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Staging of idiopathic choroidal neovascularization by optical coherence tomography

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Abstract *Purpose:* To assess the clinical course of idiopathic choroidal neovascularization (ICNV) by optical coherence tomography (OCT). *Methods:* Thirty-two patients with a clinical diagnosis of ICNV were examined between December 1995 and October 1999. The ages of the patients ranged from 18 to 53 (mean 35.9) years, and the mean period of observation was 5.8 months. Color fundus photography, fluorescein angiography, Indocyanine green angiography, and OCT were performed. The stage of the ICNV was classified as active, intermediate, or cicatricial, based on past history, fundus findings, and fluorescein angiography (FAG). The characteristic OCT images at these three stages were determined. *Results:* OCT revealed that there were characteristic tomographic images of the choroidal neovascularization (CNV) at each stage. In the active stage, OCT revealed the CNV as a highly reflective, multi-layered area protruding into the subretinal space. In the intermediate stage, the reflectivity of the CNV became stronger and its margin in the subretinal space became smooth. With regression of the ICNV, the lesions consisted of two different areas: a most reflective area corresponding to the fibrotic changes of the CNV (imaged white in OCT images), and a reddish highly reflective area representing a compound protrusion of the CNV. In the cicatricial stage, the ICNV was observed as a moderately high reflective area covered by a dome-shaped highly reflective layer corresponding to the retinal pigment epithelium. *Conclusion:* These findings demonstrated clearly the changes in the OCT images during the development and regression of ICNV. OCT was useful for following the clinical course and understanding the mechanism of the CNV regression.

Introduction

Idiopathic choroidal neovascularization (ICNV) is a type of neovascular maculopathy that is seen in relatively young individuals [1, 13]. ICNV is characterized by small neovascular lesions under the sensory retina in the macular area, corresponding to type 2 lesion in Gass' classification [5]. In some cases, there is spontaneous regression of the ICNV [9]. The mechanism of spontaneous regression has only been inferred from funduscopic and fluorescein angiographic (FAG) observations because only a small number of histological studies has been performed on eyes from patients with ICNV.

In this study, we investigated the course of ICNV and the changes during the regression process by optical coherence tomography (OCT).

Subjects and methods

Thirty-two eyes of 32 patients with ICNV were studied with OCT at the Department of Ophthalmology in Kansai Medical University between December 1995 and October 1999. Among the 32 pa-

tients, 25 underwent OCT measurement once, 6 underwent measurement twice, and 1 patient underwent measurement 3 times. In all, 40 OCT examinations were performed to analyze the features of ICNV. The ICNVs were then classified into three stages.

Ophthalmoscopy, slit-lamp examination, FAG (TRC, Topcon, 50AX, Japan), Indocyanine green (ICG) videoangiography and OCT (Humphrey, USA) were performed on all patients. The tomographic structure of the CNV and the retinal changes in the macula were documented by OCT. Vertical and horizontal scans (scan length 2.83–5.62 mm) were performed in all cases in order to encompass the center of the lesions and the surrounding normal tissues. OCT images are color-coded so that as the reflectivity increases, the color changes from black to blue, green, yellow, red, and white,i.e. from low to high reflectivity.

Ophthalmoscopy and slit-lamp examination with a fundus lens showed exudative changes such as serous retinal detachment and subretinal hemorrhage. FAG showed well-defined CNV in all patients at the initial visit. In general, when both subretinal hemorrhage and serous retinal detachment have disappeared completely, it is considered that the CNV activity has resolved. However, in this study, the activity of CNV was considered to have subsided when the serous retinal detachment had disappeared and/or when there was only a small amount of residual subretinal hemorrhage. Choroidal neovascular (CNV) lesions were classified into three stages based on past history, fundus findings, and FAG. Eyes that showed subretinal hemorrhages, retinal detachment, and CNV lesions with active leakage of fluorescein in the late phase were classified as being in the active stage. Eyes were placed in the intermediate stage if they had prolonged symptoms of visual impairment, residual exudative changes from the CNV, and early signs of cicatricial changes. Finally, eyes that showed complete regression of the CNV, disappearance of the exudative changes around the CNV, and CNV lesion with no leakage of fluorescein in the late phase were classified as being in the cicatricial stage.

We studied three points at each stage: the rate of CNV detection by OCT, the OCT features of the CNV, and the OCT features of the neurosensory retina.

