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The Clinical Spectrum and a New Theory of Pathogenesis of True Exfoliation Syndrome

Chaiwat Teekhasaenee, MD,[1] *Yanin Suwan, MD,*[1] *Wasu Supakontanasan, MD,*[1] *Wasee Tulvatana, MD,*[2] *Robert Ritch, MD*[3]

Purpose: To describe the clinical spectrum and a new theory of pathogenesis of true exfoliation syndrome.
Design: Cross-sectional and prospective, observational case series.
Participants: Consecutive patients with characteristic peeling of the anterior lens capsule.
Methods: After maximal mydriasis, slit-lamp biomicroscopy, and photography, imaging of the anterior capsule and zonules was performed. The condition was classified into 4 clinical stages: annular anterior capsule thickening with a distinct splitting margin (stage 1), an inward detached crescentic flap lying on the anterior lens (stage 2), a floating and folding translucent membrane behind the iris (stage 3), and a broad membrane within the pupil (stage 4). Serial photography was performed at each 3-month follow-up visit. Ultrastructural examination of dislocated lenses and excised anterior capsules was performed.
Main Outcome Measures: Detached membrane morphologic features, zonular defects, pigment deposition, glaucoma, phacodonesis, and cataract.
Results: We enrolled 259 patients (424 eyes). Ages ranged from 52 to 97 years (mean age, 75.2±7.1 years). Eleven patients were associated with trauma (n = 1) or intense heat (n = 10), whereas 248 were idiopathic. Two hundred ten patients were followed up every 3 months, with a mean follow-up of 9.6±6.1 months (range, 3–50 months). The detachment started along the anterior zonular insertions in association with zonular disruption. It progressed centrally to higher stages, manifesting a spectrum of disease. Several stages coexisted in a single eye. At the final visit, including 49 patients who were examined once, there were 70, 87, 85, and 17 patients in stages 1, 2, 3, and 4, respectively. All stages shared common histologic findings consisting of diffuse capsular lamellar separation and anterior zonular disruption. All developed cataract. Pigment deposition on the membrane was present in 178 patients (68.7%). Twenty-six patients (10%) had spontaneous phacodonesis. Eighteen eyes (4.2%) demonstrated secondary delamination.
Conclusions: Capsular lamellar separation and anterior zonular disruption are characteristic findings. Aging, heat exposure, and trauma are risk factors. Initial capsular splits occur along the insertions of disrupted anterior zonules. The peeling progresses centrally in association with iris movement and aqueous flow. A second detachment can occur. *Ophthalmology 2016;123:2328-2337 © 2016 by the American Academy of Ophthalmology*

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True exfoliation syndrome (TEX) or capsular delamination is characterized by the peeling of a translucent membrane from the anterior lens capsule. Major ocular complications include partial capsulorrhexis masquerade or double-ring sign (DRS)[1–5] and glaucoma.[2,6–11] Being exceedingly thin and hidden behind the iris, the membrane tends to be missed on routine examination. Several patients were diagnosed during surgery when the pupil was maximally dilated, allowing a bright red reflex or occurrence of the DRS.[1,3–5] Since it was first described in 1922,[12,13] 121 cases of TEX have been reported in 37 English and Japanese articles (85 patients diagnosed by the presence of the membrane, 25 diagnosed by the DRS, and 11 diagnosed by histologic examination).[1–11,14–39] Most were small case series. The largest series diagnosed by the presence of the membrane comprised 18 patients.[10] Furthermore, those who were diagnosed by the DRS or histologic examination lacked clinical details. We describe the clinical spectrum and propose a new theory of pathogenesis of TEX in the largest series (259 patients) to date.

Methods

The study was approved by the Ramathibodi Institutional Review Board/Ethics Committee and followed the Declaration of Helsinki. Informed consent was obtained. From January 9, 2012, through April 13, 2016, Thai patients older than 50 years seen in our glaucoma and general eye services, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, underwent complete ocular examination. Maximal mydriasis of more than 7.0 mm was performed in eyes with open angles or angle closure with patent laser iridotomy (LI). Those having characteristic circular anterior lens capsule thickening with a distinct splitting margin or a translucent detached membrane were enrolled. Histories of sustained intense

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heat exposure, ocular inflammation, trauma, and radiotherapy were recorded. Patients with pseudoexfoliation (PEX) material or the classic 3-ring sign and intraoperative DRS alone were excluded.

The membrane and the zonules were photographed with a photo slit lamp (Haag-Streit BX900, Haag-Streit AG, Switzerland). Membrane morphologic features, extent, and location were assessed in relation to the adjacent zonules. Pigment deposition on the membrane was recorded. Anterior segment imaging including ultrasound biomicroscopy (UBM; Aviso; Quantel Medical, Inc. France), Scheimpflug photography (Pentacam; Oculus, Optikgeräte GmbH, Wetzlar, Germany), and spectral-domain optical coherence tomography equipped with the Anterior Segment Module external lens kit (Spectralis; Heidelberg Engineering, Inc. Heidelberg, Germany) were performed to evaluate the membrane, lens position, and anterior chamber angles. Dynamic UBM was performed in a dark room when the pupils physiologically dilated, followed by shining a flashlight into the contralateral eye to induce miosis in the examined eye. The condition was classified into 4 successive stages based on characteristic changes in the anterior capsule, including annular capsule thickening with a distinct splitting margin (stage 1), segmental inward detachment along the margin exhibiting a crescentic flap lying on the anterior lens (stage 2), a floating and folding translucent membrane with a serpentine free edge behind the iris (stage 3), and a broad membrane within the pupil (stage 4). The highest stage was counted if several stages coexisted in an eye or the membrane unfolded and reverted to a lower stage. Similarly, the highest stage was counted in patients with bilateral asymmetrical involvement. Lens opacities were recorded as cortical or nuclear cataracts. Lens dislocation or subluxation was diagnosed by the presence of phacodonesis in correlation with A-scan immersion ultrasound biometry and imaging.

