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Optical Coherence Tomography and Optic Coherence Tomography Angiography in Eyes with Tamoxifen Retinopathy

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Abstract

Purpose: To determine the morphology of eyes with tamoxifen retinopathy by optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA).

Methods: Eight eyes of 4 patients (1 man, 3 women; mean age 62.8 years) with crystallin deposits in the retina associated with tamoxifen retinopathy were studied. The presence of abnormalities in the inner and outer retinal layers in the OCT (Topcon) and OCTA (Optovue) images were determined. The area of the central foveal avascular zone (FAZ) and retinal vessel density (RVD) in the superficial and deep capillary plexus were determined. Eight eyes of age-matched healthy subjects were evaluated in the same way and served as the control group.

Results: The mean duration of tamoxifen use was 4.6 years. The mean best-corrected visual acuity was 0.10 ± 0.17 logarithm of the minimum angle of resolution (logMAR) units with a range of -0.08 to 0.40 logMAR units. OCT showed cystic changes in the inner retinal layer in one eye and disorder of the ellipsoid zone in the outer retinal layer in six eyes. The area of the FAZ and RVD in the superficial and deep capillary plexuses in the eyes with tamoxifen retinopathy did not differ significantly from that of normal control eyes (all $P > 0.1$).

Conclusion: The minor changes in the inner layers in the OCT images and the absence of significant changes in the FAZ and RVD in the superficial and deep capillary plexus suggest that tamoxifen retinopathy may be preceded by outer retinal layer abnormalities.

Keywords: *Ellipsoid Zone; Vessel Density; Foveal Avascular Zone; Superficial Capillary Plexus; Deep Capillary Plexus*

Abbreviations

MacTel: Macular Telangiectasia; OCT: Optical Coherence Tomography; OCTA: Optical Coherence Tomography Angiography; BCVA: Best-Corrected Visual Acuity; logmar: Logarithm of the Minimum Angle of Resolution; FAZ: Foveal Avascular Zone; RVD: Retinal Vessel Density

Introduction

Tamoxifen is an oral estrogen receptor antagonist and is the standard treatment for estrogen receptor-positive breast cancer. Although not frequent, ocular toxicities have been reported with tamoxifen use [1,2]. Ophthalmoscopy has shown that tamoxifen retinopathy is associated with crystallin deposits, macular edema, and retinal pigmentation [3-6]. Interestingly, the features of tamoxifen retinopathy are similar to those of macular telangiectasia (MacTel) type 2, and the two retinal disorders are occasionally difficult to differentiate [7,8].

MacTel type 2 is associated with perifoveal telangiectasia, and recent studies have shown that MacTel type 2 is accompanied by outer retinal layer abnormalities from the early stages of the disease process. This suggested that the vascular abnormalities were probably secondary to the disease [9-15].

There are only a few reports on the optical coherence tomography angiographic (OCTA) findings in tamoxifen retinopathy [16-18].

Purpose of the Study

The purpose of this study was to determine the morphology of eyes with tamoxifen retinopathy. To accomplish this, we examined the images obtained by OCT and OCTA from 4 patients with tamoxifen retinopathy.

Materials and Methods

This was a retrospective study, and the procedures used conformed to the tenets of the Declaration of Helsinki. The Institutional Review Board of the Tokyo Women's Medical University School of Medicine approved the procedures used. All examinations were performed after a signed informed consent was obtained from the patients.

Eight eyes of 1 man and 3 women whose average age was 62.8 ± 16.2 years were studied. All patients were taking tamoxifen to treat breast cancer, and all had crystallin deposits in the retina associated with tamoxifen retinopathy. For controls, the data of 8 normal eyes of an age-matched group was collected from our normal database that included 267 eyes of 255 patients (mean age 60.4 years) [19] without retinal and choroidal disorders. Only the data of the right eyes of normal volunteers and the fellow normal eyes in cases of unilateral rhegmatogenous retinal detachment or senile cataract were used.

The best-corrected visual acuity (BCVA) was measured with a Japanese standard decimal visual chart, and the decimal visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) for the statistical analyses. The average duration of the tamoxifen use was also recorded.

