Journal of Glaucoma

Atopic glaucoma—clinical and pathophysiological analysis

--Manuscript Draft--

Manuscript Number:	JOG-D-13-00144R3
Full Title:	Atopic glaucoma—clinical and pathophysiological analysis
Article Type:	Original Study
Keywords:	glaucoma; Atopic dermatitis; inflammation; Cytokines
Corresponding Author:	akira matsuda, MD, PD Juntendo University Graduate School of Medicine Tokyo, Tokyo JAPAN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Juntendo University Graduate School of Medicine
Corresponding Author's Secondary Institution:	
First Author:	Kanae Takakuwa
First Author Secondary Information:	
Order of Authors:	Kanae Takakuwa
	Teruhiko Hamanaka
	Kazuhiko Mori
	Shinki Chin
	Yasuhiro Shinmei
	Toshinari Funaki
	Nobuyuki Ebihara
	Koichi Ono, MD, PhD, MPH
	Akira Murakami
	akira matsuda, MD, PD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	JAPAN
Abstract:	Abstract Purpose: Open-angle glaucoma associated with severe atopic dermatitis (atopic glaucoma) tends to be severe and difficult to treat due to ocular surface/eye lid inflammation. To determine the validity of regarding atopic glaucoma as a clinical entity, we carried out retrospective analysis and pathological investigations. Methods: 45 cases (62 eyes) of atopic glaucoma were reviewed retrospectively. During surgical treatment, aqueous humor and scleral specimens were obtained. The aqueous humor samples were analyzed by multiplex cytokine assay. The surgical specimens were analyzed histologically. Results: Atopic glaucoma was often associated with atopic cataracts (43 eyes) and retinal detachments (19 eyes). A history of glucocorticoid medications was absent in 12 cases. A total of 50 eyes required surgical interventions due to advanced visual field defects and/or high intraocular pressures. Bleb associated post-surgical infections were observed in 7 eyes. Elevated levels of inflammatory cytokines (IL-8, and CCL2) were observed in the aqueous humor samples obtained from atopic glaucoma patients compared to those from senile cataract patients. Ultrastructural analysis of trabecular meshwork tissues obtained from atopic glaucoma patients showed abnormal accumulation of 10-30 nm fibers in the corneoscleral meshwork. Conclusion: We would like to propose atopic glaucoma as a new clinical entity, ranging from pure atopic glaucoma to a mixed type of atopic/steroid-induced

	glaucoma, that should be considered one of the clinical features of atopic ocular complications.

26/Oct /2013

Dr. George Cioffi
Editor-in-Chief
Journal of Glaucoma

Dear Dr Cioffi,

We greatly appreciate the valuable comments that we received from the reviewer concerning our manuscript titled "**Atopic glaucoma-clinical and pathophysiological analysis**" Here you will find our point-by-point responses to all of the instructive comments. We sincerely hope that you will now find our manuscript suitable for publication in *Journal of Glaucoma*.

Thank you very much for your kind consideration. I am looking forward to hearing from you.

Akira Matsuda MD, PhD

Department of Ophthalmology

Juntendo University School of Medicine

Tokyo, Japan

Reviewer #1: Much improved from the previous version. I still expect controversy but consider this a good thing

few minor points:
Conclusion of the abstract. The statement is too emphatic. You should propose a new clinical entity rather than saying 'is'

Thank you very much for your comment. As suggested, we changed the conclusion to the following: We would like to propose atopic glaucoma as a new clinical entity, ranging from pure atopic glaucoma to a mixed type of atopic/steroid-induced glaucoma, that should be considered one of the clinical features of atopic ocular complications.

Results:
Page 12: it is good you have added the results of other cytokines. However when you say 'most' samples were below the detectable limit, I am not sure what that means. Does that mean that some samples had a detectable concentration? If so, you should quantify that.

Thank you for your comment. As suggested, we described two samples that had a detectable concentration as follows:

The concentrations of other cytokines (IL-4, IL-5, IL-13, IFN-gamma and TNF-alpha) were below the detection limit except for IFN-gamma (17.13pg/ml) in one sample from patient No. 31, and IL-13 (1.75pg/ml) in a sample from patient No.42.

Reviewer #2: I think my concerns have mostly been addressed.