All patients were examined, photographed, and imaged at the initial examination by the first author (C.T.). Patients were followed up every 3 months and serial photography with or without imaging was performed at each visit. Patients with symptomatic cataracts underwent phacoemulsification and intraocular lens implantation. Capsulorrhexis was performed with a cystotome after trypan blue staining of the anterior capsule. Extreme care was taken to avoid iatrogenic injuries. Those with symptomatic anteriorly dislocated or subluxated lenses underwent intracapsular cataract extraction and scleral-fixated intraocular lens implantation. To preserve the delicate membrane, lenses were expressed manually through an oversized scleral incision. Cryoextractor and capsule forceps were avoided. The excised anterior capsules or extracted lenses were processed for light and transmission, for scanning electron microscopy, or both. The extracted lenses were halved and fixed in a position for scanning electron microscopy of the equator and the anterior and posterior surfaces. A search for TEX in the English and Japanese literature was performed. Incomplete clinical data in past reports were obtained formally from authors when possible.[14,26,37,40]

Results

Patient Characteristics

We enrolled 259 patients (424 eyes) comprising 118 men and 141 women. Mean age at initial presentation was 75.2±7.1 years (range, 52−97 years). Forty-nine patients were seen once and were either lost to follow-up or underwent cataract surgery. The others (n = 210) were followed up every 3 months. Mean follow-up was 9.6±6.1 months (range, 3−50 months). Ten patients had worked for more than 30 years in oven burning (n = 4), steel (n = 3) or gold (n = 1) smelting, steel welding (n = 1), or glass blowing (n = 1) without heat protection. A patient with unilateral TEX had an ipsilateral blunt contusion. The remaining 248 patients (138 women and 110 men) had idiopathic TEX. Fifty-five patients had undergone LI before presentation. At least 6 patients underwent LI with a neodymium:yttrium−aluminum−garnet laser. Initial location and extent of TEX did not correspond to the LI site in 31 patients; the others (n = 24) were not examined. None had uveitis or radiotherapy.

Laterality

On initial examination, 94 patients were phakic unilaterally and 165 patients were phakic bilaterally. Of the 94 unilaterally phakic patients, 2 had a history of heat exposure and 92 had idiopathic disease. Of the 165 bilaterally phakic patients, 8 had undergone heat exposure and had bilateral TEX, 1 had sustained blunt trauma and had ipsilateral TEX, and 156 had idiopathic disease. Of these 156 patients, 17 (9 in stage 1 and 8 in stage 2) had unilateral TEX and 139 had bilateral TEX. Mean age of the 17 unilateral patients was 69.7±6.2 years (range, 61−80 years) and mean age of the 156 bilateral patients was 75.2±7.4 years (range, 52−97 years). The 17 unilateral patients were significantly younger than the 156 bilateral ones ($P = 0.004$, Student's t test). Three of the 17 unilateral patients showed TEX in the contralateral eye during follow-up. Most of the 156 bilateral patients demonstrated TEX symmetrically in both stage and location between eyes (Table 1, available at www.aaojournal.org).

Clinical Spectrum of True Exfoliation Syndrome

The clinical spectrum of TEX is outlined in Table 2 (available at www.aaojournal.org).

Stage 1. The initial lesion appeared as a pale sector on the anterior lens with a curved distinct margin along the innermost anterior zonular insertions (Fig 1A). It typically occurred first in the nasal or temporal quadrant(s), or both, and progressively involved the inferior and superior quadrants successively, until a complete disc with a smooth sharp margin was formed. Disc diameters varied with anterior zonular insertions and patient age, ranging from 6.0 to 8.0 mm. The central disc appeared hazy, contrasting with the outer capsule, and could wrinkle. Specular reflection of the central capsule abruptly terminated along the disc margin (Fig 2A). Trypan blue staining of extracted dislocated lenses clearly accentuated the central disc (Fig 3, available at www.aaojournal.org). Slit-lamp biomicroscopy at high magnification (≥×25) of the disc margin revealed microscopic splitting and peeling of the anterior capsule. Tangential examination with a gonioscopy lens demonstrated subtle elevation of the splitting margin and missing anterior zonules (Fig 4A, available at www.aaojournal.org). Retroillumination highlighted the disc margin in locations whose anterior zonules were either sparse or absent (Fig 5, available at www.aaojournal.org).

Stage 2. Inward segmental peeling developed along the disc margin. It typically occurred before the central disc of stage 1 was formed completely. The detached membrane flipped centrally and lay flat on the central disc capsule, showing a characteristic narrow crescent with tapered, sharp ends (Fig 1B). The crescent typically occurred first in the nasal or temporal quadrant, or both, with the sharp ends situated at the 2-o'clock and 4-o'clock positions, the 8-o'clock and 10-o'clock positions, or both. Segmental peeling distorted the central disc and exposed the deeper layer of the capsule as a gray crescent exhibiting a mirror image of the flipped flap (Fig 2B). The denuded capsule slowly faded out and blended with the outer capsule. The peeling occurred exclusively in the locations whose anterior zonules were missing and terminated wherever the zonules remained. Bordering zonules were always

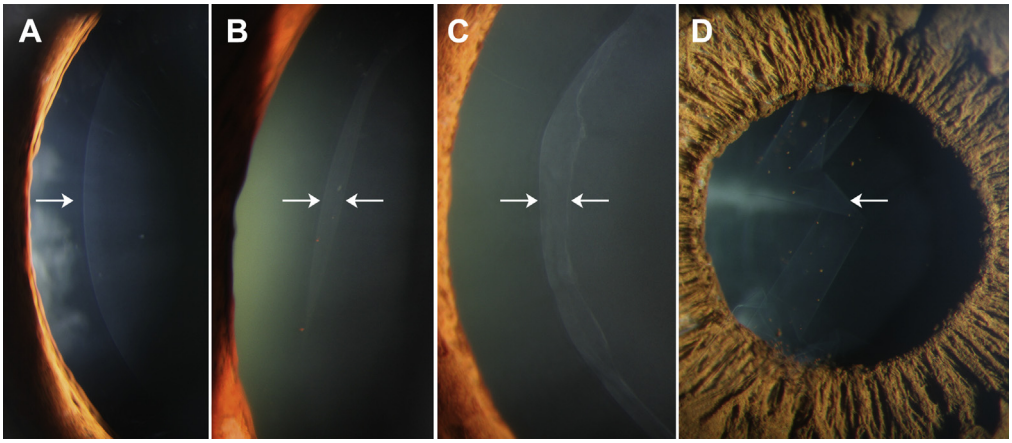

Figure 1. Slit-lamp photographs of successive true exfoliation syndrome stages. **A**, Stage 1, pale sector with distinct margin (*arrow*). **B**, Stage 2, flipped crescent flap with sharp terminal and straight edge (*arrows*). **C**, Stage 3, centrally curled membrane with serpentine edge (*arrows*). **D**, Stage 4, floating membrane within pupil (*arrow*).

present in front of the terminals of the detached flap (Fig 6A, available at www.aaojournal.org). Also, junctional zonules were always present between 2 adjacent flaps (Fig 6B, available at www.aaojournal.org). Gonioscopy revealed disappearance of the anterior zonule with persistence of the corresponding posterior zonules. In addition, lens equatorial notching arising from reduced zonular tension could be observed (Fig 4B, C, available at www.aaojournal.org). The detached flap elongated circumferentially and broadened radially. Serial photographs demonstrated that disruption of the bordering zonules preceded the elongation (Fig 7). The zonular degeneration progressed from the inserting end toward the ciliary end (Fig 6A, available at www.aaojournal.org, and Fig 7). The flap terminal elongated after the deformed zonules totally disappeared. Similarly, when the junctional zonules disrupted, the adjacent flaps merged together.