All eyes were examined by swept-source OCT (DRI-OCT, Topcon, Japan), and the images were used to evaluate the inner and outer retinal structures. All eyes were also examined by OCTA (RTVue AVANTI, Optovue Inc, Fremont, CA) with a scan of 3 × 3 mm centered on the fovea. The en face OCTA images were auto-divided into four depth layers to examine the superficial capillary plexus, deep capillary plexus, outer retina, and choriocapillaris. The area of the foveal avascular zone (FAZ) and the retinal vessel density (RVD) were measured in the superficial capillary plexus and deep capillary plexus (Figure 1).

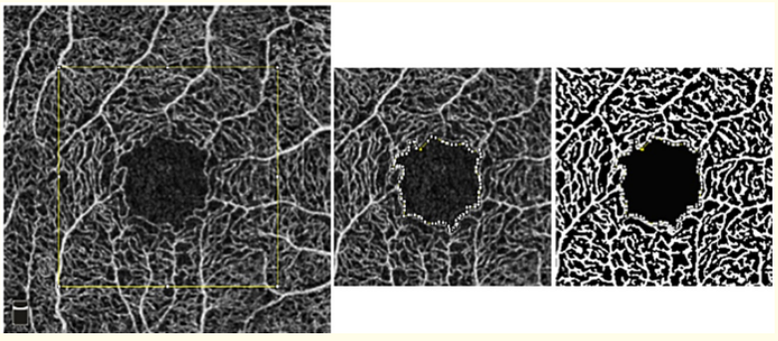

Figure 1: *En face optical coherence tomography angiographic (OCTA) images showing the foveal avascular zone (FAZ) and the region where the retinal vessel density (RVD) measurements were made.*

Left: OCTA image cropped to 2 x 2 mm.

Middle: FAZ area measurement by polygon selection tool.

Right: RVD measurement after binarization using ImageJ Niblack method except FAZ area,

FAZ = Foveal Avascular Zone; RVD = Retinal Vessel Density.

All OCTA image analyses were done by the ImageJ software (National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index. html). We analyzed the cystic changes in the inner retinal layer and the irregularities and/or disruptions of the ellipsoid zone of the photoreceptors in the cross-sectional OCT images. The area of the FAZ and the density of the retinal vessels in the superficial and deep capillary plexuses were analyzed in the OCTA images. The area of the FAZ in each image was measured by three co-authors (KS, IM, and MT), and their values were averaged. To analyze the images, they were imported to ImageJ, and the scale was set at 2 x 2 mm for the horizontal and vertical size. The FAZ area was measured with the polygon selection tool.

Retinal vessel density (RVD)

The RVDs in the superficial capillary plexus and the deep capillary plexus were calculated by measuring them in the central 2 x 2 mm area. First, the central 2 x 2 mm area from the superficial and deep plexus layer in the OCTA image was imported to ImageJ. The images were binarized using ImageJ Niblack method to remove the artifacts. Then, the average optical density of 3 points of low reflection within the FAZ was measured and set to be the cut-off value. The RVD was calculated by the following formula:

RVD (%) = microvascular dimension/(4 mm^2 - FAZ area).

Statistical analyses

All tests to determine the significance of differences were two-tailed, and a P-value < 0.05 was considered statistically significant. The significance of the differences in the median was determined by Mann-Whitney U tests. All statistical analyses were performed with the EZR free software with the customization capabilities of R (The R Foundation for Statistical Computing, Vienna, Austria) [20].

Results

The demographics of the eyes with tamoxifen retinopathy and healthy normal control are shown in table 1 and 2. The mean duration of tamoxifen use was 4.6 years with a range of 2 to 6.5 years. The mean BCVA at the initial visit was 0.10 ± 0.17 logMAR units with a range from -0.08 to 0.40 logMAR units.

