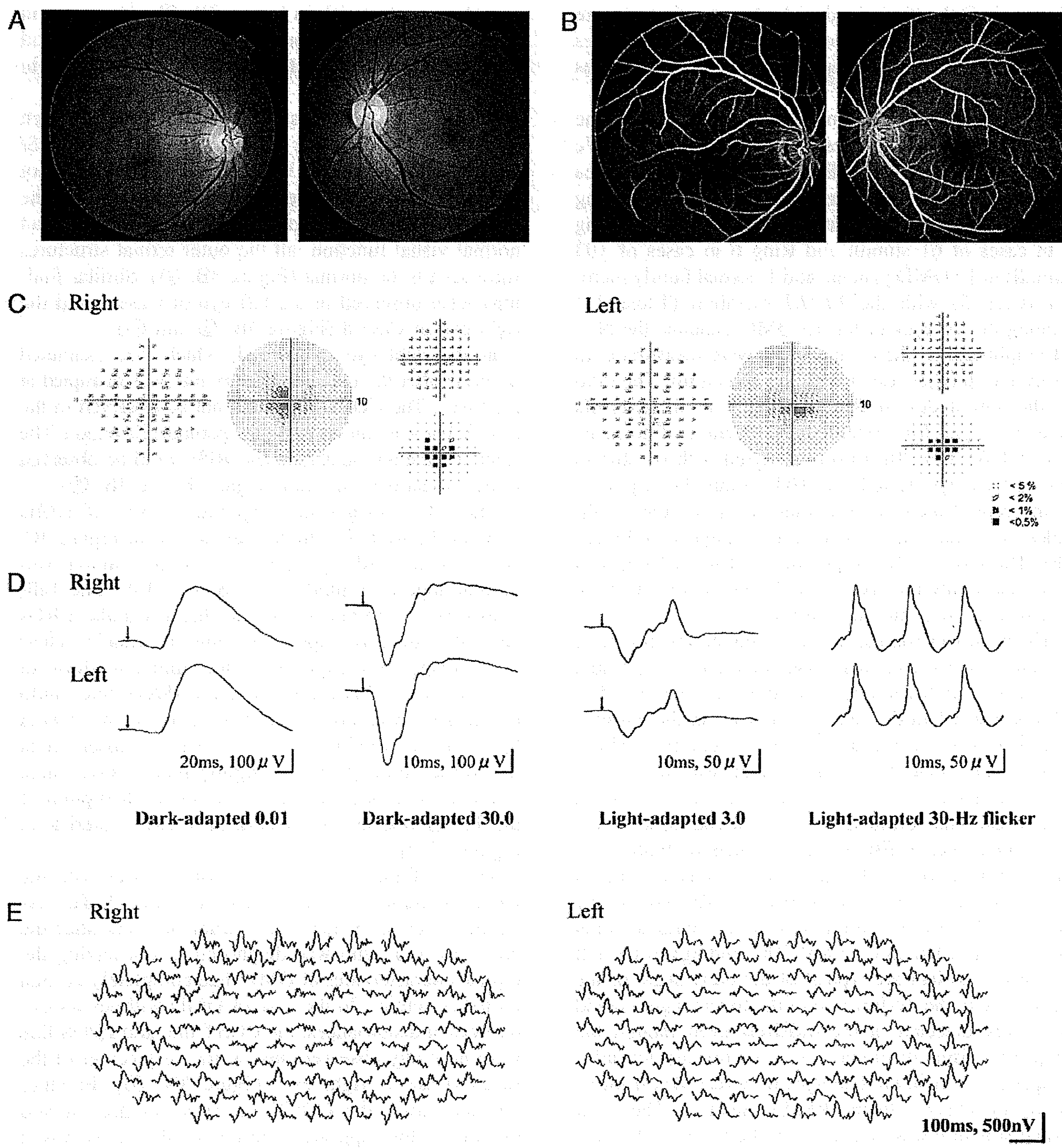

Fig. 2. Results of ocular examination of Patient 11. The data in (A) to (E) were collected 3 years after the onset of the visual disturbance at age 50 years. At this time, the patient had not noticed a decrease in the visual acuity in her left eye. The BCVA was 0.1 in the right eye and 1.2 in the right eye. A, and B. Fundus photographs and FAs showing no abnormal findings. C. Static visual field test (Humphrey Visual Field Analyzer, 10-2) showing relative central scotoma in both eyes. D. Full-field rod, mixed rod–cone, cone ERGs, and 30-Hz flicker responses. All the responses are normal in both eyes. E. Trace arrays of mfERGs tested with 103 hexagonal stimuli shown without spatial averaging. The responses of the central locus are extinguished in both eyes.

after the onset. This patient first noticed visual disturbances at age 20 years and was diagnosed with OMD at age 73 years. The appearance of the macula and optic disk at age 83 years was still normal >60 years after the onset of the symptoms.

Rod, mixed rod–cone, and cone full-field ERGs were recorded from 7 patients using the International Society of Clinical Electrophysiology and Vision standard protocol, and all of them showed normal rod and cone responses as in the representative case shown in

Figure 2. Only the mixed rod–cone responses were recorded from Patient 9, and only the cone responses were recorded from Patient 10, and these responses were also normal.

The amplitudes of the mfERGs were reduced in the central region of both eyes in all the 13 patients. We quantified the relative mfERG responses at the fovea by dividing the N1–P1 amplitudes of the central ring (Ring 1) by those in the outermost eccentric ring (Ring 5 in cases of 61 stimuli and Ring 6 in cases of 103 stimuli) in 13 OMD patients and 1 normal family member (Case 5) with the *RP1L1* mutation (Table 2).[4] Among the 26 eyes of the 13 OMD patients, the N1–P1 amplitudes of the central locus were measurable in 12 eyes in 6 cases tested with the 61 stimuli. The ratio of the amplitudes of Ring 1/Ring 5 in these OMD patients ranged from 0.60 to 2.74 (average of normals: 4.34 ± 0.67, $n = 20$). In 6 eyes tested with 61 stimuli and all the 8 eyes tested with 103 stimuli, the responses in the central locus were extinguished and the amplitudes were not measurable (see examples in Figure 2E). The ratio of the amplitudes of Ring 1/Ring 5 in a normal family member (Case 5, right eye) was 4.24, which was within the normal range.

The results of routine ocular examinations in Patient 11 at the age 50 years, when she did not have any visual disturbances in her left eye, are shown in Figure 2. The BCVA was 0.1 in the right eye and 1.2 in the left eye. The fundus and FA were normal in both eyes. Humphrey visual field tests (SITA Standard and pattern deviation 10-2) showed a relative central scotoma in both eyes. The full-field rod, mixed rod–cone, cone, and 30-Hz flicker ERGs were normal in both eyes. The mfERGs were reduced in and around the region of the central scotoma in both eyes. The Humphrey visual field test (30-2) did not detect a central scotoma in either eye (data not shown). The findings in the left eye of this patient are typical of the early stage of the OMD, where the dysfunction of the foveal region could be clearly detected in the mfERGs even though the subjective visual disturbance was almost undetectable.

