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Ultrasound Biomicroscopic Classification of Zonules in Exfoliation Syndrome

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Purpose: Exfoliation changes in the zonules or ciliary processes may be the earliest clinical sign of the exfoliation syndrome (XFS). In the present study we investigated the usefulness of ultrasound biomicroscopy (UBM) for detecting the early changes of XFS in zonules.

Methods: Both eyes of 11 patients with unilateral XFS and the unilateral eyes of 11 subjects without evidence of XFS were examined using UBM. The incidence of zonular changes was compared among the XFS-positive eyes of the patients, their contralateral XFS-negative eyes, and the healthy eyes of the subjects without XFS.

Results: Using UBM, we could successfully describe the zonules in all UBM images of all subjects. In the four quadrants, the incidence of granular-type zonules was statistically different among the three groups: it was higher in XFP-positive eyes than in XFS-negative eyes, and it was higher in XFS-negative eyes than in healthy eyes.

Conclusions: UBM can detect the zonular changes that may occur early in XFS. A granular-type change in the zonules may be the most typical finding in the presence of exfoliation material. Diagnostic criteria are proposed for the early detection of XFS, based on the changes found in the zonules by UBM. **Jpn J Ophthalmol 2002;46:502–509** © 2002 Japanese Ophthalmological Society

Key Words: Exfoliation syndrome, prospective case series, ultrasound biomicroscopy, unilateral cases, zonular apparatus.

Introduction

The characteristic feature of the exfoliation syndrome (XFS) is a grayish-white deposit layered on the anterior lens surface.[1] The classic pattern of XFS consists of three distinct zones: a relatively homogeneous central disc; a granular, and often layered, peripheral zone; and a clear area separating the two. The central disc is absent in about 20% of cases,[2] but the peripheral zone is always present.

While it is necessary to dilate the pupil for the diagnosis of XFS, eyes with XFS often dilate poorly[3] and are predisposed to posterior synechia formation between the iris pigment epithelium and the anterior lens capsule,[4] even in the absence of miotic therapy. In fact, many cases go undetected due to failure to dilate the pupil. Histopathologic examination of lenses after cataract extraction suggests that XFS is underdiagnosed.[5]

XFS is the most common identifiable specific disease entity leading to the development of open-angle glaucoma. In fact, glaucoma has been shown to occur more commonly in eyes with XFS than in those without it. In eyes with XFS, Kozart and Yanoff[6] found glaucomatous optic nerve or visual field damage in 7% of the cases studied and ocular hypertension in 15% of the cases studied. Glaucoma in XFS has a more serious clinical course than primary open-angle glaucoma. Persons with XFS but without glaucoma have a higher mean intraocular pressure (IOP) than those without XFS.[7] Patients with XFS presenting with newly discov-

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ered glaucoma have a higher IOP and more severe visual field defects and optic nerve head changes than those with primary open-angle glaucoma. Moreover, the glaucomatous damage progresses more rapidly in patients with XFS and glaucoma than in those with primary open-angle glaucoma.[8,9]

Mizuno and Muroi[10] used cycloscopy to identify pseudoexfoliative deposits in the zonules and ciliary processes of more than one half the unilaterally affected fellow eyes and concluded that they may be an early and consistent characteristic of pseudoexfoliation.

High-frequency ultrasound biomicroscopy (UBM) provides high-resolution images of eyes in vivo and is useful for distinguishing subtle changes in the anatomy and pathology within the anterior segment.[11,12] This technology also has the capability of imaging the zonular apparatus.[13,14] Thick, well-defined zonules coated with exfoliation material have been described by UBM.[15] The results of these previous studies suggest that XFS could be detected with UBM by imaging the zonules even in eyes without clinically apparent *XFS* features.

The goal of the present study was to assess the capability of UBM to describe the early characteristics of XFS in the zonules of eyes that show no apparent signs of XFS in the iris or lens.