	Age	Gender	eye	BCVA	Crystalline deposit	Cystic change	EZ disorder	FAZ (sf)	FAZ (dp)	RVD (sf)	RVD (dp)
1	85	Male	OD	0.22	+	-	+	0.56	0.43	0.360	0.343
			OS	0.40	+	-	+	0.36	0.39	0.361	0.366
2	71	Female	OD	0.05	+	-	+	0.40	0.26	0.372	0.378
			OS	0.30	+	+	+	0.49	0.44	0.372	0.388
3	44	Female	OD	0.10	+	-	+	0.35	0.35	0.357	0.399
			OS	-0.08	+	-	+	0.41	0.42	0.352	0.389
4	51	Female	OD	-0.08	+	-	-	0.43	0.43	0.370	0.381
			OS	-0.08	+	-	-	0.41	0.41	0.360	0.380
Mean	62.8	m:f =		0.10	8	1	6	0.43	0.39	0.363	0.378
SD	16.2	1:3		0.17				0.06	0.05	0.007	0.016

Table 1: *Clinical characteristics in eyes with tamoxifen retinopathy.*

BCVA = Best-Corrected Visual Acuity; EZ = Ellipsoid Zone; FAZ = Foveal Avascular Zone; RVD = Retinal Vessel Density; sf = Superficial Capillary Plexus; dp = Deep Capillary Plexus.

	Age	Gender	Eye	FAZ (sf)	FAZ (dp)	RVD (sf)	RVD (dp)
1	43	Female	OD	0.43	0.30	0.372	0.384
2	46	Female	OS	0.39	0.58	0.344	0.361
3	52	Female	OD	0.44	0.46	0.360	0.378
4	52	Female	OD	0.26	0.43	0.368	0.366
5	71	Female	OS	0.35	0.31	0.376	0.385
6	72	Female	OS	0.42	0.27	0.363	0.364
7	85	Male	OD	0.43	0.34	0.365	0.368
8	85	Male	OD	0.41	0.29	0.360	0.375
Mean	63.3	m:f = 2:6		0.39	0.37	0.363	0.373
SD	16.0			0.05	0.10	0.009	0.008

Table 2: *Clinical characteristics in eyes with healthy normal control.*

FAZ = Foveal Avascular Zone; RVD= Retinal Vessel Density; sf = Superficial Capillary Plexus; dp = Deep Capillary Plexus.

OCT showed cystic changes in the inner retinal layer in only one eye and a blurredness or disruption of the ellipsoid zone in the outer retinal layer in six eyes.

The OCTA images of all eyes are shown in figure 2. There were no right-angle venule lesions in the perifoveal region in any of the eyes. The mean area of the FAZ in the superficial capillary plexus was 0.43 ± 0.06 mm^2 and that for the deep capillary plexus was 0.38 ± 0.10 mm^2 in the eyes with tamoxifen retinopathy. Both were larger than that of the control group at 0.39 ± 0.05 mm^2 and 0.37 ± 0.10 mm^2 respectively. However, the differences were not significant (P = 0.75 and P = 0.92).

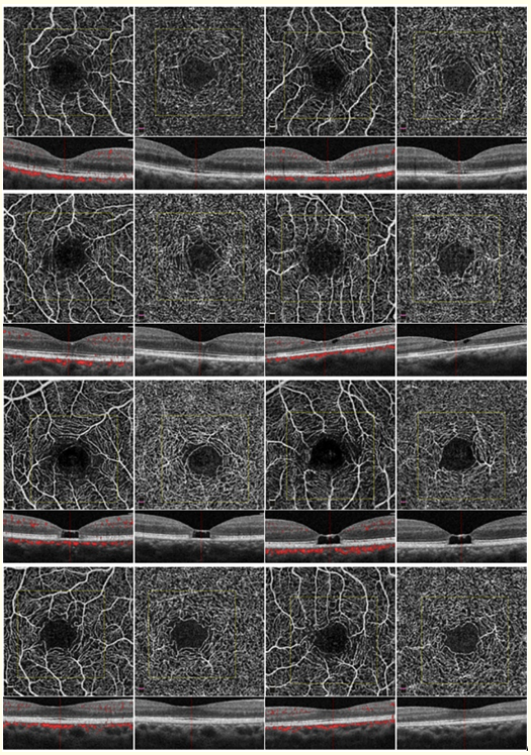

Figure 2: *Optical coherence tomography (OCT) and OCT angiography (OCTA) images of all eyes with tamoxifen retinopathy.*