Spectral-domain OCT images were recorded from 11 family members with the *RP1L1* mutation. The outer retinal structure was considered to be normal when the external limiting membrane, photoreceptor inner/outer segment (IS/OS) line, cone outer segment tip (COST) line, and retinal pigment epithelium (RPE) were clearly detected in the OCT images (Figure 3A).[11,23]

The OCT images of 5 representative OMD patients are aligned in the order of years after the onset in Figure 3B. The right eye of Case 1, which had electrophysiologically confirmed macular dysfunction but did not have subjective visual disturbances, showed a normal IS/OS line and COST line but only at the foveal center (asterisk in Figure 3B, ①). However, in the parafoveal region, the IS/OS line was blurred and the COST line could not be observed (arrowheads in Figure 3B, ①).

In the right eye of Case 11, the OCT images which were taken 10 years after the onset showed that the IS/OS line at the fovea was very blurred and thick but not disrupted. The COST line could not be observed in the macular area. In the perimacular region that had normal visual function, all the outer retinal structures were seen to be normal (Figure 3B, ②). Similar findings were observed in the left eye of Case 1 and the right eye of Case 8 (Figure 3B, ③ and ④).

In the right eye of Case 4, which was examined 63 years after the onset, the IS/OS line was disrupted at the fovea. The COST line could not be observed in the macula but was still visible in the perimacular region. The external limiting membrane and RPE could be observed to be normal over the entire region (Figure 3B, ⑤).

The OCT images of 2 sporadic cases of OMD without the *RP1L1* mutation are shown in Figure 3C. Both patients had a progressive central scotoma with normal-appearing fundus and normal FA. The full-field ERGs were normal but the focal macular ERGs elicited with a 10° spot were not recordable. Their OCT images, however, were not similar to those in patients with *RP1L1* mutation; the IS/OS line could be clearly observed at the fovea (Figure 3C, ①and ②), and the COST line could also be observed at the fovea, although it was slightly more blurred than in the normal cases. There was a minute disruption of the IS/OS line at the foveola in 1 case (asterisk in Figure 3C, ①).

The OCT findings in 21 eyes of 11 cases with the *RP1L1* mutation are summarized in Table 3. The examined eyes are listed in the order of years after the onset. Case 5, who was diagnosed as not having the typical characteristics of OMD, had completely normal retinal structures. In the case of OMD without subjective visual disturbances, the COST line and IS/OS line were normally observed only at the very center of the fovea (Case 1, right eye, Figure 3B, ①). In other affected cases, the COST line was not present and the IS/OS line appeared blurred in the entire fovea (Cases 14, right eye to 8). In patients with longer duration OMD, the IS/OS line was disrupted or not present as in Cases 2 and 4.

The retinal thickness at the foveola was measured as the distance from the internal limiting membrane to the inner border of the RPE. Considering the variation in the thickness in normals, we classified that the retina at the foveola was abnormally thin when the thickness was <160 μm. All the affected eyes with disease duration ≤ 12 years had normal foveal thickness (right