Stage 3. When the chord length of the crescentic flap elongated more than 90°, the lying crescent flap lifted from the central disc capsule and curled centrally (Fig 1C). The straight free edge became wavy. Progressive inward peeling broadened the detached membrane while correspondingly constricting the central disc. Further circumferential curling and radial folding transformed the curled membrane into a folding, fan-shaped structure. Since the last portion to detach lay in the superior quadrant, the incomplete central disc typically assumed a comet shape with an upward tail whose anterior zonules remained (Fig 8, available at www.aaojournal.org). When the superior zonules became totally disrupted, subsequent detachment resulted in a

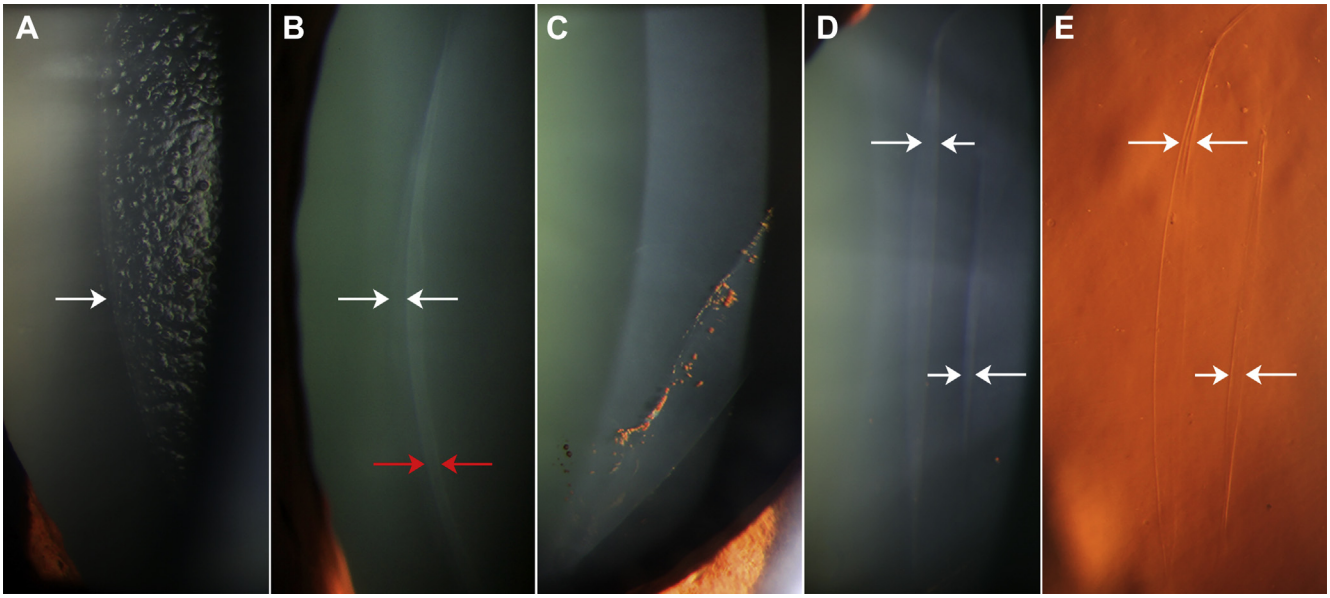

Figure 2. Slit-lamp photographs showing (**A**) abrupt termination of specular reflection along the central disc margin (*arrow*); (**B**) exposed lower layer of peeled capsule manifesting a gray crescent (*white arrows*) and a mirror image of the detached flap (*red arrows*); (**C**) pigment deposition along the free edge and on the anteriorly curled underside of a stage two crescent flap; and 2 parallel stage 2 crescent flaps (*arrows*) with sharp terminals photographed with (**D**) tangential illumination and (**E**) retroillumination.

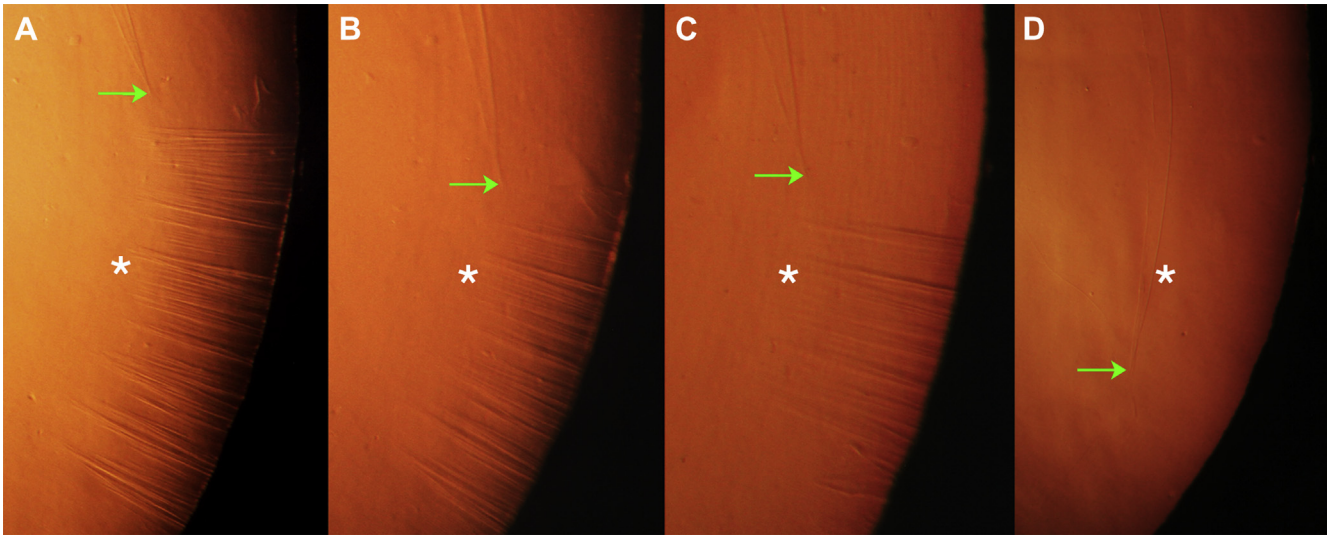

Figure 7. Serial retroillumination photographs (**A**, 3/2015; **B**, 6/2015; **C**, 10/2015; and **D**, 2/2016) of stage 2 true exfoliation syndrome revealing progressive anterior zonular disruption preceding elongation of the crescentic flap terminal (*green arrows*). Ciliary remnants of degenerative zonules remained along the lens equator. *Asterisks* represent corresponding locations.