Results

There were 12 men and 20 women aged 18–53 years, with a mean of 35.9±9.2 years. Characteristics of the 32 patients and their CNV are shown in Table 1. Thirteen patients had active CNV, 10 had intermediate CNV, and 9 had cicatricial CNV. The interval between first symptoms of visual impairment to initial OCT ranged from 4 days to 24 months, with a mean of 5.4±5.3 months. Forty OCT examinations were conducted on 32 patients. Among the six patients who had two OCT measurements, one patient showed active stages in both measurements, one patient changed from active to intermediate stage, one patient changed from active to cicatricial, and three patients changed from intermediate to cicatricial. The one patient who had three OCT examinations demonstrated a CNV that was in the active stage in two measurements and had become cicatricial by the time of the third measurement. Thus, overall, by OCT examinations, 15 eyes demonstrated the active stage of CNV, 11 eyes showed the intermediate stage, and 14 eyes were in the cicatricial stage.

Table 1 Characteristics of patients and stage of choroidal neovascularization (CNV) at initial visit

Characteristic	Stage of CNV		
	Active	Intermediate regressive	Cicatricial
Number of patients	13	10	9
Age, years (mean ± SD)	37.2±9.4	37.6±9.9	34.2±7.9
Gender (M:F)	3:10	4:6	5:4
Duration* (months)	2.9±3.2	5.0±4.1	9.9±6.8

* Time from presenting symptoms to initial visit

Detection rate of CNV by OCT

In 36 (90.0%) of 40 eyes that had FAG and in 27 (93.1%) of 29 eyes which were examined by ICG, hyperfluorescence from the CNV could be clearly seen in each of the three stages. In all of these cases, the OCT image of the CNV area showed a thickening appearance, including the retinal pigment epithelium (RPE) layer, such as a multilayered or fusiform highly reflective area, or a dome-shaped, highly reflective elevation, which was continuous with the highly reflective layer corresponding to the RPE.

In addition, the CNVs in the other four eyes in which they had not been detected by FAG and the two eyes in which they had not beendetected by ICG were detectable on OCT by virtue of abnormal reflection in the CNV area. In eyes that showed a multilayered highly reflective appearance on OCT, the reflection, mostly red in color, projected towards the subretinal space. Such reflection was also clearly delineated from the other surrounding subretinal tissues, except for fresh subretinal hemorrhage, which usually shows high reflection on OCT. However, in the seven cases which showed fusiform thickening of RPE, it was difficult to distinguish between RPE and CNV on the OCT image because of the obscurity of the borders and the similarity in transparency.

ICG angiograms showed a continuously or intermittent hypofluorescent (dark) rim around neovascular membranes in the late phase in 22 (75.9%) of 29 eyes. While dome-shaped reflection of RPE was seen in 16 of the 22 eyes with a dark rim on ICG angiography, two of seven eyes were without a dark rim.

OCT features of CNV

Active stage

In the active stage, the CNV was observed by OCT as a disruption of the most reflective layer (imaged white) which corresponded to the RPE and choriocapillaris (Fig. 1). In the region of the disruption, there was a sub-

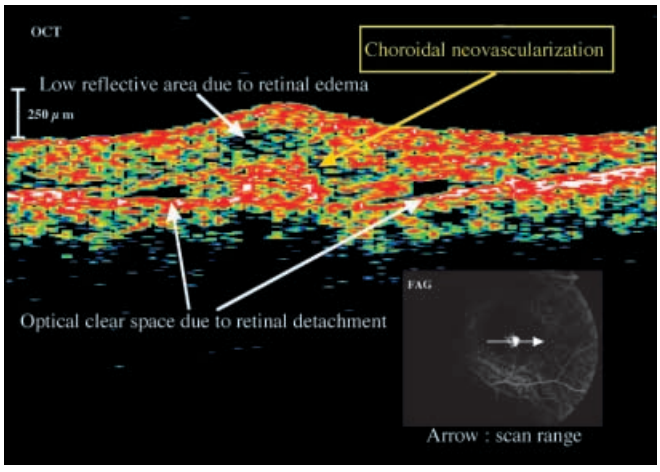

Fig. 1 The appearance of the fundus of a 23-year-old woman, 1 month after the onset of ICNV. A subfoveal lesion with serous retinal detachment is seen in the macula. FAG showed lacy hyperfluorescence in the early phase and active dye leakage from the CNV in the late phase. The OCT image (*arrow* in FAG) shows disruption of a white-colored, highly reflective layer corresponding to the RPE and choriocapillaris and a nodular elevation of multi-layered, red-colored, high reflection in the subretinal space. In the outer retinal layers, a low-reflective area with an optically clear space due to retinal detachment can be seen. This represents retinal edema