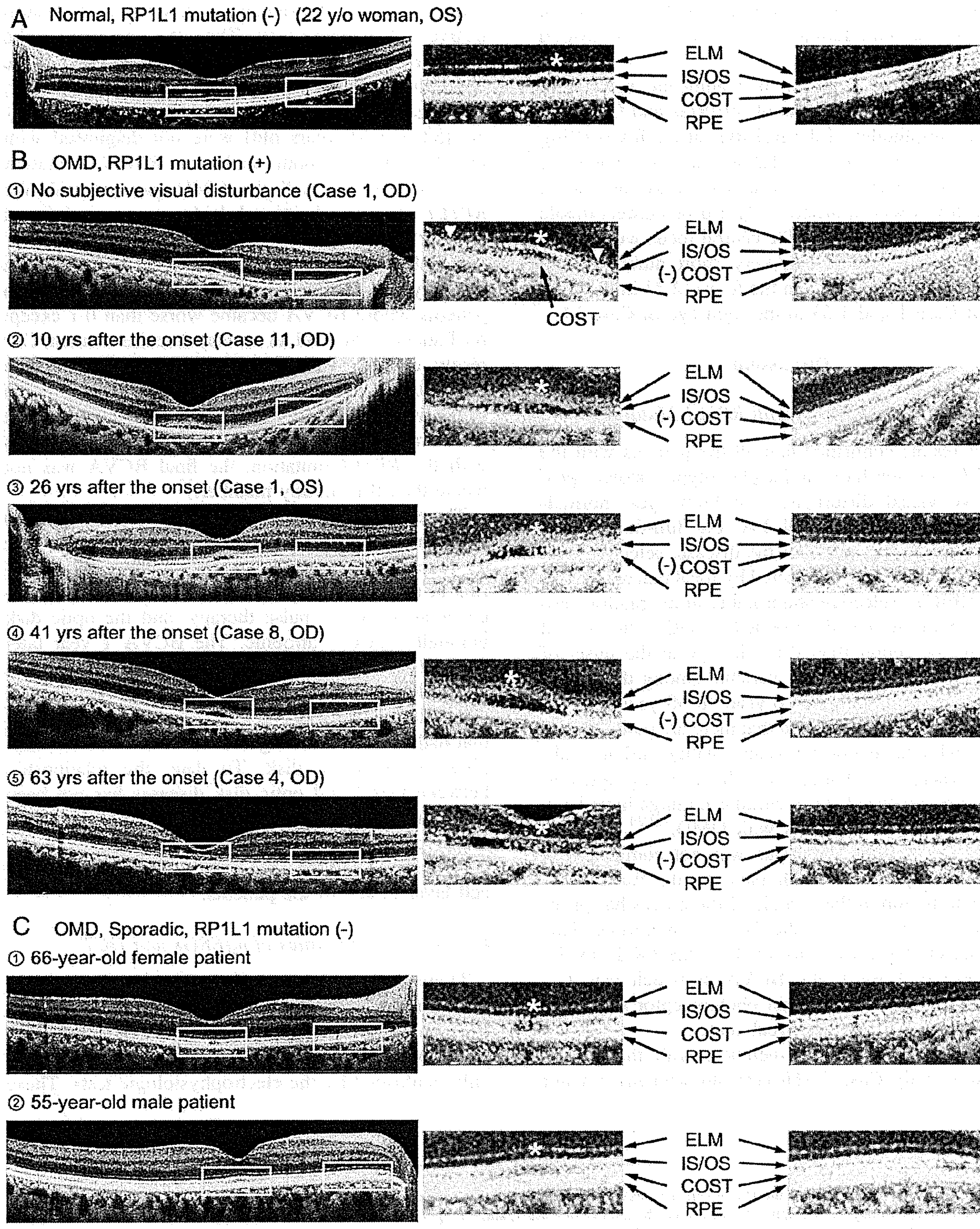

Fig. 3. Optical coherence tomography images horizontally profiled along the foveola (left) and magnified images in the fovea and the perimacular region (right). Outer retinal structures, such as external limiting membrane (ELM), photoreceptor IS/OS line, COST line, and RPE, are indicated by arrows. The foveal center is indicated by an asterisk. All the OCT images were taken with the HD-OCT (Carl Zeiss). **A.** Optical coherence tomography image of a normal control without the *RP1L1* mutation (22-year-old woman). All the outer retinal structures, for example, external limiting membrane, IS/OS line, COST line, and RPE, are clearly observed both in the fovea and the perimacular region. **B.** Optical coherence tomography images of patients affected by OMD with the *RP1L1* mutation. ①. Optical coherence tomography image of the right eye of Case 1, which did not have subjective visual disturbances. The COST line is present in the foveal center (black arrow), but not in the parafoveal region (arrowheads). The IS/OS line is clearly

eye of Cases 1 to Case13), whereas the fovea of all the affected eyes with durations ≥20 years were classified as thin (Case 7 to Case 4).

To determine whether a significant correlation existed between the results of mfERGs and OCT, the relative amplitudes of the mfERGs at the fovea (Ring 1/Ring 5 or 6) are listed in Table 3. In cases where the disease durations was ≥3 years, the relative amplitude at the fovea was approximately 1.0 or nonrecordable because the responses of the central locus were extinguished. Only cases with very short durations had mildly reduced mfERGs in the fovea (2.34 in the right eye of Case 1 and 1.63 in the right eye of Case 14).

Discussion

Course of OMD Patients with RP1L1 Mutation

Our results confirmed that all the patients with the *RP1L1* mutation had similar phenotypes; slowly progressive visual disturbances of both eyes, normal-appearing fundus, normal FA and full-field ERGs during the entire course of the disease, selective dysfunction at the macula detected by focal macular ERGs and mfERGs, selective abnormality of the photoreceptor layer in the macula revealed by OCT, and a final BCVA not poorer than 0.1. The age at the onset of OMD was, however, very variable among the family members and varied from 6 years to 50 years.

Our study also confirmed that there are patients with OMD who have normal visual acuity and no subjective visual disturbances until the disease progressed to a more advanced stage. Similar findings have been reported for other patients with OMD,[1,2,24] although the etiology of these patients was not confirmed by genetic analyses. For such patients, the function of the small region in the foveola of these eyes has probably been spared so that the BCVA was normal. This was morphologically confirmed by the OCT; in the right eye of Case 1, the BCVA of which was 1.2, the OCT image showed that photoreceptor structures were spared only at the foveal center.

Among the 14 family members with the *RP1L1* mutation, only Case 5 (60-year-old woman) did not show any signs of macular dysfunction in both subjective and objective tests. Thus, this woman may be a carrier of a mutated gene, but we cannot exclude the possibility that macular dysfunction may appear later. In our genetic study of 4 other OMD families, 2 brothers (58 and 55 years old) were not diagnosed with OMD, although both had the *RP1L1* mutation (p.Arg45Trp).[12] In all the OMD patients with the *RP1L1* mutation, the visual dysfunction was detected no later than 50 years of age.[12]

Occult macular dystrophy has been reported to be a slowly progressive disease; however, there were no patients whose BCVA became worse than 0.1 except for Patient 7 who had an untreated senile cataract. Our results confirmed that once the BCVA is reduced to 0.1 to 0.2, the disease becomes stationary and both the subjective and objective visual functions do not deteriorate thereafter. Similarly, in 3 other families with the *RP1L1* mutation, the final BCVA was not worse than 0.15 in any member.[12]

There was 1 family member (asterisk, Figure 1) who had a sudden decrease of vision in the left eye at age 49 years, but she was diagnosed with retrobulbar neuritis at the Niigata University. Her vision did not recover after steroid pulse therapy, and the optic disk gradually became atrophic. The BCVA 1 year later was 1.2 in the right eye and 0.07 in the left eye. We concluded that the vision reduction was not related to the OMD. Nakamura et al[25] reported a case of OMD that had normal-tension glaucoma with abnormal cupping of the optic disk. To date, the relationship between OMD and optic disk diseases has not been determined. In our family, the optic disks of all the OMD patients appeared normal, and OCT did not show any thinning of the nerve fiber layer or ganglion cell layer in any of the patients.

Diagnostic Reliabilities of mfERGs and OCT

There were patients, such as Case 6 (both eyes), Case 1 (right eye), and Case 11 (left eye), with OMD from an *RP1L1* mutation who did not have any subjective visual disturbances and whose diagnosis were only confirmed by the electrophysiologic tests. These

Figure 3. (continued) observed at the foveal center (asterisk) but appears blurred in the parafoveal region (arrowheads). ②, ③, and④. Optical coherence tomography image of the right eye of Case 11, the left eye of Case 1, and the right eye of Case 8, which show typical signs of OMD. The COST line is not present over the entire macula but is present in the perimacular regions. The IS/OS line is blurred and thick in the fovea. ⑤ Optical coherence tomography image (vertical section) of the right eye of Case 4. This image was obtained 63 years after the onset of visual symptoms The IS/OS line is disrupted at the fovea. The COST line cannot be seen in the macula but is still visible in the perimacular region There is an apparent thinning of the photoreceptor layer at the fovea. C. Optical coherence tomography images of sporadic cases of OMD without the *RP1L1* mutation. ① and ②. Both patients had progressive central scotoma with normal-appearing fundus and normal FA. The full-field ERGs were normal but focal macular ERGs elicited by a 10° spot were not recordable. The IS/OS line could be clearly observed at the fovea in both cases, except in minute disruption at the foveola in ① (asterisk) The COST line could be observed at the fovea in both cases, although slightly more blurred than in the normal case.