bowl-shaped membrane around the central disc (Fig 9, available at www.aaojournal.org). The wavy free edge and the folding membrane glistened when illuminated and frequently demonstrated pigment deposition (Fig 10A, available at www.aaojournal.org). Six patients demonstrated limited membrane tearing and 2 showed shredded pieces attached to the inferior pupil border (Fig 10, available at www.aaojournal.org). Thickness of the membrane varied among individuals and also at various locations in an eye. A thicker membrane appeared more greyish and less translucent than a thinner one.

Stage 4. The broadest floating membrane appeared within the physiologic pupil and could protrude into the anterior chamber (Fig 1D). It stirred with eye and pupil movement and wobbled when limbal indentation was performed, forcing aqueous from the posterior to the anterior chamber. The confined membrane in the iris–lens channel and posterior chamber floated in the anterior chamber when the pupil dilated beyond the central disc. The broad membrane could reach the corneal endothelium in eyes with shallow anterior chambers (Fig 11A). Despite extensive detachment, the central disc was always preserved and never constricted beyond the pupil margin. Total separation of the membrane from the lens was never observed.

Combination and Progression of the Clinical Stages

The capsular detachment occurred irregularly in various locations, and multiple stages frequently existed in a single eye (Fig 8, available at www.aaojournal.org). There was sequential progression from the lower to higher stages accompanied by corresponding constriction of the central disc. During follow-up, 26 patients showed circumferential elongation of the detachment. Seventeen patients progressed from stage 1 to 2, 8 patients progressed from stage 2 to 3, and 1 patient progressed from stage 3 to 4. However, the membrane could unfold and revert to a lower stage. At the final visit, including those who were examined once (n = 49), there were 70, 87, 85, and 17 patients in stages 1, 2, 3, and 4, respectively. Average ages of the patients in stages 1 or 2 and in stages 3 or 4 were 73.5±7.2 and 77.8±6.0 years, respectively. Patients in stage 1 or 2 were significantly younger than those in stage 3 or 4 ($P < 0.001$, Student's t test).

Double Delamination

Eighteen eyes demonstrated two parallel segmental flaps in stage 2 (n = 8; Fig 2D, E), stage 3 (n = 8), combined stages 1 and 2 (n = 1), and combined stages 2 and 3 (n = 1).

Pigment Deposition

Pigment deposition on the membrane was observed in 22 patients (31.4%), 58 patients (66.6%), 81 patients (95.2%), and 17 patients (100%) in stages 1, 2, 3, and 4, respectively. The deposition occurred locally as discrete granules or clumps of reddish-brown granules (Figs 1B, D and 2C). Two patients demonstrated diffuse iris pigment accumulation after trabeculectomy along the capsular split and cleavage.

Lens Displacement

Twenty-six patients with idiopathic TEX demonstrated spontaneous phacodonesis or anterior lens dislocation, of whom 14 also had angle-closure glaucoma and 2 had open-angle glaucoma. Twelve of them had undergone unilateral cataract surgery. Among the remaining 14 bilaterally phakic patients, 4 and 10 had unilateral and bilateral phacodonesis, respectively. Another patient with unilateral TEX demonstrated ipsilateral anterior lens dislocation and secondary angle closure after a severe blunt injury associated with hyphema (Fig 11A). Another with bilateral idiopathic TEX demonstrated unilateral lens dislocation after a mild blunt injury.

Lens Opacity

All patients demonstrated cataracts, predominantly nuclear sclerosis. Ninety-four eyes (22.2%) demonstrated visual disturbance requiring cataract surgery. During surgery, the peeling membrane in stages 2 through 4 could be extended centrally by anterior chamber injection with either balanced salt solution or, more effectively, a viscoelastic (Fig 12, available at www.aaojournal.org). The DRS (Fig 13, available at www.aaojournal.org) during capsulorrhexis