Minor comments:

Comment #1: It is the prior surgery for cataracts or retinal detachments that may be accounting for the glaucoma. The first Discussion paragraph and Figure 4 only mention the association with atopic cataracts and/or retinal detachment but does not mention their surgical treatments, which are well-recognized risk for secondary glaucoma. This should be mentioned in the Discussion.

Thank you very much for your comment. As suggested, we changed the discussion sentence to the following: Atopic glaucoma is open-angle glaucoma associated with severe atopic dermatitis, and often associated with atopic cataracts and/or retinal detachment and subsequent surgical treatments for cataracts and/or retinal detachment.

The added sentence to the Discussion on page 9, "it often required multiple medical/surgical treatments," may be misleading as there was a selection bias for the more "refractory" cases.

Thank you for your comment. As suggested, we deleted the sentence.

Atopic glaucoma—clinical and pathophysiological analysis

Kanae Takakuwa MD,[1] Teruhiko Hamanaka MD, PhD,[2] Kazuhiko Mori MD, PhD,[3] Shinki Chin MD, PhD,[4] Yasuhiro Shinmei MD, PhD,[4] Toshinari Funaki MD, PhD,[1] Nobuyuki Ebihara MD, PhD,[1] Koichi Ono MD, PhD, MPH, [1] Akira Murakami MD, PhD[1] and Akira Matsuda MD, PhD[1]

[1]Department of Ophthalmology, Juntendo University Graduate School of Medicine, Tokyo, Japan; [2]Department of Ophthalmology, Japan Red Cross Society Medical Centre, Tokyo, Japan; [3]Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan; [4]Department of Ophthalmology, Hokkaido University School of Medicine, Sapporo, Japan.

Correspondence to: Dr. Akira Matsuda, Laboratory of Ocular Atopic Diseases, Department of Ophthalmology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-Ku, Tokyo 113-8431, Japan. Tel: +81-3-5802-1228; Fax: +81-3-5689-0394

E-mail: akimatsu@juntendo.ac.jp

Funding: This study was supported by Grants-in-Aid from MEXT Japan (No. 24592652 to A. M.). **Conflicts of interest:** None to be declared for all authors.

Word count: 2227

Abstract

Purpose: Open-angle glaucoma associated with severe atopic dermatitis (atopic glaucoma) tends to be severe and difficult to treat due to ocular surface/eye lid inflammation. To determine the validity of regarding atopic glaucoma as a clinical entity, we carried out retrospective analysis and pathological investigations. **Methods:** 45 cases (62 eyes) of atopic glaucoma were reviewed retrospectively. During surgical treatment, aqueous humor and scleral specimens were obtained. The aqueous humor samples were analyzed by multiplex cytokine assay. The surgical specimens were analyzed histologically. **Results:** Atopic glaucoma was often associated with atopic cataracts (43 eyes) and retinal detachments (19 eyes). A history of glucocorticoid medications was absent in 12 cases. A total of 50 eyes required surgical interventions due to advanced visual field defects and/or high intraocular pressures. Bleb associated post-surgical infections were observed in 7 eyes. Elevated levels of inflammatory cytokines (IL-8, and CCL2) were observed in the aqueous humor samples obtained from atopic glaucoma patients compared to those from senile cataract patients. Ultrastructural analysis of trabecular meshwork tissues obtained from atopic glaucoma patients showed abnormal accumulation of 10-30 nm fibers in the corneoscleral meshwork. **Conclusion:** We would like to propose atopic glaucoma as a new clinical

entity, ranging from pure atopic glaucoma to a mixed type of atopic/steroid-induced glaucoma, that should be considered one of the clinical features of atopic ocular complications.

Key Words: Glaucoma; Atopic dermatitis; Inflammation; Cytokines

Introduction

Ocular complications of atopic dermatitis such as atopic keratoconjunctivitis[1], atopic cataracts[2] and retinal detachment[3], are well recognized. Although the relationship between atopic dermatitis and glaucoma was first suspected by Harris at 1960[4], the glaucoma associated with atopic dermatitis is often considered as an adverse effect of glucocorticoids, which are widely used for treatment of severe atopic dermatitis.

We would like to propose atopic glaucoma as a clinical entity for the following reasons. First, we experienced several patients with severe atopic dermatitis patients who had advanced glaucoma, but who had been refusing for glucocorticoid therapy due to the fear of adverse effects. Second, many atopic glaucoma patients showed had poor visual outcomes due to severe glaucomatous optic nerve changes and the coexistence of other atopy-related ocular complications like cataracts and retinal detachment. Third, atopic glaucoma often requires surgical interventions due to high intraocular pressure, and

tends to be severe glaucoma because of scar formation at the ocular surface.