Table 3. Optical Coherence Tomography Findings in 21 Eyes of 11 Family Members with RP1L1 Mutation in the Order of Years After the Onset

Years After the Onset (Years)	Case	OD/OS	BCVA	Relative Amplitude in mfERG at fovea (Ring 1/Ring 5 or 6)	OCT Findings at Fovea				Other Findings
					Disappearance of COST at fovea	Blurring of IS/OS Junction at Fovea	Abnormality of RPE	Thinning of Fovea (Thickness <160 μm)	
None	5	OD	1.2	4.24	−	−	−	−(217)	Not diagnosed as OMD
Unknown	1	OD	1.2	2.34	±*	±*	−	−(200)	No subjective visual disturbance
2	14	OD	1.0	1.63	+	+	−	−(160)	
3	11	OS	0.4	Not measurable	+	+	−	−(168)	
6	12	OD	0.3	0.98	+	+	−	−(174)	
		OS	0.3	1.03	+	+	−	−(168)	
10	14	OS	0.6	0.66	+	+	−	−(160)	
10	11	OD	0.1	Not measurable	+	+	−	−(164)	
12	13	OD	0.2	Not measurable	+	+	−	−(181)	
		OS	0.15	Not measurable	+	+	−	−(177)	
20	7	OD	0.1	Not measurable	+	+	−	+(134)	
		OS	0.07	Not measurable	+	+	−	+(142)	
31	1	OS	0.1	0.60	+	+	−	+(150)	
38	10	OD	0.1	Not measurable	+	+	−	+(150)	
		OS	0.1	Not measurable	+	+	−	+(153)	
41	8	OD	0.1	1.01	+	+	−	+(148)	
		OS	0.1	1.30	+	+	−	+(148)	
46	2	OD	0.4	Not measurable	+	+†	−	+(156)	
		OS	0.5	Not measurable	+	+†	−	+(154)	
63	4	OD	0.2	Not measurable	+	+†	−	+(77)	
		OS	0.2	Not measurable	+	+†	−	+(76)	

*The COST and IS/OS junction were normal only at the foveal center. In the parafovea, the COST could not be observed and the IS/OS junction was blurred.
†The IS/OS junction was disrupted at the fovea.

findings indicate that mfERGs or focal macular ERGs are sensitive enough to detect very early macular dysfunction in OMD.

Similarly, OCT could be another sensitive tool for the detection of early OMD because an abnormality of the COST line and the IO/OS line in the macula was observed in all the affected cases. However, we believe that the mfERG is more sensitive than OCT in detecting early dysfunctions of the macula in eyes with OMD. For example, Case 14 was a 28-year-old man whose BCVA was 1.0 (right eye) and 0.6 (left eye), but his fundus and visual field tests did not show any differences between the 2 eyes. He did notice a visual disturbance in his left eye 8 years before the onset in his right eye. In the OCT images, both the COST line and the IS/OS line were similarly affected for both eyes at the fovea, and the retinal thickness at the fovea was 160 μm in both eyes (Table 3). The mfERGs, on the other hand, were different in the 2 eyes; the relative amplitude of mfERG at the fovea (Ring 1/Ring 5) was 1.63 (38.2/23.5) in his right eye and 0.66 (15.8/23.8) in his left eye (Table 3). Thus, we believe that both the mfERGs and OCT can be useful in the diagnosis of OMD, but mfERGs are more reliable in detecting and evaluating minimal macular dysfunction at the early stage of the disease. The abnormalities in the OCT, however, progress slowly and continuously until the late stage, and thus they may be more useful for following the long-term progression of OMD.

Roles of RP1L1 Gene and Occurrence of OMD

Our study confirmed that all the affected patients with *RP1L1* mutation had abnormalities of the photoreceptor structures; the IS/OS line was very blurred and thick and the COST line could not be observed in the macula (Figure 2). But in the perimacular region, which had normal visual function, all the outer retinal structures were seen to be normal. During the whole disease process, neither the external limiting membrane nor the RPE had any significant changes and remained normal. In some of sporadic cases of the OMD, similar abnormalities in the OCT could not be observed, although localized macular dysfunction was confirmed electrophysiologically (Figure 3C).

The location of COST line coincided with the location where the outer segment disks are renewed in the cones.[23,26] The disappearance of the COST line indicates an early stage of dysfunction of the cone photoreceptors as has been found in acute zonal occult outer retinopathy.[11] Recently, ultrahigh-resolution OCT with adaptive optics has revealed that the IS/OS line corresponds to the ellipsoids of the photoreceptor inner segments, which are rich in mitochondria and play important roles in cellular metabolism.[27]

Immunohistochemistry for the *RP1L1* gene in retinal section of cynomolgus monkeys showed that it was expressed in both the inner and outer segments of the rod and cone photoreceptors, although the exact site within the photoreceptor has not been confirmed.[12] *RP1L1* is believed to play important roles in the morphogenesis of photoreceptors, and once the function of *RP1L1* is disrupted by a mutation, both the electrophysiologic responses and structures of the photoreceptor can be altered. Cellular dysfunction because of an *RP1L1* mutation affects either the inner or outer segment, or both, of the photoreceptors, which first becomes apparent as an abnormality of both the COST line and IS/OS line in the OCT images.

Considering that the OCT abnormalities in sporadic cases did not show similar pattern as patients with the *RP1L1* mutation, the phenotypically confirmed OMD surely consists of diseases caused by several independent etiologies. In any case, the abnormalities in the mfERGs and OCT observed in OMD in this family strongly support the contribution of *RP1L1* mutation to the presence of this disease.

There are still some important questions of the disease process in OMD that are unsolved. First, why is only the macular region affected while the perimacular region remains intact both functionally and morphologically even at a very advanced stage? Second, why do OMD patients have normal fundus appearance until the end stage, and why does the RPE remain intact until the end stage when the photoreceptor structures are markedly damaged (Figure 3B, ⑤)? Fujinami et al[28] demonstrated that the fundus autofluorescence images in the macula of OMD patients are normal, indicating that the RPE is normal. Third, why does the disease progression stop when the BCVA decreases to 0.1 to 0.2?

These characteristics in the disease process are peculiar to the OMD and not observed in other macular dystrophies. More detailed investigations on the function of *RP1L1* should provide information to answer these questions.

We suggest that OMD is not a single disease caused by a specific gene mutation, *RP1L1*, but may represent different disease entities with similar retinal dysfunctions. Considering all our findings on OMD, we can phenotypically define the OMD as a slowly progressing bilateral dysfunction of the photoreceptors located in the macula, not accompanied by either vascular or RPE damage. The etiology of OMD cases without the *RP1L1* mutation is now under investigation with large number of cases and some of them might be found to be because of other autosomal recessive mutations.

Key words: electroretinography, focal macular ERG, multifocal ERG, occult macular dystrophy, optical coherence tomography, *RP1L1*.