Top (Case 1). OCT and OCTA images from an 85-year-old-man.
Upper OCTA raw image: Superficial and deep capillary plexus in right and left eye. There are no significant vascular changes.
Lower row. Horizontal OCT scan with and without blood flow information of right and left eyes. Ellipsoid zones are seen blurredly at the foveal area.
2nd row. (Case 2). OCT and OCTA images of a 71-year-old-woman.
Upper row: OCTA en face image shows no significant vascular change.
Lower row: OCT images showing that the ellipsoid zone is blurred at the foveal area in both eyes. Cystic changes in the inner retinal layer are observed in the left eye.
3rd row (Case 3): OCT and OCTA images of a 71-year-old-woman with tamoxifen retinopathy.
Upper row: OCTA image showing that there are no significant vascular changes.
Lower row: OCT image showing a disruption of the ellipsoid zone at the foveal area in both eyes.
4th row (Case 4): OCT and OCTA images of a 51-year-old-woman with tamoxifen retinopathy.
Upper row: OCTA images show that are no significant vascular changes.
Lower row: OCT image showing a normal ellipsoid zone at the foveal area in both eyes.

The RVD of the superficial capillary plexus was 36.3% of that of the normal eyes and that of the deep capillary plexus was 37.8% of that of the normal eyes in the eyes with tamoxifen retinopathy. The differences in the densities were not significant (P = 0.96, P = 0.20).

Discussion

Our results showed that area of the FAZ and the RVD in the OCTA images of eyes with tamoxifen retinopathy were not significantly different from the corresponding values of the normal control eyes. On the other hand, the changes in the inner and outer retinal layers in the OCT images of eyes with tamoxifen retinopathy were mainly in the outer retinal layer and only one eye had changes in the inner retinal layer [11-15]. These results suggest that the outer retinal layer is the primary affected area in tamoxifen retinopathy.

Although the incidence of tamoxifen retinopathy is low, it requires rapid attention because it can progress to changes that are irreversible if left untreated. Crystallin deposits are the most typical finding, however, OCT showed minor changes in the outer and inner retinal layers. It is rare for a retinal disease to have such damages in both the inner and outer retinal layers.

A typical condition with such findings is MacTel type 2 [7,8] which is characterized by bilateral, minimal exudation, occult juxtafoveal telangiectasis, retinal crystalline deposits, right angle venules, and occasionally subretinal neovascularization [9,10]. OCT also show a retinal cavitation without retinal thickening and tears in the ellipsoid zone in the outer retinal layers in Mac Tel type 2 retinal disease indicating a wide range of abnormalities from the inner to the outer retinal layers.

It has recently been suggested that degeneration of the Müller cells is the primary pathological abnormality of MacTel type 2 retinopathy, and that the telangiectasia is a secondary change [9-15]. Tamoxifen retinopathy is a disorder with similar findings to MacTel type 2, although it is not clear whether Müller cell abnormalities are primary in tamoxifen retinopathy. Because it is associated with abnormalities in the inner and outer retinal layers, the presence of abnormalities in the inner and outer layers of the retina suggests the possibility of Mueller cell-mediated changes similar to those in MacTel type 2. In our case, there were no alterations of the retinal blood flow and no appearance of right-angle venules. Because MacTel type 2 also initially shows abnormalities of only the ellipsoid zone, tamoxifen reti-

nopathy may also develop vascular lesions after a long period of time. Lee., *et al.* [17] examined a case of tamoxifen retinopathy by OCTA, and they reported the presence of saccular capillary telangiectasia and right-angle venules in the deep capillary plexus. In addition, they reported a lower density of foveal vessels in the superficial capillary plexus, However, their mean duration from start of tamoxifen therapy to diagnosis of retinopathy was 8.3 years. Thus, a longer follow-up might be necessary in our case.

The main limitations of this study were the small number of cases and the short follow-up periods.

Conclusion

In conclusion, OCT and OCTA showed few significant changes in the inner retinal layers in eyes with tamoxifen retinopathy. These findings suggest that tamoxifen retinopathy may be preceded by damage in the outer retinal layers, and the cystic changes and telangiectasia in the inner retinal layer may be secondary changes.

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Conflict of Interest

Dr. Shinozaki reports personal fees from Senju Pharmaceutical Co., Otuska Pharmaceutical Co., Novartis, outside the submitted work.

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Dr. Taketani has nothing to disclose.

Dr. Kawakami has nothing to disclose.

Dr. Kawai has nothing to disclose.

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