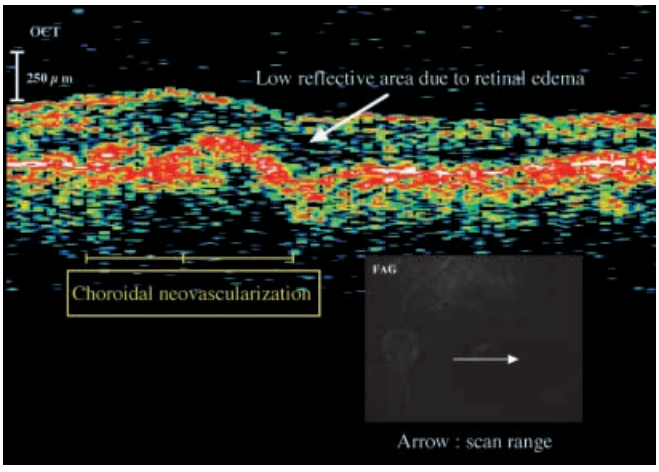

Fig. 2 The appearance of the fundus of a 52-year-old woman, 9 months after the onset of disease. Funduscopy shows localized edema and hemorrhage around the lesion, and FAG shows mild dye leakage from CNV in the late phase. OCT shows a whitish, dome-shaped elevation continuous with the highly reflective retinal pigment epithelium on the right side and a red, irregularly multi-layered, highly reflective area on the left. The right half of the lesion is in the active stage and the left half of the lesion is in the cicatricial stage. In this case, the mixed findings in different stages were observed in the same scanning image of OCT

retinal elevation of a multilayered, highly reflective area (imaged red). These findings correspond to type 2 CNV lesion in Gass'classification.

Intermediate stage

The reflection from the CNV in the intermediate stage tended to be stronger than that in the active stage. Such CNV lesion was observed by OCT as having characteristics of both active and cicatricial stages (Fig. 2). In 8/11 eyes (72.7%) at this stage, the CNV was observed as a multiplex highly reflective area that showed a mixture of reflections of various densities. The reflection from the periphery of the lesion was smooth and was continuous with the highly reflective layer corresponding to the RPE. The center of the lesion still showed a reddish high reflection (Fig. 3).

In 3 (27.3%) of 11 eyes, the reflection corresponding to the CNV appeared as a fusiform, highly reflective area that was covered by a dome-shaped, highly reflective layer corresponding to the RPE. This appearance was the same as in most cases in the cicatricial stage except for the appearance of retinal edema or retinal detachment.

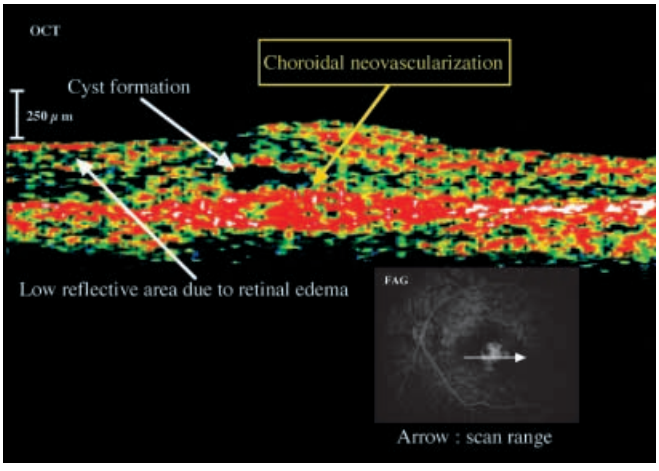

Fig. 3 The appearance of the fundus of a 23-year-old woman, 7 months after the onset of disease. Retinal detachment has disappeared, although cystoid macular edema with surrounding exudate and residual mild hemorrhage can be seen. Late dye leakage from CNV is not noted on FAG. OCT scanning reveals cystoid and diffuse edema in the sensory retina. The CNV is imaged as a multilayered highly reflective area that is continuous with the highly reflective layer of RPE. Smooth elevation from the highly reflective layer of RPE is seen in the peripheral area of the lesion. The reflection color is redder in the central part of the lesion