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Highly Reflective Foveal Region in Optical Coherence Tomography in Eyes with Vitreomacular Traction or Epiretinal Membrane

Kazushige Tsunoda, MD,[1] Ken Watanabe, MD,[2] Kunihiko Akiyama, MD,[2] Tomoaki Usui, MD,[3] Toru Noda, MD[2]

Objective: To report the optical coherence tomography (OCT) findings in eyes with vitreomacular traction (VMT) or with an epiretinal membrane (ERM).

Design: Retrospective case series.

Participants: Fifty-four eyes of 45 consecutive patients with subjective visual disturbances resulting from VMT or idiopathic ERM were studied.

Methods: The morphologic features of the photoreceptor layer at the foveal center were determined and the central foveal thickness (CFT) was measured by spectral-domain (SD) OCT.

Main Outcome Measures: The morphologic characteristics of the foveal region observed by SD OCT.

Results: A roundish or diffuse highly reflective region was observed between the photoreceptor inner segment/outer segment junction line and the cone outer segment tip line at the center of the fovea. This highly reflective region was present in 7 of 7 cases of VMT and 30 of 47 cases of ERM. In the ERM cases, the mean CFT of the cases with the highly reflective region was significantly thicker than that in cases without it. The highly reflective region disappeared when the inward traction on the fovea was released surgically or spontaneously.

Conclusions: The highly reflective region is a characteristic sign observed in the OCT images of eyes with VMT and ERM, and it has been termed the *cotton ball sign* after its appearance. The presence of the cotton ball sign indicates an inward traction on the fovea and may be a predictor of visual impairment.

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Vitreomacular tractions (VMTs) and epiretinal membranes (ERMs) cause morphologic distortions of the retinal surface and lead to functional changes such as metamorphopsia and decreased visual acuity.[1–4] Surgical removal of the VMT or ERM is effective in restoring good visual function. Similar recovery is obtained when the traction is released spontaneously.

Optical coherence tomography (OCT) has shown that a vertical or tangential traction of the retina causes wrinkling of the internal limiting membrane, flattening of the foveal pit, and intraretinal cystic changes.[5–11] Moreover, recent spectral-domain (SD) OCT has shown that eyes with VMT and ERM have structural abnormalities of the photoreceptors at the fovea, for example, loss of the photoreceptor inner/outer segment (IS/OS) junction line.[12–17] The abnormalities in the IS/OS junction line were correlated significantly with poorer visual function; however, the relationship between these abnormal OCT findings and the foveal traction has not been determined definitively. The SD OCT studies have shown a roundish or diffuse highly reflective region at the center of the fovea in all of the cases of VMT and in cases of ERM with increased central foveal thickness (CFT). The authors named this highly reflective region the *cotton ball sign*, after its appearance.

The aim of this study was to determine the characteristics and correlations of this abnormal sign in the OCT images and the retinal physiologic features. This study showed that the cotton ball sign disappeared when the foveal traction was released surgically or spontaneously. The presence of the cotton ball sign is good evidence that there is inward traction on the photoreceptors.

Patients and Methods

This was a retrospective case series performed in the Department of Ophthalmology, National Tokyo Medical Center, Tokyo, Japan. Informed consent was obtained from all of the subjects for the tests after an explanation of the procedures to be used. The procedures used adhered to the tenets of the Declaration of Helsinki, and approval to perform this study was obtained from the Review Board/Ethics Committee of the National Tokyo Medical Center.

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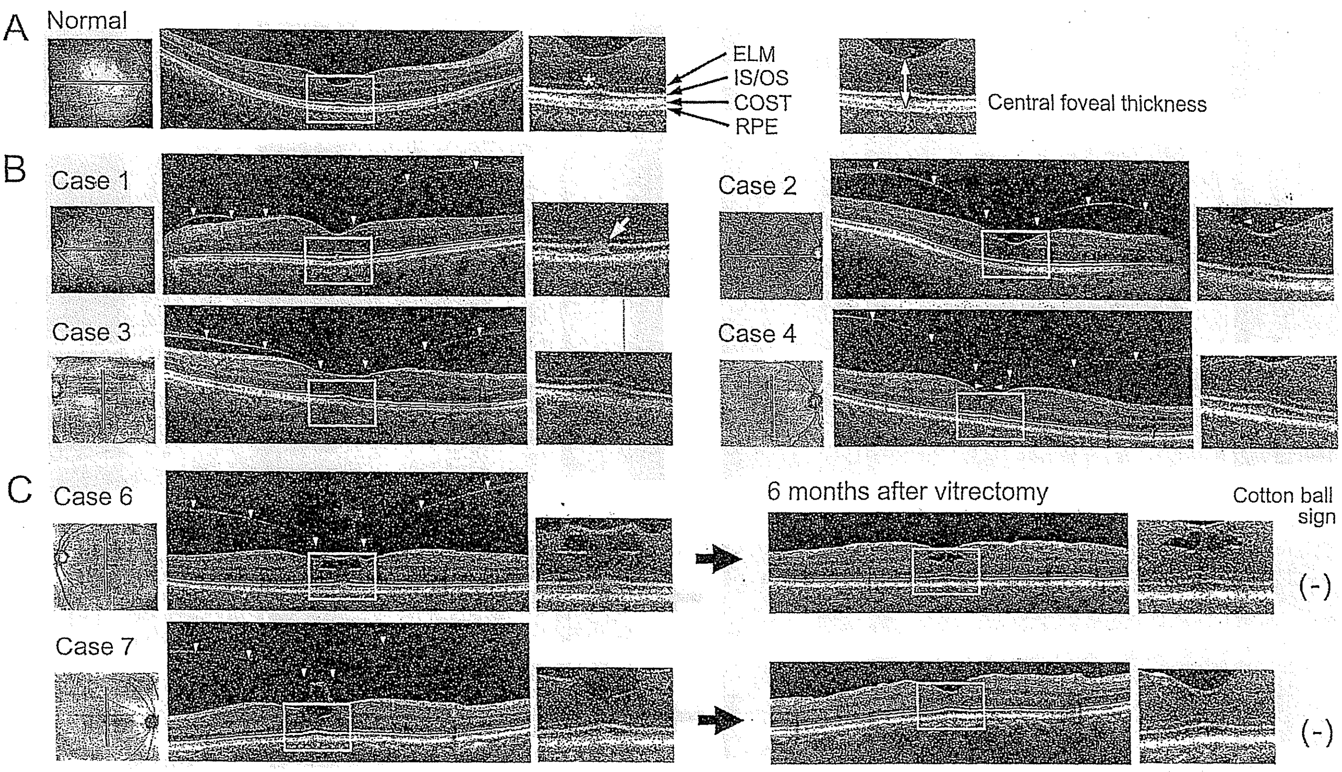

Figure 1. Optical coherence tomography (OCT) images of eyes with vitreomacular traction (VMT) with the foveal images magnified on the right. Fundus images on the left indicate the location of the OCT scans. A, Normal control OCT image from a 22-year-old woman. Outer retinal structures with high reflectivity are indicated by arrows: external limiting membrane (ELM), photoreceptor inner segment/outer segment (IS/OS) junction, cone outer segment tip (COST) line, and retinal pigment epithelium (RPE). The foveal bulge is indicated by an *asterisk*. The central foveal thickness is measured as the distance between the inner retinal surface and inner border of the RPE (*white arrow*). B, Optical coherence tomography images of eyes with VMT. The border of the posterior vitreous is indicated by *arrowheads*. The roundish highly reflective region between IS/OS junction line and COST line is the cotton ball sign and is identified by a *white arrow* in case 1. C, Two eyes with VMT before and 6 months after vitrectomy. In both cases, the vitreous traction was released and the cotton ball sign was not present after the surgery.