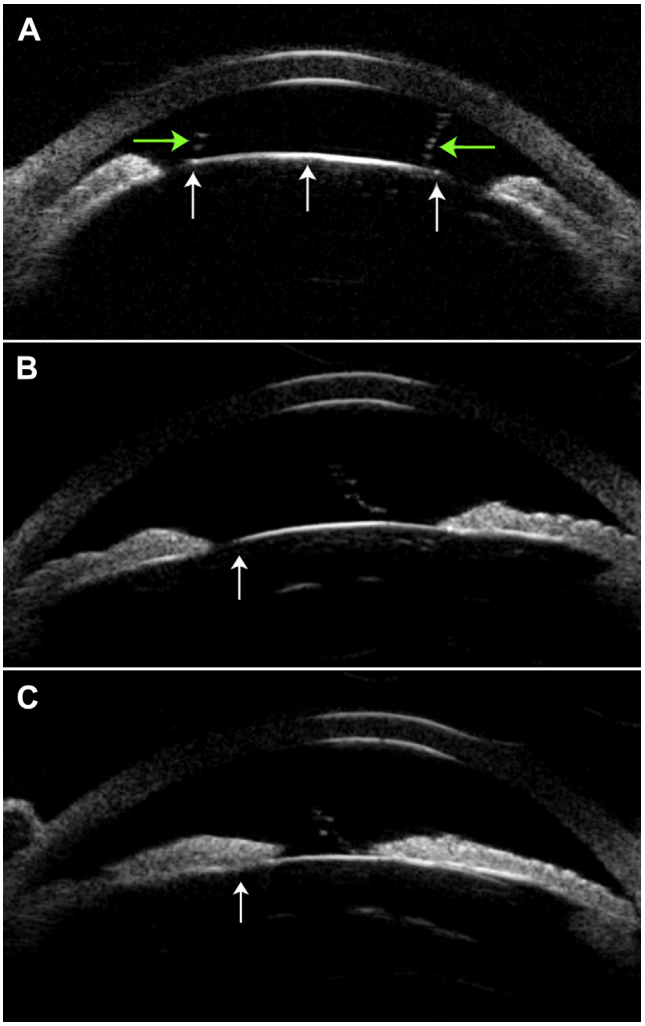

Figure 11. Ultrasound biomicroscopy (UBM) imaging of true exfoliation syndrome. **A**, An eye with anterior lens dislocation with secondary angle closure showing stage 3 floating membrane (*green arrows*) with pigment deposition (reflective dots) touching the corneal endothelium, thickened central disc capsule (*white arrows*), and paralytic mydriasis. **B**, **C**, Dynamic UBM in another patient (stage 4): (**B**) in the dark, when the pupil physiologically dilated beyond the central disc (*white arrow*), the membrane floated in the anterior chamber, and (**C**) subsequent induced miosis flattened and gathered the floating membrane within the pupil.

occurred in all clinical stages, although more frequently and extensively in stages 3 and 4. In eyes with combined stages, it typically occurred in the highest stage segment. Three eyes needed separate capsulorrhexis of the superficial and the deeper capsules. In eyes with spontaneous lens dislocation or subluxation, uneventful intracapsular cataract extraction was performed easily.

Glaucoma

Twenty-six patients demonstrated acute (n = 10) and chronic (n = 16) primary angle-closure glaucoma. Fifteen were primary angle-closure suspects. Fourteen demonstrated acute (n = 12) and chronic (n = 2) angle closure secondary to lens subluxation or dislocation. Forty-seven had primary open-angle glaucoma (POAG). Eleven patients with POAG also had preclinical signs of PEX, including radial pigmented deposits, mid-periphery clefts, and a faint central disc. The intraocular pressure control in glaucoma eyes with TEX was not notably different from that of those without TEX.

Imaging

The imaging devices successfully visualized the membrane and affected capsule (Fig 14, available at www.aaojournal.org). Image acquisition of a thicker membrane was more accessible than a thinner one. Pigmented deposits on the membrane appeared as hyper-reflective dots. The involved central capsule in all stages was thicker and more reflective than the peripheral unaffected one. Real-time UBM effectively illustrated dynamics of the membrane. When the pupil was in the physiologic position, stage 3 and 4 membranes were visualized floating within the pupil, lying on the anterior lens in the posterior chamber, or both. It could not be imaged in the iris–lens channel, whose space was too narrow for UBM resolving power. When the pupil physiologically dilated beyond the central disc in the dark, the entire broad membrane floated in the anterior chamber. When the pupil constricted in response to a consensual reflex, the floating membrane was flattened, unfolded, and gathered within the pupil (Fig 11B, C).

Histological Examination

Excised lens capsules and extracted lenses of patients with idiopathic TEX (n = 67) and those associated with trauma (n = 1) and heat (n = 1) underwent light microscopy (n = 67), transmission electron microscopy (n = 2), and scanning electron microscopy (n = 13). The examination revealed horizontal lamellar separation of the anterior layer of the capsule at various depths and a characteristic tapering rim that continued as a thin folding membrane (Fig 15A). In eyes with double delamination, the outer flap originated from a split in the deeper layer of the capsule. Entrapped pigment deposits consisted of dark melanin, erythrocytes, and eosinophilic materials (Fig 15B). The central anterior capsule was always thicker than the outer one. Maximal thickness of the detached flap varied from 6 to 15 μm in various locations in an eye and also among eyes. The excised capsules from eyes with various clinical stages had similar histologic findings, although more extensive lamellar dehiscence was observed in eyes with more advanced detachment TEX. Histologic findings in excised capsules with idiopathic TEX and those associated with trauma or heat were similar. Scanning electron microscopy of extracted lenses with early TEX (stage 1) showed the initial capsular split along the innermost anterior zonular insertions accompanied by sparseness of anterior zonules (Fig 16A). Those with more advanced TEX (stages 2–4) completely lacked the anterior zonules. The meridional and posterior zonules mostly were preserved. The equatorial and posterior capsules appeared intact (Fig 16B).

Discussion

Although originally described in individuals who had chronic intense heat exposure, TEX also has been reported to be associated with other factors. Among the 121 reported patients with clinical details, TEX was associated with heat (n = 19), uveitis (n = 2), trauma (n = 1), LI (n = 2), radiotherapy (n = 1), and abnormalities of protein components of the lens capsule (n = 1), although most were idiopathic (n = 78).[1–11,14–39] In our series, 248 cases were idiopathic, whereas 11 cases were associated with heat

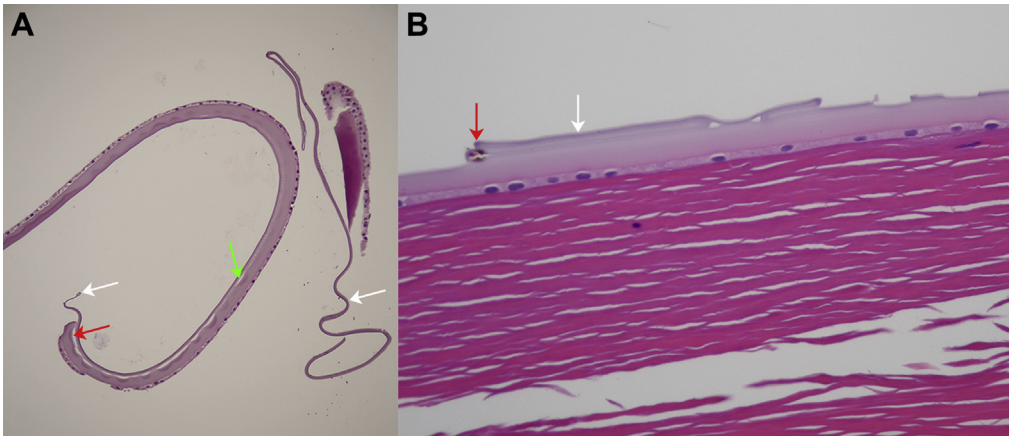

Figure 15. Light micrographs of stage 2 true exfoliation syndrome (TEX): (**A**) excised anterior capsule and (**B**) extracted lens of Figure 9 (available at www.aaojournal.org) (stage 3 TEX) stained with hematoxylin and eosin. **A**, Surface-parallel lamellar separation of anterior layer of lens capsule (*red arrow*) and folding membrane with characteristic tapered rim (*white arrows*). The separation occurred not only at the detached margin, but also in the central capsule away from the detached edge (*green arrow*). **B**, Entrapped pigment particle (*red arrow*) containing dark melanin and eosinophilic material in folding membrane (*white arrows*) above thickened central capsule.