In this study we retrospectively analyzed 45 atopic glaucoma patients, and describe the clinical features of atopic glaucoma. We also examined aqueous humor and trabecular meshwork tissue obtained from atopic glaucoma patients to investigate the effects of inflammation and status of aqueous outflow pathways.

Material and Methods

Patients

For this study, 45 patients with atopic glaucoma (62 eyes) were recruited from glaucoma clinic in Juntendo University Hospital, the Japan Red Cross Society Medical Centre, Kyoto Prefectural University Hospital, and the Hokkaido University Hospital in Japan. Detailed clinical information of the patients is summarized in Table 1.

Atopic dermatitis is a pruritic, typical eczematous dermatitis and its symptoms chronically fluctuate with remissions and relapses. All the patients had severe or very severe atopic dermatitis according to the criteria of atopic dermatitis of the Japanese Dermatological Society.[5] In the criteria, rashes with severe inflammation are observed on 10-30% of the body surface area in severe atopic dermatitis and more than 30% of the body surface area in very severe atopic dermatitis. All the patients had severe eczematous dermatitis on the face. Atopic glaucoma was defined as the presence of

severe or very severe atopic dermatitis with glaucomatous cupping having a vertical cup ratio of >0.7 and/or notching or saucerization with compatible visual field loss and IOP>21mmHg (Table 2). Clinical specimens (aqueous humor and trabecular meshwork tissues) were obtained from patients during glaucoma surgery and/or cataract surgery after receiving written informed consent. For aqueous humor analysis, we excluded the samples from patients with glucocorticoid usage. All procedures were approved by the ethical committee of Juntendo University, the Japan Red Cross Society Medical Centre, Kyoto Prefectural University of Medicine, and Hokkaido University and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Multiplex cytokine analysis of aqueous humor

Multiplex cytokine analysis was carried out using the Bio-Plex Pro custom-made immunobeads assay (measuring IL-4, IL-5, IL-6, IL-8, IL-13, IFN-gamma, MCP-1, and TNF-alpha) and Bio-Plex 200 suspension array system purchased from Bio-Rad Laboratories Inc. (Hercules, CA), according to manufacturer's protocols. The volume of aqueous humor obtained from patients was 150-200μl, depending on the condition of the eye. The aqueous humor was kept frozen until the multiplex cytokine analysis. For multiplex assay, 50μl of aqueous humor was used in one well, and the analysis was carried out in duplicate. All the samples were assayed together in one batch. Clinical

information on the patients is summarized in Table 3.

Ultrastructural analysis of trabecular meshwork tissue.

Ultrastructural analysis of trabecular meshwork tissue was carried out as previously described.[6] In brief, blocks of human trabecular meshwork tissues obtained during TLE surgery were fixed with a mixture of 1% formalin and 1% glutaraldehyde. We examined 3 trabecular meshwork tissue samples from atopic glaucoma patients (cases no 6, 7, and 11) and 18 specimens from primary open angle glaucoma (POAG) patients (17 to 84 years old, including three samples from patients with prior histories of cataract surgery). The samples were embedded in epoxy resin and ultrathin sections were made. The ultrathin sections were then examined using a transmission electron microscope (JEM-1010; JEOL, Tokyo, Japan).

Results

Clinical characteristics of atopic glaucoma (Table 4)

Atopic glaucoma was often associated with atopic cataracts (43 eyes, 69.4%) and retinal detachments (19 eyes, 30.6%). The onset of and surgery for cataract and retinal detachment were before the onset of glaucoma. The typical gonioscopic finding for atopic glaucoma was open angle without any specific changes. A history of glucocorticoid medications was absent in 12 cases (14 eyes, 22.6%) and no recent usage

was noted for 6 cases (8 eyes, 12.9%), and the remaining cases used glucocorticoid ointments. A total of 50 eyes (80.6 %) required surgical intervention (trabeculectomy, trabeculotomy or tube implant surgery) due to advanced visual field defects and/or high intraocular pressure, and multiple surgical procedures were carried out for 23 eyes (37.1%). Bleb-associated post-surgical infections were observed in 7 eyes (11.3%). The highest intraocular pressure was 39.4 ± 8.8mmHg (mean ± standard deviation).