Materials and Methods

Using UBM (Model 840, Carl Zeiss-Humphrey Systems, San Leandro, CA, USA), we carried out our investigations at 50 MHz, providing lateral and axial physical resolutions of approximately 50 μm and 25 μm, respectively. The tissue penetration was approximately 4–5 mm. UBM was performed with the subject in the supine position under standardized illumination. After topical anesthesia with oxybuprocaine solution, a 17-mm diameter eyecup was gently placed on the globe to be tested and filled with saline solution as a coupling medium. Fixation and accommodation were held constant by having the subject fixate on a ceiling target with the fellow eye.

Images were obtained in the zonule and angle regions at the 12:00, 3:00, 6:00, and 9:00 o'clock positions, with the subject fixating on the ceiling target. The oscillations of the transducer head were oriented radially toward the limbus. To obtain clear images of the zonules, the scanning planes were oriented perpendicular to the zonule path, with the zonules in the center of the images. We standardized the estimation by taking three images at each location.

The ultrasonographic images were visualized in real time, and captured and saved digitally on a diskette. They were then displayed and printed simultaneously on a video printer.

In a preliminary study, with UBM we examined 15 eyes of 9 XFS cases having an apparent deposit of exfoliative material on the anterior lens surface. We classified the zonules in these eyes into types and defined a diagnostic criteria for XFS by UBM.

To test the validity of these criteria, we examined the eyes of 11 cases with unilateral XFS (22 eyes) and the eyes of 11 subjects confirmed as not having XFS (11 control eyes) using UBM. The presence of exfoliative material on the lens and iris had been the criterion for the diagnosis of XFS in the patients. The absence of exfoliative material had been confirmed in the controls by slit-lamp examination after dilation.

These examined eyes were categorized into three groups on the basis of the following clinical features:

1. XFM-positive eyes—the affected eyes of 11 patients with unilateral XFS
2. XFM-negative eyes—the contralateral eyes of the above 11 patients
3. Eyes without XFS—the eyes of 11 control subjects

All subjects in this study were ethnic Japanese. In the unilateral XFS group, there were 6 men (55%) and 5 women (45%), with a mean age of 70.1 ± 6.7 (SD) years. In the control group, there were 4 men (36%) and 7 women (64%), with a mean age of 65.0 ± 7.4 (SD) years. The groups were not individually matched for age, sex, or refractive error, although the comparison of statistical indices among the groups demonstrated no significant differences (Table 1).

Patients with a history or findings of trauma, lens (sub-)luxation, aphakic eyes, pseudophakic eyes, or eyes with poor dilation had been excluded from the study.

The incidence of positive exfoliative changes was compared in the three groups of eyes. In evaluating the images, 12 images, ie, 3 images for each quadrant of each eye, were utilized. Images were exported to a computer in the PCX format. The second author (D.T.) judged whether there was evidence of XFS on the zonule and determined the type of change, in a randomly determined order, without knowledge of the diagnosis by other participating ophthalmologists.

Statistical analysis was performed in each quadrant and for the total images, using the Fisher exact probability test or χ– test (Tables 2–6).

Results

The zonules in the IBM images obtained in our preliminary study were divided into four types: gran-

Jpn J Ophthalmol
Vol 46: 502–509, 2002

Table 1. Characteristics of Subjects in Study

	Unilateral XFS* Patients	Control Group	*P*
Age†	70.1 ± 6.7 (57–77)	65.0 ± 7.4 (52–72)	NS‡
Sex§			
Male	6 (55)	4 (36)	NS‖
Female	5 (45)	7 (64)	NS‖
Refractive error (diopters)			NS¶
XFM-positive#	0.34 ± 1.8	−1.4 ± 2.2	
Control group	−0.32 ± 2.2	−1.4 ± 2.2	

*XFS: exfoliation syndrome.
†Age: mean ± SD (range).
‡Fisher extract probability test.
§Sex: number of patients (%).
‖Mann-Whitney *U*-test.
¶Kruskal-Wallis test.
#XFM: exfoliative material.

ular type, winding type, fan-shaped type, and healthy type. Granular type, winding type, and fan-shaped type were observed in 15 eyes, 12 eyes, and 4 eyes, respectively. On the basis of these preliminary results, we defined the diagnostic criteria for the early evidence of XFS obtained by UBM, which is the deposit of exfoliative material (XFM) on the zonule.