(n = 10) or trauma (n = 1). Fifty-five of our idiopathic patients had undergone LI for angle closure. It was proposed previously that the laser energy was converted into heat after iris absorption and secondarily caused TEX.[2,11] However, the initial location and extent of the detachment in our patients did not correspond to the laser site. Although LI generally was performed superiorly under upper lids, the initial detachment occurred in the palpebral fissure. Our 6 patients whose LI was performed with a neodymium:yttrium−aluminum−garnet laser, which does not generate heat, demonstrated TEX. Furthermore, the preoperative dilated examination results were unavailable. The relation between LI and TEX remains questionable.

Our series consisted primarily of elderly patients in their eighth decade. Patients with unilateral idiopathic TEX were in the earlier stages (stages 1−2) and were 5.5 years significantly younger than those with bilateral involvement. Patients in stage 3 or 4 were 4.3 years significantly older than those in stage 1 or 2. The number of patients also increased linearly from stages 1 to 3, but declined in stage 4, possibly because of mortality or cataract surgery. Most reported patients also had advanced ages in or beyond the eighth decade.[5−7,10] Of the 121 reported patients with documented ages, the mean age was 76.9±10.6 years (range, 45−93 years).[1−11,14−39] Aging seems to be a significant risk factor for the development of TEX.

Twenty-one of 210 patients who were followed up regularly demonstrated sequential advancement of the detachment from the lower to higher stages. The progression was observed more frequently and rapidly in eyes with stage 1 or 2 disease than those with stage 3 or 4 disease. Three of the patients with unilateral idiopathic TEX demonstrated delamination in the contralateral eye. Progression could be observed within 3 months. Frequent and chronic use of pharmacologic mydriasis was suggested to participate in the development of TEX in a patient with uveitis and posterior synechiae.[18] Although unlikely, mydriasis every 3 months could be a possible accelerator in our patients. Our follow-up was limited by the presence of disturbing cataracts requiring surgery and patient mortality.

Double delamination is a new finding that has not been described previously. Histologic studies revealed that the outer detachment occurred deeper in the capsule than the inner one. The outer and inner detachments occurred separately, resulting in a combination of flaps in different stages. Second delamination typically occurred in the location where the most advanced initial detachment existed. It also followed the first detachment in morphologic features and orientation and eventually produced a similar parallel flap.

Pigment deposition on the membrane was a common associated finding in our patients with brown irides. In PEX, rubbing of the posterior iris and sphincter against the rough, rigid lens capsule liberates iris pigment. Released pigment granules characteristically align as radial spokes in the mid periphery of the anterior lens. They also disperse in the anterior chamber and deposit on several intraocular structures. We believe the pigment granules on the TEX membrane similarly derive from rubbing of the posterior iris and sphincter by the soft membrane. Undulating folds and the waving edge of the membrane not only scrape the iris, but also knead the released tissue. This kneading mixes and aggregates detached melanin and tissue debris into larger adhesive particles, analogous to making sticky bread dough or compacting soil. Histologic studies confirmed that the pigment deposition was composed of entrapped melanin granules and eosinophilic proteinaceous substances. The deposition was present locally along the surfaces of contact, including the splitting margin, free edge, anteriorly curled underside of the flipped membrane, and central disc. Real-time imaging showed pigment granules as hyper-reflective dots clinging to the waving membrane. Pigment adhesion was firm enough to remain on the membrane despite forceful anterior chamber irrigation. Although transient, it could persist on the membrane for a prolonged period of up to 2 years. In addition to iris rubbing, capsular split and cleavage also could trap iris particles released after surgery.

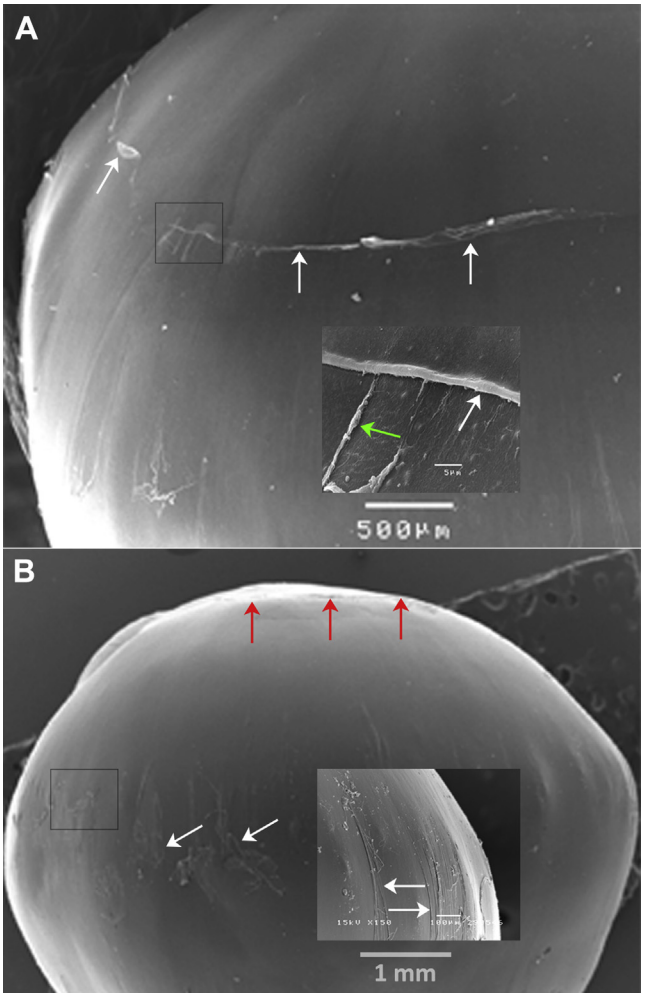

Figure 16. Scanning electron microscopy of dislocated lenses in Figures 3 and 9 (available at www.aaojournal.org). **A**, Stage 1 true exfoliation syndrome (TEX) capsular delamination (*white arrows*) along anterior zonular insertions (original magnification, ×35). Higher magnification of inset disclosed a peeling edge (*white arrow*) and reduced anterior zonules (*green arrow*; original magnification, ×3500). **B**, Stage 3 TEX membrane on anterior lens (*red arrows*) and complete absence of anterior zonules (original magnification, ×15). Higher magnification of inset revealed persistent posterior zonules (*white arrows*; original magnification, ×150).