Cicatricial stage

In 10 of 14 eyes showing the cicatricial stage of CNV, OCT depicted a dome-shaped most reflective elevation that was continuous with the highly reflective layer corresponding to the RPE. This was associated with a moderately reflective area located deeper in the tissue. There were no findings suggestive of retinal edema or retinal detachment. In 4/14 eyes (28.6%), OCT detected fusi-

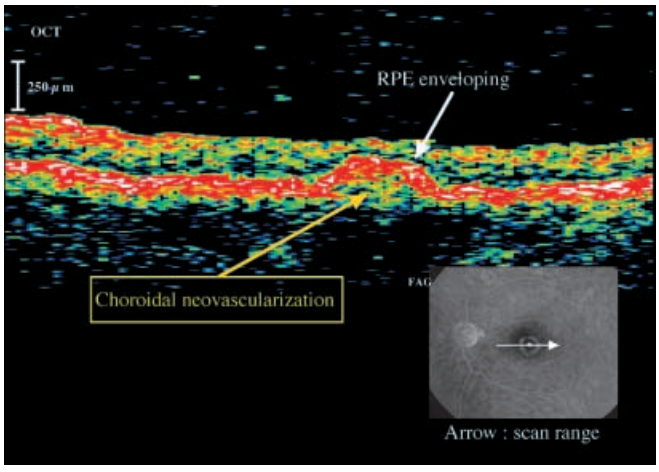

Fig. 4 The appearance of the fundus of a 35-year-old man, 3 months after the onset of the disease. Funduscopy shows slightly pigmented, cystoid lesions in the subretinal space, and the serous retinal detachment has already disappeared. There is no late dye leakage from the CNV, although the CNV is noted as hyperfluorescent area on FAG. OCT scanning of the lesion shows a whitish, dome-shaped, elevation continuous with the highly reflective layer corresponding to the RPE associated with a moderately reflective area located posteriorly. There are no signs suggesting retinal edema or retinal detachment

form lesions with a mixture of reflections of various densities that corresponded with the funduscopic appearance of advanced fibrosis in the area of CNV. These findings suggested a regressive course of CNV with the envelopment of the CNV by the RPE. A typical case in the cicatricial stage is shown in Fig. 4.

OCT features of the neurosensory retina

Among 25 eyes with an ICNV that showed a retinal detachment funduscopically, OCT detected the detachment in only 9 eyes (36.0%). Macular edema was detected by OCT in the other 16 eyes (64.0%). The OCT image of the sensory retina around the CNV showed diffuse, low reflection due to retinal edema especially in the active stage. Cystoid macular edema (CME) was found by OCT in only three eyes. In the active stage, 2 (13.3%) of 15 eyes showed CME and 6 (40%) showed an optically clear space corresponding to an exudative retinal detachment. The retinal detachment gradually disappeared in the intermediate stage (3/11 eyes, 27.3%); no retinal edema or retinal detachment of the sensory retina was seen by OCT in the cicatricial stage.

Discussion

Optical coherence tomography was initially reported by Huang et al. in 1991 [10], and it has been widely used in clinical practice as a noninvasive method to study the fine features of the posterior pole of the eye [7, 8, 12, 15, 18]. Prior to OCT, FAG and ICG angiography were developed to supplement standard funduscopy to detect ocular fundus diseases. These procedures proved very useful for detecting CNV [20, 21]; however, they were limited because it was difficult to evaluate the three-dimensional structure of a CNV.

The OCT images of the CNV lesions had different features at the three stages, and the relationship between the RPE and neovascularization could be evaluated by OCT at each stage. The reflection of the CNV that showed a multilayered, highly reflective area in the subretinal space in the active stage corresponded well with type 2 CNV in Gass'classification [5]. Thereafter, the envelopment of the CNV by the RPE progressed gradually. In the cicatricial stage, this envelopment was observed as a dome-shaped, most reflective layer that was continuous with the RPE.

The neovascular lesion of an ICNV is similar to type 2 CNV in Gass'classification [5]. ICNV is characterized as a smaller lesion than that in age-related macular degeneration (AMD), and the exudative changes in the macula tend to have a self-limiting course. In addition, the ICNV lesion regresses spontaneously, leaving cicatricial tissue in some cases.