XFM-positive Zonule

1. Granular type: The zonule is described as a group of dots with no observable fibrous structure (Figure 1).
2. Winding type: The zonule shows winding with a sclerotic change (Figure 2).
3. Fan-shaped type: A fan-shaped zonule is described with a deposit on each fiber (Figure 3).

XFM-negative Zonule

Found in the healthy eye, it has a straight, clear course, appearing as a white line, and each fiber structure is evident (Figure 4).

Using the criteria defined above, with UBM we examined three groups of 11 eyes each: the affected eyes of 11 patients with confirmed unilateral XFS,

Table 2. Prevalence of Zonular Changes in the Three Groups: Four Quadrants Total*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Value
Granular type	10	82	24	
				<.05†
				< .05†
Winding type	0	3	3	NS
Fan-shaped type	1	21	5	
				<.05‡
XFM-positive images	9 (2)	92 (14)	30 (2)	
				<.05†
				<.05†
Total number of images examined	132	132	32	

*Twelve images of each eye (132 images) for 11 patients in each of three groups. Values in parentheses are the number of images that have two types of change. XFM: exfoliative material.
†χ^2 test, $P < .05$.
‡Fisher exact probability test, $P < .05$.

Table 3. Prevalence of Zonular Changes in the Three Groups: The Superior Quadrants*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Value
Granular type	1	17	2	
		†	†	<.05†
Winding type	0	0	0	NS
Fan-shaped type	0	2	0	NS
XFM-positive images	1	19	2	
		†	†	<.05†
Total number of images examined	33	33	33	

*Three images of each eye (33 images) for 11 patients in each of three groups. XFM: exfoliative material.

†Fisher exact probability test, $P < .05$.

their 11 contralateral unaffected eyes, and 11 eyes of controls.

We found that in the four quadrants, the prevalence of the granular type zonule increased from healthy eyes to XFM-negative eyes in unilateral XFS, and also from XFM-negative eyes in unilateral XFS to XFM-positive eyes in unilateral XFS. This trend was statistically significant (χ^2 test, $P < .05$) (Table 2). In each quadrant, the prevalence of the granular type zonule was significantly higher in XFM-positive eyes than in XFM-negative eyes and healthy eyes (Tables 3–6). Six images of these *XFM*-positive eyes showed a fan-shaped zonule, inferiorly, compared with none in the healthy eyes (Table 4). Eight images of *XFM*-positive eyes showed a fan-shaped zonule, temporally, compared with one in healthy eyes (Table 5). These differences in the fan-shaped zonule changes were statistically significant.

No statistical difference was found in the incidence of the winding type zonule among the three groups.

The total number of XFM-positive images increased from healthy eyes to XFM-negative eyes in unilateral XFS, and also from XFM-negative eyes in unilateral XFS to XFM-positive eyes in unilateral XFS. This trend was statistically significant in the four quadrants and in the temporal section (Tables 2 and 5).

It is noteworthy that all types of zonules were found not only in the affected eyes of the 11 patients, but also in their supposedly unaffected contralateral eyes.

The exfoliation type was not necessarily consistent in the 12 images taken in 1 eye. Perfectly consistent diagnoses were obtained in 5 of 11, 1 of 11, and 1 of 11 in healthy eyes, unaffected eyes, and affected eyes, respectively.