The extent and prevalence of the deposition increased with disease advancement. More than 95% of the eyes with stage 3 or 4 disease demonstrated the pigment deposition.

There was a high prevalence (10%) of spontaneous phacodonesis and lens dislocation in our series. Phacodonesis was reported previously in 4 of 22 patients in a study.[5] The lens displacement in our patients occurred only anteriorly, resulting in acute (n = 12) and chronic (n = 2) secondary angle closure in 14 patients. Ultrastructural examination of the extracted lenses suggested that phacodonesis was associated with a lack of anterior zonular support.

Almost all previously reported patients with either heat-induced or idiopathic TEX had cataracts requiring surgery.[1–11,14–39] All our patients demonstrated lens opacities, predominantly nuclear sclerosis. It was suggested that the detached capsule exhibited abnormal permeability, disturbing lens metabolism.[12,20] Further investigation is needed to establish the association because aging and heat exposure[13] also cause cataract. In addition, whether TEX causes cataract or vice versa needs to be determined. Although capsulorrhexis in eyes with TEX is complicated by DRS, radial tears of the capsule were uncommon,[2,21,29] and most patients underwent uneventful phacoemulsification.[1,7,10,14,16,25,27,28] One of our 3 eyes that needed separate capsulorrhexis of the superficial and deeper capsules demonstrated a radial tear of the superficial one. The other 2 eyes demonstrated localized capsular bag dehiscence during cortical removal. In the absence of anterior zonular support, inadvertent aspiration of the anterior capsular tag could break the posterior zonules effortlessly. Similarly, the spontaneously dislocated or subluxated lenses also were expressed easily. Spontaneous dislocation of an in-the-bag intraocular lens has been reported in association with absence of the anterior zonules.[33]

Of the 121 reported patients, open-angle and angle-closure glaucoma were reported in 9 (7.4%) and 14 patients (11.6%), respectively.[1–11,14–39] Possible association between glaucoma and TEX has been suggested.[6,7,10] In our series, 47 patients (19.5%) demonstrated POAG, 26 patients (10.0%) demonstrated primary angle-closure glaucoma, and 15 patients (5.8%) were considered to be primary angle-closure suspects. Although the high prevalence of glaucoma in our series seemed to support the association, it may represent biased patient recruitment from glaucoma clinics or, less likely, may be accentuated by LI. In addition, subclinical PEX could coexist in the 11 patients with POAG who also manifested preclinical signs of PEX.

The translucent, centrally curled membrane with a smooth glistening edge in TEX is sufficiently characteristic to distinguish it from other acquired membranes, particularly in PEX[15,41] and uveitis. The granular, hazy, and thicker membrane in PEX has a serrated and turbid edge. The capsular peeling in PEX occurs along outer and inner edges of the central disc and peripheral ring, resulting in 2 separate membranes curling inward and outward, respectively. Pigment deposition in TEX occurs as discrete granules along the free edge of the membrane and in PEX as finer, radially oriented particles in the mid periphery of the lens. The pathognomonic so-called dandruff materials and the 3-ring sign unequivocally differentiate PEX from TEX. Although different, TEX and PEX can occur commonly in the same eye.[38,42] An iridocyclitic membrane occurs irregularly and frequently is accompanied by an anterior chamber reaction, synechiae, vascularization, and a distorted iris and pupil.

True exfoliation syndrome classically was diagnosed when a broad floating membrane (stages 3–4) was observed on the anterior lens. However, we found that it could be recognized earlier by the presence of the lying crescentic flap (stage 2) or the splitting capsule (stage 1) before the floating membrane developed. Our histologic studies of the excised capsules with various clinical stages showed typical structural alterations consistent with previous reports. Coexistence of several stages in a single eye, sequential progression from the lower to higher stages, and identical histologic findings suggested their common basic pathologic

features. Furthermore, previous studies in eyes manifesting intraoperative DRS alone showed similar histologic changes. The DRS has been considered a precursor or forme frust of TEX.[1,3,4] We believe our 4 clinical stages as well as DRS represent the same condition and constitute a spectrum of disease. Moreover, the similar histologic findings in idiopathic TEX and those associated with trauma and heat also suggested their universal pathologic nature.

Our study first demonstrated that the initial capsular rupture starts along the innermost disrupted anterior zonular insertions. The disruption began with zonular disinsertion followed by degeneration of the zonules toward the ciliary end. Our ultrastructural studies showed lamellar separation not only along the detached margin, but also in the central capsule away from the detached edge. The findings are consistent with previous reports.[3,4,25] Ultrasound biomicroscopy, spectral-domain optical coherence tomography, and Scheimpflug photography unanimously demonstrated generalized thickening and hyper-reflectivity of the central disc capsule before the zonular disruption. The findings suggested that the structural alterations were the primary event that diffusely affected the central capsule and consequently led to zonular disinsertion. It was recently shown that the anterior capsule is thinnest along the zonular insertions regardless of age. The thinning in an individual increases with aging.[43] It is possible that the zonular insertions may represent weakness in the anterior capsule. Zonular disinsertion could further aggravate the weakness and could provoke the initial splitting.

Our findings clarify why eyes with longer anterior zonules have correspondingly smaller initial central discs. Aging eyes demonstrate a central shift of the zonular insertions,[44] and thus have smaller discs. Our findings also explain why blunt trauma, which can disrupt the zonules directly, aggravates the detachment. However, it remains unclear why the initial rupture preferably occurs in the nasal and temporal quadrants followed by the inferior and the superior quadrants. An anatomic predisposition and eyelid protection are possible mechanisms. Of the 121 reported patients with documented races or ethnicities, there were 45 Japanese patients, 34 Chinese patients, 18 white patients, 1 Korean patient, 1 Arab patient, and 1 black patient.[1–11,14–39] The condition seemed to be reported predominantly in Asians. Our patients belong to Thai or Chinese ethnic groups inhabiting Southeast Asia. Dark brown irides, shallow anterior chamber depth, small aqueous volume, and tropical solar radiation possibly can increase heat formation and simultaneously decrease heat dissipation in the anterior chamber of Asian eyes.