Inclusion and Exclusion Criteria

Fifty-four eyes of 45 patients (average age, 69.0±9.2 years; range, 34–85 years) with subjective visual disturbances resulting from VMT or idiopathic ERM were studied. The patients were examined between October 2009 and January 2011; 7 eyes had VMT and 47 eyes had ERM (Table 1, available at http://aaojournal.org). A VMT was defined as a vitreomacular adhesion at the foveal region without an apparent ERM over the entire macular region. All of the cases with VMT were focal VMT, according to the definition of Koizumi et al.[11] The exclusion criteria were: (1) eyes with a history of retinal inflammatory or vascular diseases, such as branch vein occlusion, uveitis, and retinal detachment; (2) eyes with advanced lens opacification or any other ocular diseases that could cause visual disturbances; (3) eyes with strong vitreal traction on the retina that led to either lamellar or pseudomacular holes; (4) eyes in which the center of the fovea could not be determined in the OCT images because of a lack of a bulge-like structure of the IS/OS junction line at the fovea[18]; and (5) cases whose OCT image did not have enough signal intensity for evaluation, that is, average intensity of the OCT signal less than 8/10.

All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity using a Landolt C chart, biomicroscopy of the fundus, fundus photography, and OCT.

Optical Coherence Tomography

The OCT images were obtained with SD OCT (Cirrus HD-OCT, versions 4.5 and 5.1; Carl Zeiss Meditec, Dublin, CA). After dilatation of the pupil, patients were asked to fixate on a target, and 5-line scans with 4 averages were performed both horizontally (length, 9.0 mm) and vertically (length, 6.0 mm). The distance between each scan line was set to be 0.075 mm, or, in some cases, 0.025 mm, to determine the location of foveal bulge. The foveal bulge is a dome-shaped structure of the IS/OS junction line corresponding to the foveal center (Fig 1A, asterisk). If the foveal bulge could not be obtained by the point of fixation, the location of the scan line was shifted and the OCT images were taken repeatedly until the foveal bulge was present in the image.

The CFT was defined as the distance between inner retinal surface and inner border of retinal pigment epithelium (RPE; Fig 1A) and was measured with the built-in scale of the OCT system. The diameter of the highly reflective region was measured in one of the scanned profiles that showed the maximum diameter of the region. For patients who underwent vitrectomy, the OCT images were recorded 6 months after the surgery.

Vitrectomy for Vitreomacular Traction and Epiretinal Membranes

Two of 7 eyes with VMT and 18 of 47 eyes with an ERM underwent 23- or 25-gauge 3-port vitrectomy by 2 experienced