Table 4. Prevalance of Zonular Changes in the Three Groups: The Inferior Quadrant*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Value
Granular type	1	22	5	
		†	†	<.05†
Winding type	0	2	1	NS
Fan-shaped type	0	6	1	
		†		<.05†
XFM-positive images	1	23 (7)	6 (1)	
		†	†	<.05†
Total number of images examined	33	33	33	

*Three images of each eye (33 images) for 11 patients in each of three groups. Values in parentheses are the number of images that have two types of change. XFM: exfoliative material.

†Fisher exact probability test, $P < .05$.

Jpn J Ophthalmol
Vol 46: 502–509, 2002

Table 5. Prevalence of Zonular Changes in the Three Groups: The Temporal Quadrant*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Values
Granular type	4	18	10	
				$P < .05^{\dagger}$
				$P < .05^{\ddagger}$
Winding type	0	1	2	NS
Fan-shaped type	1	8	3	
				$P < .05^{\dagger}$
XFM-positive images	4 (1)	23 (4)	14 (1)	
				$P < .05^{\dagger}$
				$P < .05^{\ddagger}$
Total number of images examined	33	33	33	

*Three images of each eye (33 images) for 11 patients in each of three groups. Values in parentheses are the number of images that have two types of change. XFM: exfoliative material.

†Fisher exact probability test, $P < .05$.

‡χ^2 test, $P < .05$.

When the incidences of eyes with and without an XFM-positive image were compared among the three groups, a statistical difference was found only between healthy eyes and XFM-positive eyes (Table 7).

Discussion

Exfoliation material may be detected earliest on the ciliary body and zonules. Cycloscopy in patients with apparently unilateral involvement revealed XFM on the ciliary processes in all affected eyes and on the zonule or ciliary processes, or both, in 77% of fellow eyes in which XFM was not clinically visible on the lens surface or pupillary margin.[10] The fact that XFM could be described on the zonule in a clinically diagnosed XFS patient by UBM[13,15] suggested that it could also be described by UBM in the absence of visible XFM on the lens surface or pupillary margin.

Table 6. Prevalence of Zonular Changes in the Three Groups: The Nasal Quadrant*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Value
Granular type	4	25	7	
				$P < .05^{\dagger}$
				$P < .05^{\ddagger}$
Winding type	0	0	0	NS
Fan-shaped type	0	5	1	
				$P < .05^{\dagger}$
XFM-positive images	4	27 (3)	8	
				$P < .05^{\dagger}$
				$P < .05^{\ddagger}$
Total number of images examined	33	33	33	

*Three images of each eye (33 images) for 11 patients in each of three groups. Values in parentheses are the number of images that have two types of change. XFM: exfoliative material.

†Fisher exact probability test, $P < .05$.

‡χ^2 test, $P < .05$.

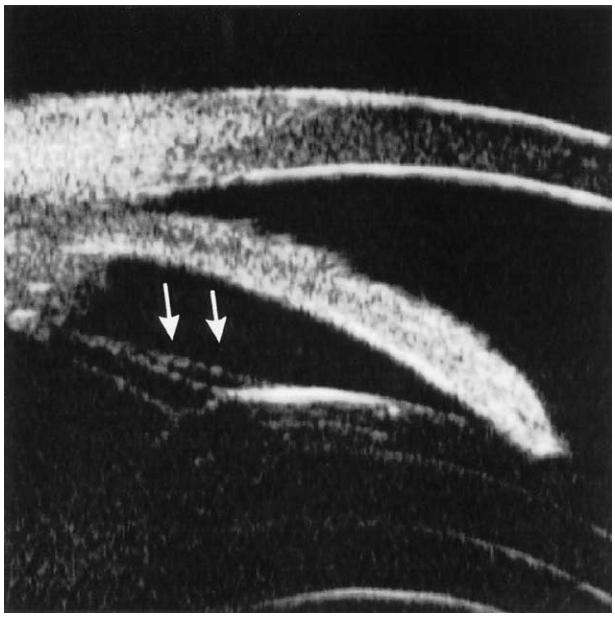

Figure 1. Ultrasound biomicroscopic image of the anterior segment in an exfoliation syndrome patient, showing granular-type zonules. The zonule is described as dots with no observable fibrous structure.