There have been contradictory reports regarding thickness of the affected capsules.[1,4,14,17,29,31] Conflicting results may derive from inconsistent tissue orientation and planes of sectioning of the shapeless excised capsules. Our findings in the extracted lenses whose plane of sectioning was uniform across the entire capsule revealed that the affected central capsule was always thicker than the unaffected peripheral one. These findings agreed with their preoperative imaging that showed a generalized increase in thickness and reflectivity of the central disc capsule compared with the outer one. The abrupt change in specular reflection at the margin of the central disc also partially reflected differences in the capsular thickness. The reported detached membrane thickness ranged from 3 to 18 μm.[15,24,25,29,31] Our study similarly revealed variable thickness (6−15 μm) of the detached membrane not only among the eyes, but also at various locations within one eye. A thicker membrane appeared less translucent and was imaged more readily than a thinner one. We also found that the advanced membrane (stages 3−4) could split further into several thinner layers, consistent with a previous study.[31]

In addition to lamellar capsular separation, we believe mechanical peeling also actively participates in disease progression. Mydriasis previously was suspected to be involved in the capsule delamination in a patient with uveitis.[5] Dynamic UBM in our patients demonstrated that the floating membrane was stretched and flattened in the posterior chamber during miosis. The iris movement unfolded and gathered the stage 4 membrane centrally within the pupil. Iris pigment deposition, membrane tearing, and shredded membranes attached to the pupil margin affirmed the iris scraping. The finding that the detachment never progresses beyond the photopic pupil where iris−capsule contact is absent further supports our hypothesis. In addition to the iris motility, we believe physiologic aqueous flow in the iris−lens channel also contributes to membrane stripping. We found that the detached flap could be peeled centrally by injection of either a viscoelastic or a nonviscous solution. We observed the broad membrane within the pupil wobbling after limbal indentation, forcing aqueous from the posterior to the anterior chamber. The 3- to 18-μm-thick membrane confined in the narrow space of a 5- to 10-μm-high iris−lens channel could impede aqueous flow from the posterior to the anterior chamber. Built up backpressure in the posterior chamber could exert force on the packed membrane and peel it centrally, similar to the effect of anterior chamber irrigation. Induced aqueous flow during accommodation, blinking, and eye rubbing theoretically can generate more powerful exerted force. Smooth symmetrical movement of iris and aqueous flow delivers homogeneous peeling force to the membrane, and thus should not tear the membrane, unless nonuniform resistance from irregular capsular separation counteracts the homogeneous peeling. Eight of our patients demonstrated membrane tearing. As in previous reports, posterior capsule and posterior zonules in our study appeared to be undisturbed.[15,17,33]

In heat-associated TEX, it has been postulated that absorption of heat by the iris damages the lens epithelium. Degenerative epithelium leads to abnormal capsular lamellar construction and subsequent dehiscence.[13] The hypothesis logically explains why TEX originates behind the iris rather than in the pupillary zone that receives direct exposure.[2,6,11] Our study pinpointed the anatomic location where the capsular split initiates. In addition, our proposed mechanism of mechanical peeling by iris and aqueous combined with the finding that structural separation exclusively occurs in the anterior capsule clarifies why the membrane curls and progresses centrally and never completely detaches from the lens.

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[1] Department of Ophthalmology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

[2] Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[3] Einhorn Clinical Research Center, New York Eye and Ear Infirmary of Mount Sinai, New York, New York.

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Conception and design: Teekhasaenee, Suwan, Supakontanasan, Tulvatana, Ritch

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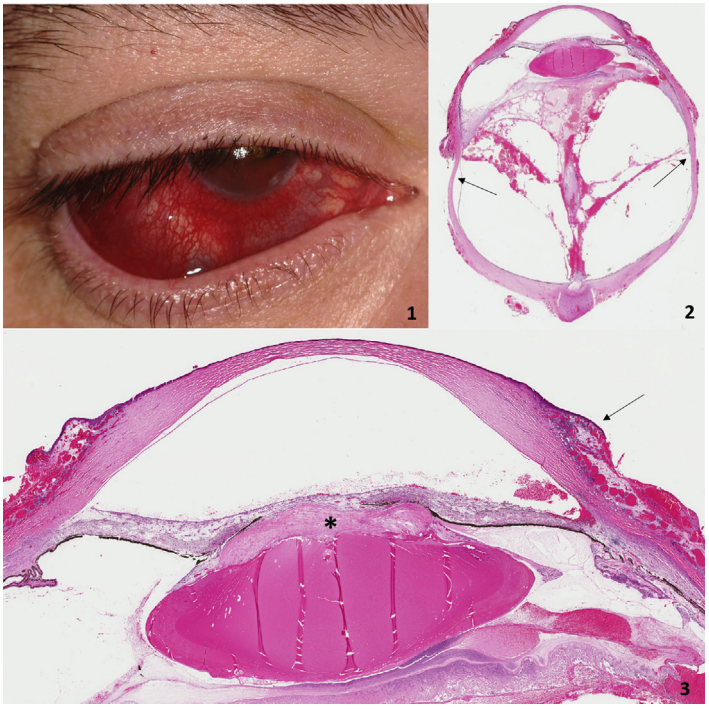
Abbreviations and Acronyms:
DRS = double-ring sign; **LI** = laser iridotomy; **PEX** = pseudoexfoliation; **POAG** = primary open-angle glaucoma; **TEX** = true exfoliation syndrome; **UBM** = ultrasound biomicroscopy.

Correspondence:
Chaiwat Teekhasaenee, MD, Department of Ophthalmology, Ramathibodi Hospital, Rama 6, Bangkok 10400, Thailand. E-mail: chai1391@gmail.com.

Pictures & Perspectives



Scleritis with Devastating Consequences

A 40-year-old man with a history of recurrent scleritis and corticosteroid-induced glaucoma developed a blind, painful eye with corneal and scleral ectasia. Histopathology revealed an enlarged globe with exceptionally thin sclera (Fig 2, *arrows*) and a chronic funnel retinal detachment. Severe lymphoplasmacytic inflammation with dilated, engorged vessels was seen throughout the conjunctiva (Fig 3, *arrow*). A fibrovascular membrane and hyphema covered the trabecular meshwork, iris, and pupil causing angle closure and pupillary occlusion. Fibrous metaplasia of the lens epithelium was also present (Fig 3, *asterisk*). Scleritis is a complex ocular inflammatory condition with the potential for sight-threatening complications.

Meisha L. Raven, DO
Christopher K.H. Burris, MD
Heather D. Potter, MD

Department of Ophthalmology and Visual Sciences, University of Wisconsin — Madison

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