There are several reports on the usefulness of photocoagulation in eyes with ICNV [1, 13, 14, 17], although careful monitoring without treatment is probably the first choice in Japan at present because of the spontaneous regression in some cases. Thus, it would be very valuable if the eyes undergoing regression could be identified by OCT at an early stage.

OCT examination is also potentially important for submacular surgery for ICNV as well as for AMD [19]. The three-dimensional images allow identification of the site of the CNV and would be useful for differentiating the two types of CNV before the beginning of surgery. The surgeon could then plan the operative procedure in advance.

Puliafito et al. [15, 16] and Giovannini et al. [6] reported the OCT findings of active CNV in ICNV. In these reports, classic CNV was observed as a fusiform thickening at the level of the RPE. Iida et al. [11] also reported OCT findings in idiopathic CNV. In their cases, CNV was seen as a moderately and highly reflective mass that protruded from the RPE or a highly reflective fusiform mass at the level of the RPE and choriocapillaris. They concluded that the protruding CNV transforms to fusiform tissue at the level of the RPE during the process of regression. In this study, 10 of 14 eyes showed a moderately reflective area beneath the dome-shaped elevation. This dome-shaped area might correspond to the RPE, which that has been described previously as protruded and fusiform reflections.

Serial cross-sectional examination of a CNV by OCT not only yields the three-dimensional structure of the

CNV but also enhances the understanding of the mechanism of development and regression of CNV. However, it has not been completely determined how accurately OCT depicts the actual CNV tissue.

In an experimental model of CNV in monkeys and rats, we observed OCT findings similar to those seen in this study, i.e. protruding high reflection in the active stage and dome-shaped elevation of RPE or fusiform reflection in the cicatricial stage [2, 3]. By correlating the OCT images with the histological appearance of the retina and RPE, we observed the process of regression of CNV and were able to identify the structures that corresponded with the OCT images.

In the intermediate stage, the CNV was observed as a multiplex, highly reflective area which showed a mixture of reflections of various densities. The reflection from the periphery of the lesion became smooth and was continuous with the highly reflective layer corresponding to the RPE. In addition, the OCT images showed a gradual reddening toward the center. These findings suggested an envelopment by the RPE that proceeded gradually from the periphery of the lesion to the central area. We suggest that the envelopment was still incomplete and the activity in the central part of the CNV remained at the intermediate stage.

The highly reflective area beneath the dome-shaped elevation in the cicatricial stage may suggest the cicatrization of CNV with the envelopment by RPE. RPE cell proliferation during the regression of CNV can be observed as a continuous or intermittent hypofluorescent rim surrounding neovascular membranes in the late phase of ICG angiography [4]. In this study there was a difference, i.e. the dome-shaped reflection of the RPE was seen in only 16 (72.7%) of the 22 eyes that showed a dark rim in the ICG angiogram. However, there is a possibility that some of the eyes with a fusiform reflection in the OCT image are also correlated with a dark rim on the ICG angiogram. The scattered highest reflections seen in the fusiform lesion as a white image in some cases in the cicatricial stage suggested a fibrotic component of the CNV membrane, because the interval from onset of the disease was longer in these cases than in others.

In eight eyes, we were able to follow the changes in the CNV from active to intermediate stage, or from intermediate to cicatricial stage. Unfrtunately, we were not able to follow any patient through all three stages via OCT. However, we feel that the tomographic images at each individual stage of CNV provide sufficient information to characterize the stages. Such information derived from OCT analysis may be very helpful not only in staging ICNV but in selecting appropriate therapy.

Among 25 eyes that showed retinal detachment ophthalmoscopically, the OCT images confirmed the retinal detachments in only 9 eyes. OCT images of the other 16 eyes suggested macular edema and retinal thickening. On the other hand, CME was shown in only three eyes. Because the OCT resolution is very fine, the tomographic features of the tissue are also fine, especially in the axial direction. We suggest that some cases previously diagnosed as retinal detachment based on ophthalmoscopic findings are in fact cases of retinal edema. Our findings suggest that retinal edema is greatly involved in the loss of visual acuity even in cases with a small CNV.

The results of our study suggest that OCT is useful for following the clinical course of ICNV and understanding the mechanism of CNV regression. The combination of OCT with other imaging techniques such as FAG and ICG may allow more detailed evaluation of the pathologic stages.

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