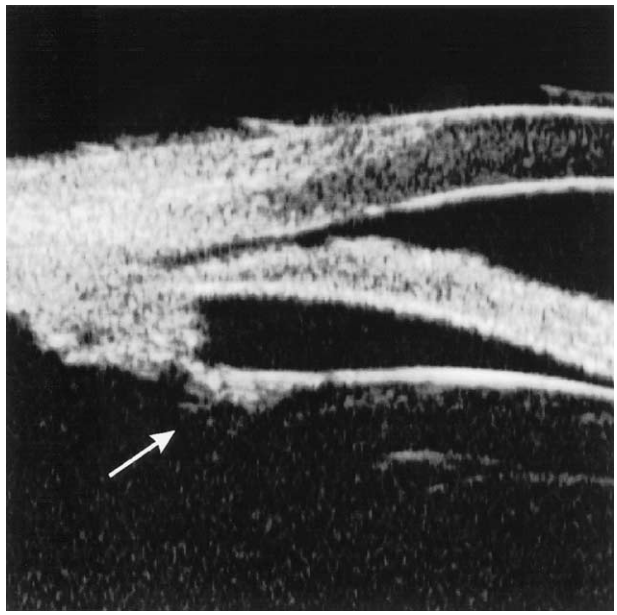

Figure 3. Ultrasound biomicroscopic image of the anterior segment of an exfoliation syndrome patient, showing fan-shaped zonule with a deposit on each fiber.

We used ultrasound to biomicroscopically examine the zonule of the three groups consisting of XFM-positive eyes in unilateral XFS patients, XFM-negative eyes in the same unilateral XFS patients, and healthy, control eyes without XFS. The incidence of granular-type zonules was significantly higher in the fellow eyes of the unilaterally affected eyes than in the healthy eyes. This fact led us to con-

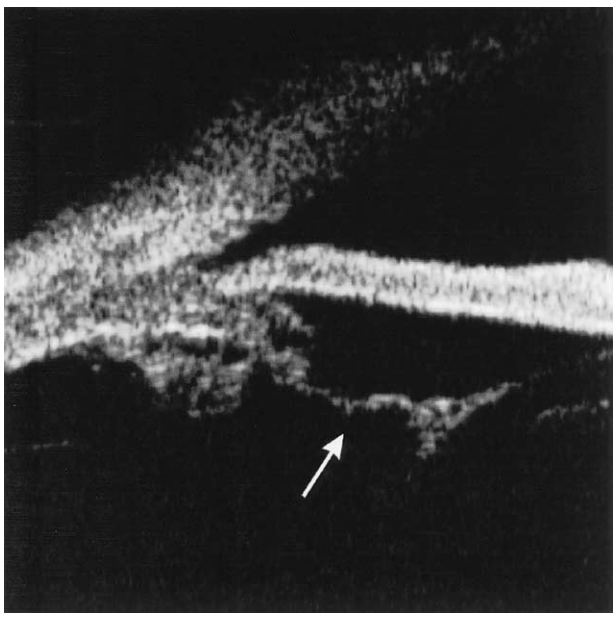

Figure 2. Ultrasound biomicroscopic image of the anterior segment in an exfoliation syndrome patient, showing winding-type zonule. The zonule shows winding with a sclerotic change.