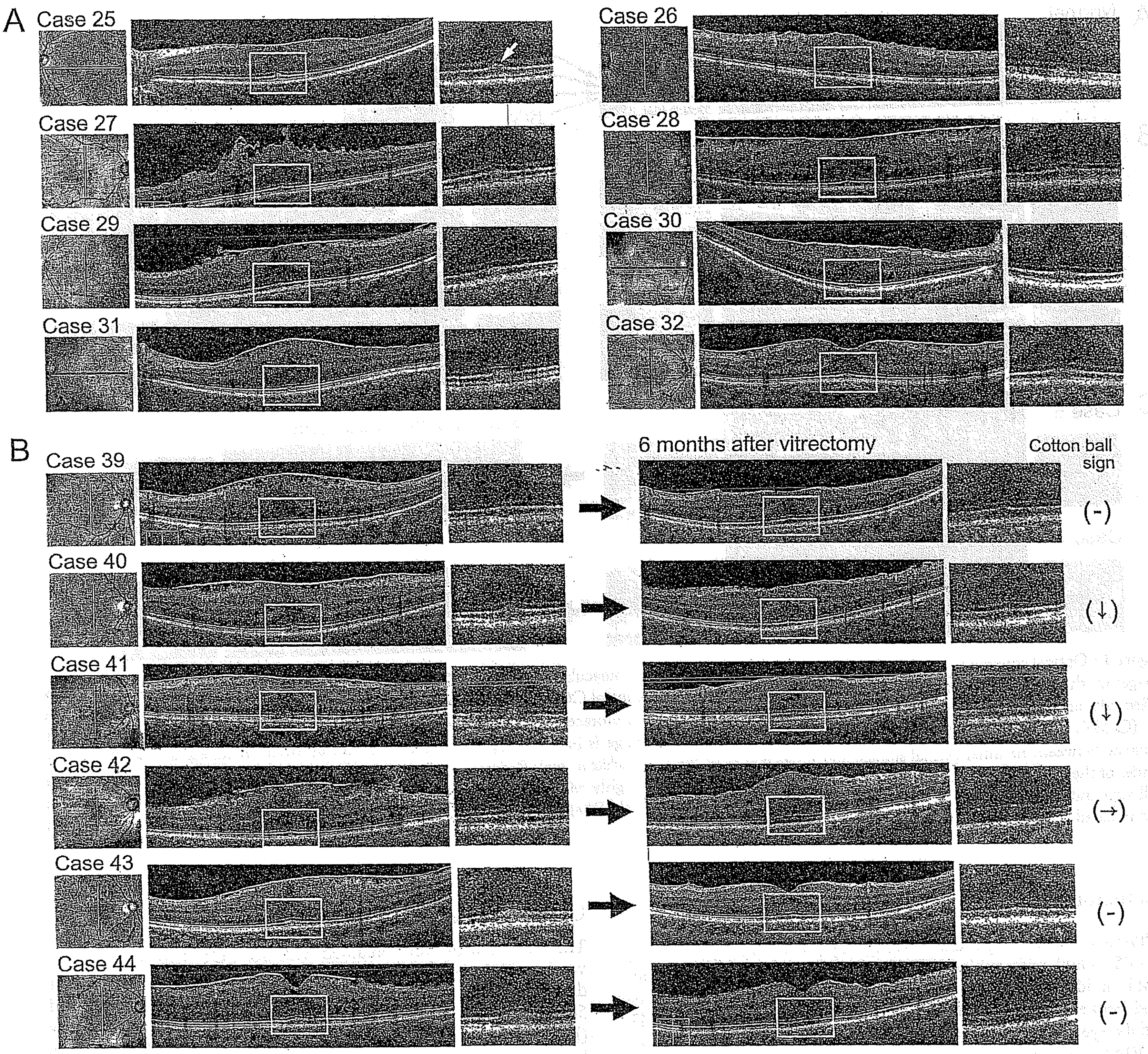

Figure 2. Optical coherence tomography (OCT) images of eyes with an epiretinal membrane (ERM) with the foveal area magnified (*right*). Fundus photographs (*left*) indicate the location of OCT scans. A, Optical coherence tomography images of eyes with an ERM. The roundish highly reflective region between inner segment/outer segment junction line and cone outer segment tip line is the cotton ball sign and is identified by a *white arrow* in case 25. B, Optical coherence tomography images of eyes with an ERM before and 6 months after vitrectomy. In cases 39, 43, and 44, the cotton ball sign disappeared after surgery. In cases 40 and 41, the cotton ball sign did not disappear, but became more indistinct after the surgery. In case 42, the cotton ball sign was still observed clearly after the surgery. The highly reflective region in cases 25, 40, and 41 appeared roundish, but that in cases 31, 43, and 44 appeared indistinct and diffuse.

surgeons (K.A. and K.W.). During the vitrectomy, a posterior hyaloid detachment was made, and the ERM was removed. The internal limiting membrane was peeled with forceps in all cases. Phacoemulsification with intraocular lens implantation was performed during the same surgery in 17 of the 20 eyes.

Statistical Analysis

Student *t* tests were performed to compare the CFT with the presence of the highly reflective region in cases of ERM before and after surgery. Statistical analysis was performed using Microsoft Office Excel 2007 (Microsoft, Redmond, WA). *P* values <0.05 were taken as statistically significant.

Results

The outer retinal structures detected in the OCT image of normal retinas consisted of (1) the external limiting membrane, (2) the IS/OS junction line, (3) the cone outer segment tip (COST) line,

Table 2. Cotton Ball Sign and Central Foveal Thickness

	Cotton Ball Sign	Central Foveal Thickness (μm)		P
		Mean	*Standard Deviation*	
VMT (n = 7)	Observed	252.0	87.1	
ERM before surgery (n = 47)	Not observed (n = 17)	289.3	96.0	0.0000076*
	Observed (n = 30)	445.7	102.2	
	Total (n = 47)	389.1	124.7	
ERM after surgery (n = 16)	Disappeared (n = 8)	300.0	28.6	0.00033†
	Not disappeared (n = 8)	423.3	59.0	

ERM = epiretinal membrane; VMT= vitreomacular traction.
**t* test between ERM with and without cotton ball sign.
†*t* test between ERM with and without the disappearance of cotton ball sign after vitrectomy.

(4) the RPE, and (5) the foveal bulge, which is a dome-like structure of the external limiting membrane and IS/OS junction line caused by an elongation of the cone outer segments at the fovea (Fig 1A).[18–20]

A highly reflective region was present in all of the eyes with VMT (Table 1, available at http://aaojournal.org). The OCT images of 6 VMT cases without (Fig 1B) or with (Fig 1C) vitrectomy are shown with the foveal images magnified. In all the cases, a separation of the vitreous from the retina occurred except in the limited region around the center of the fovea (Fig 1A, B, arrowheads), and the foveal center was pulled toward the vitreous cavity. In case 1, a roundish, highly reflective region resembling a cotton ball can be seen between the IS/OS junction line and COST line at the center of the fovea. The COST line can be seen to be pulled inward just below the highly reflective region and is separated from the RPE (Fig 1B, case 1, white arrow). Similar findings were observed in cases 2 and 6. In all of the other cases (cases 3, 4, and 7), the highly reflective region was observed at the same location, but its borders were more indistinct than in cases 1, 2, and 6. Two of the eyes with VMT underwent vitrectomy, and the highly reflective region could not be observed in the OCT image obtained 6 months after the vitrectomy (Table 1, available at http://aaojournal.org; Fig. 1C).

The SD OCT examinations of the 47 eyes with an ERM showed that the highly reflective region was present in 30 eyes (63.8%; Table 1, available at http://aaojournal.org). The OCT images of 8 ERM cases without (Fig 2A) or with (Fig 2B) treatment are shown with the foveal images magnified. In all the cases, the epiretinal membrane covered the entire macular region, and the tangential traction elevated the retinal surface at the fovea, leading to a loss of the foveal pit. In case 25, the highly reflective region was observed between the IS/OS junction line and COST line at the center of the fovea (Fig 2A, case 25, white arrow). As in the eyes with VMT, the COST line was pulled inward just below the highly reflective region and was separated from the RPE. The highly reflective region was observed at the same location in all eyes. The regions appeared roundish in some cases (e.g., cases 25, 40, and 41) and indistinct and diffuse in other cases (e.g., cases 31, 43, and 44).

Vitrectomy was performed on 16 eyes with an ERM, and 6 months after surgery, the highly reflective region was not observed in 8 cases, became smaller and more indistinct in 2 cases, or could still be observed in 6 cases (Table 1, available at http://aaojournal.org; Fig 2B).

The diameter of the highly reflective region varied from 96 to 180 μm with a mean 130.4±36.4 μm in the eyes with a VMT and from 80 to 288 μm with a mean of 172.7±65.8 μm in eyes with an ERM. The highly reflective region was always present between the IS/OS junction and COST lines, except for case 41, where the IS/OS junction line was disrupted at the foveal center and the round, highly reflective region penetrated into the outer nuclear layer (Fig 2B).

The mean CFT was 252.0±87.1 μm in eyes with VMT and 389.1±124.7 μm in eyes with an ERM (Table 2). For the 47 eyes with an ERM, the mean CFT of the eyes with the highly reflective region was 445.7±102.2 μm, which was significantly thicker than that in eyes without the highly reflective region at 289±96.0 μm. For the 16 eyes with an ERM for which vitrectomy was performed, the CFT was measured 6 months after surgery. The mean CFT of the 8 eyes in which the highly reflective region did not disappear was 423.3±59.0 μm, which was significantly thicker than that in the 8 eyes in which the highly reflective region disappeared at 300.0±28.6 μm.

In one case (case 5) with a spontaneous vitreous detachment, there was a recovery of the microstructural damage of the photoreceptor layer in the OCT images. Case 5 was a 34-year-old woman who had a sudden decrease of her vision together with floaters in her right eye (Table 1, available at http://aaojournal.org; Fig 3). Her best-corrected visual acuity was 0.6 in the right eye and 1.2 in the left eye. She was referred to the authors' hospital 10 days after the onset of her symptoms, and fundus biomicroscopic examination showed that a thick posterior hyaloid membrane was detached from the posterior pole in her right eye. In the OCT image, there was a clear, highly reflective region, although the vitreomacular traction had been released (Fig 3A). Moreover, the photoreceptor IS/OS junction line seemed to be pulled inward at the foveal center, and there was a local defect of the COST line just beneath the highly reflective region (Fig 3A, white arrow). In the OCT image obtained 30 days after the onset, the highly reflective region was not present, and the photoreceptor structures, including the IS/OS junction and COST lines, appeared normal (Fig 3B, white arrow). The visual acuity also recovered to 1.0 at that time.

Discussion

The SD OCT findings showed that all eyes (n = 7) with VMT and 63.8% of the eyes (30/47) with an ERM have a highly reflective region at the center of the fovea. This region can be roundish in some cases or diffuse and indistinct in other cases, and it was always located between the IS/OS junction and COST lines. This area was termed the *cotton ball sign* after its appearance. Related articles were searched for in PubMed with the following terms: *vitreomacular traction*, *epiretinal membrane*, and *optical coher-*

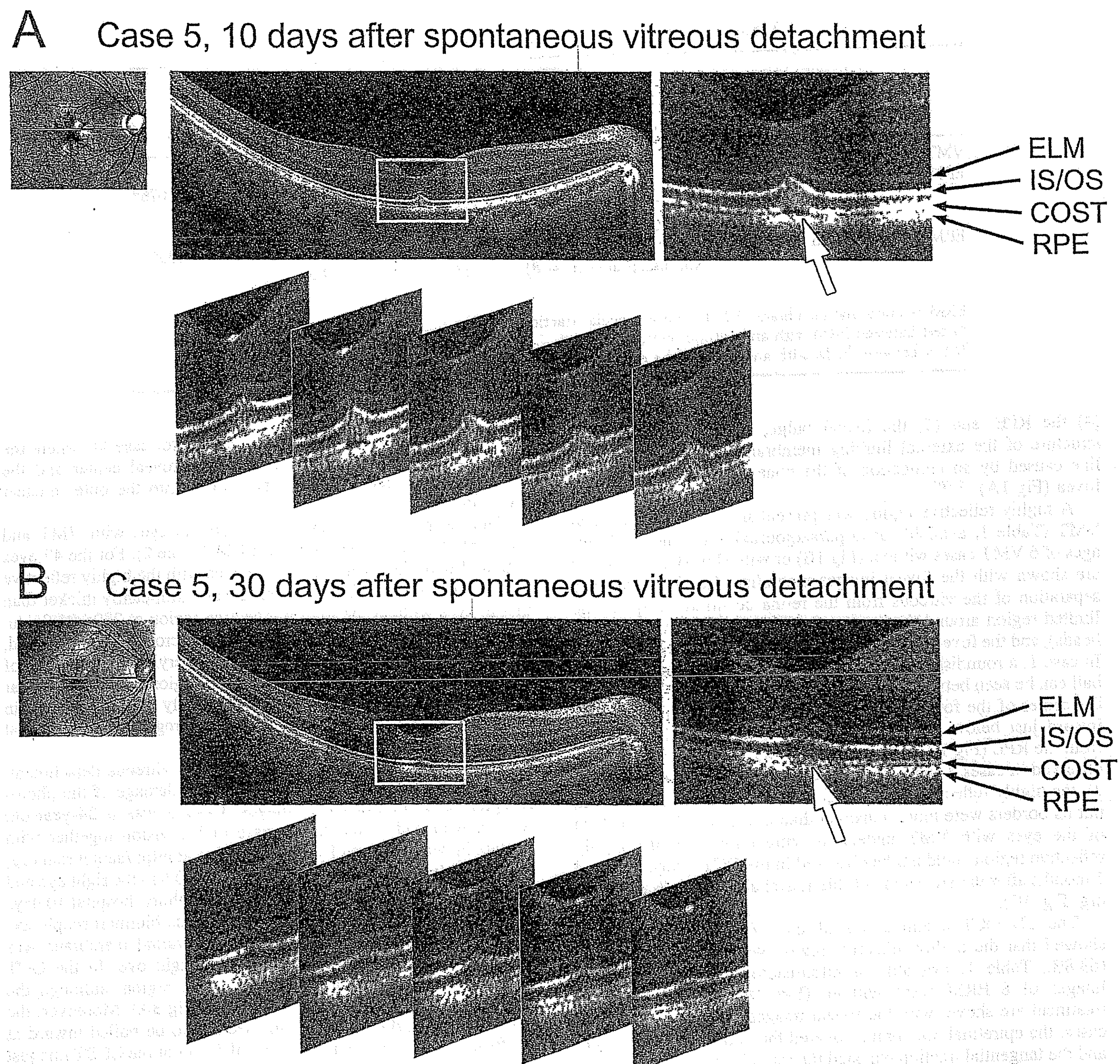

Figure 3. Optical coherence tomography (OCT) images of eyes with vitreomacular traction (case 5) in which a posterior vitreous detachment occurred spontaneously without surgery. Five horizontal OCT scans were obtained with an interscan distance of 20 μm. Five sequential profiles of the foveal region are aligned at the bottom, covering the central region of 80 μm of the fovea. A, Optical coherence tomography image obtained 10 days after spontaneous vitreous detachment. A round, highly reflective region (cotton ball sign) is present between the inner segment/outer segment (IS/OS) junction and cone outer segment tip (COST) lines at the foveal center. The center of IS/OS junction line is pulled inward and appears protruded compared with that in a normal OCT image (Fig 1A). The COST line is disrupted just below the highly reflective region (*white arrow*). B, Optical coherence tomography image obtained 30 days after the spontaneous vitreous detachment. The cotton ball sign is not present. The protrusion of IS/OS junction line is not distinct, and the COST line is continuous over the entire foveal region (*white arrow*). ELM = external limiting membrane; RPE = retinal pigment epithelium.

ence tomography. These articles were read, and none of them describes the same feature.

Even with the improved OCT instruments with higher spatial resolution, the region easily can be missed if the scanned lines do not pass through the foveal center, the intensity of the OCT signal is not strong enough, or both. Three-dimensional volume scans do not have enough traverse resolution, so OCT should be made with multiple scans with the highest resolution available. The mean diameter of the highly reflective region varied from 96 to 180 μm with a mean of 130.4±36.4 μm in the eyes with VMT and from 80 to 288 μm with a mean of 172.7±65.8 μm in