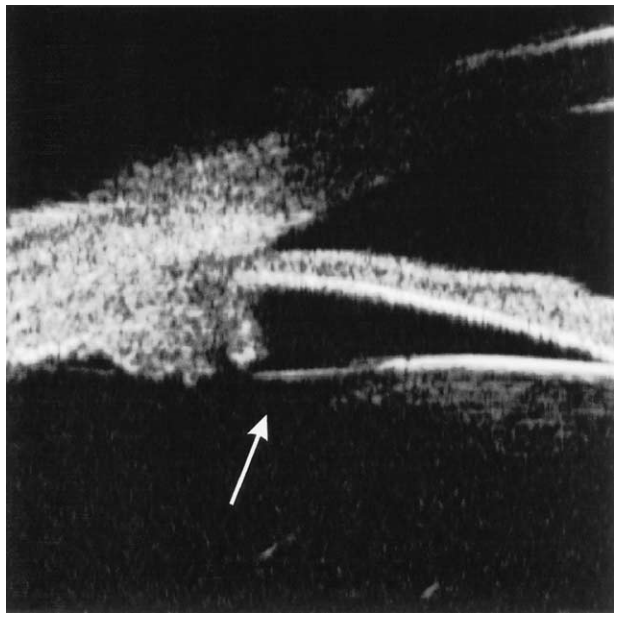

Figure 4. Ultrasound biomicroscopic image of the anterior segment of a control subject, showing a healthy zonule which is described as a straight, clear line, with each fiber structure evident.

Jpn J Ophthalmol
Vol 46: 502–509, 2002

Table 7. Number of Eyes That had Exfoliative Material (XFM)-Positive Zonules*

	Healthy Eyes	XFM-positive	XFM-negative	*P* Value
No. of eyes with XFM-positive zonule	6	11	10	$P < .05^{\dagger}$
No. of eyes without XFM-positive zonule	5	0	1	NS

*Total number of patients: 11 in each group.
†Fisher exact probability test, $P < .05$.

clude that this early and consistent characteristic of pseudoexfoliation may be detected by UBM.

While the cycloscopic observation of pseudoexfoliation in the zonule or ciliary processes was sometimes hindered by a cortical cataract,[10] there was no technical difficulty in describing the zonule in a UBM examination.

In a previous electron microscopic study of XFS, some types of degenerative changes in the zonular fibers were found.[16] One case with phakodonesis showed fragmented and degenerated zonular fibers with XFM. Another case with phakodonesis showed degenerated zonules and XFM. Cases without phakodonesis showed zonules with relatively normal shape and course with XFM.

In our observation of zonules in patients with clinically apparent XFS, there were three types of morphological changes of the zonules: granular type, winding type, and fan-shaped type. In the granular type, the zonules had a normal shape and course without a clear, straight, consecutive signal. These zonules appeared to consist of dots. This grade is thought to correspond to the findings in cases examined by electron microscopy showing zonules of relatively normal shape and course with XFM. In the winding type or fan-shaped type of zonule, there is an absence of normal course and shape, and no straight line is observed. By electron microscopy, this grade is characterized by fragments and degenerated zonular fibers mixed with XFM.

Ciliary processes and zonules encrusted with XFM have been observed by light microscopy.[17] Cycloscopy revealed bush-like zonules with XFM.[10] Comparing our findings in this study, there seems to be a clear correspondence of the fan-shaped zonules seen by UBM to the zonules encrusted with XFM or bush-like ones seen by cycloscopy. In addition, scanning electron microscopy has shown nodular exfoliation aggregates on zonular fibers[17] that correspond to the granular type zonules seen by UBM.

As shown in Table 7, in the 11 cases of unilateral XFS, 90.9% of eyes without apparent XFS had these kinds of zonular changes when examined biomicroscopically using ultrasound. This finding is consistent with those in a previous study.[10]

Direct visualization of the presence of XFM on the lens surface or pupillary border using slit-lamp biomicroscopy is the gold standard for the diagnosis of XFS. However, it is also possible to observe XFM on the zonule using UBM, which provides new information that may aid in our understanding of the pathophysiology of this disease. Examination by UBM is particularly useful when inadequate pupillary dilation or opaque media exists.

After completing this study, we believe that UBM has the potential to aid in the diagnosis and management of XFS.

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