Analysis of aqueous humor obtained from atopic glaucoma patients

High levels of three inflammatory cytokines (IL-6, IL-8, and CCL2) were detected in the aqueous humor samples obtained from atopic glaucoma patients (n=5) compared to those of control (senile cataract [n=9] and POAG [n=6]) patients. (Figure 1) The concentrations of other cytokines (IL-4, IL-5, IL-13, IFN-gamma and TNF-alpha) were below the detection limit except for IFN-gamma (17.13pg/ml) in one sample from patient No. 31, and IL-13 (1.75pg/ml) in a sample from patient No.42. The Kruskall-Wallis test was employed to determine if there were significant differences in the medians of IL-6, IL-8, and CCL2 among the 3 groups, i.e. atopic glaucoma, senile cataract, and POAG. All pairwise comparisons were performed using the Wilcoxon rank sum test. Any rank sum test with a p-value < 0.016666 (=.05/3) was judged statistically significant (Bonferroni-corrected alpha). The IL-8 and CCL2 concentration of atopic

glaucoma samples were significantly higher than in senile cataract samples but there was no significant difference between atopic glaucoma and POAG samples. There was no significant difference in the IL-6 concentrations among the three groups. Statistical analysis was performed using Stata/SE 11.2 for Windows (Statacorp, Texas, US).

Histological analysis of trabecular meshwork tissues obtained during surgery.

Ultrastructural analysis of trabecular meshwork tissue from atopic glaucoma patients showed deposition of 'electron-dense microtubules of 10-30nm'[7] in the spaces of corneoscleral meshwork and juxta-canalicular tissue (JCT). (Figure 2 and Supplementary Figure 4, arrows). In POAG eyes, the 10-30 nm fibers (Figure 3B, arrows) were observed in JCT, but mostly with elastic fibers (Figure 3B, open arrows) and intermingled with granular materials (Figure 3B, arrowheads). Conspicuous deposition of 10-30 nm fibers in the corneoscleral meshwork was observed in the samples from atopic glaucoma patients. This abnormal accumulation of 10-30 nm fibers was not observed in any of the samples obtained from POAG patients.

DISCUSSION

In this study we presented a case series of atopic glaucoma. Atopic glaucoma is open-angle glaucoma associated with severe atopic dermatitis, and often associated with atopic cataracts and/or retinal detachment and subsequent surgical treatments for

cataracts and/or retinal detachment. Of the 45 cases, 12 cases had no history of glucocorticoid usage, and 6 were glucocorticoid free for more than 6 months at the time of diagnosis (Table 1 and 4). In the remaining 27 cases, glucocorticoid ointment was used but we excluded those cases showing an apparent relation between the glucocorticoid usage and intraocular pressure.

Several clinical features of atopic glaucoma were noted: (1) frequent association with middle-aged males (mean age 38.13, male:female ratio, 4:1), with a long history of chronic atopic dermatitis, consistent with male-dominant occurrence of atopic retinal detachment (male:female ratio, 1.75:1) in Japan[3], (2) severe IOP elevation with significant visual field loss and corresponding defects of retinal nerve fiber/glaucomatous cupping was also observed (Supplementary Figure 3). The highest intraocular pressure (IOP) among atopic glaucoma patients was 39.4 ± 8.8mmHg, which was higher than the average IOP of POAG patients in the Tajimi study (15.2-15.4mmHg, 115 subjects) [8] and the IOP of patients treated with intravitreal triamcinolone acetonide (only 3 of 172 patients showed IOP>35mmHg, 3 months after injection).[9] Among our 45 cases of atopic glaucoma, both eyes were affected in 17 and the other 28 were unilateral. As is the case of glaucoma in exfoliation syndrome [10], the fellow eyes of atopic glaucoma may be affected subclinically. Considering the relatively young age of

atopic glaucoma patients, the rate of bilateral cases may increase further with aging.

Atopic glaucoma often requires surgical intervention. In some cases trabeculotomy (TLO) is successful; however, re-elevation of IOP is common after TLO surgery due to unknown reasons. This clinical feature is different from glucocorticoid-induced glaucoma, which is generally well controlled by TLO surgery.[11] Complications of trabeculectomy (TLE) are common among atopic glaucoma patients, and include encapsulated blebs, leaking blebs, bleb infection, a reduced filtration due to fibrosis and previous buckling surgery (Table 4, Supplementary Figure 1 and 2). The rate of bleb infection for TLE with mitomycin-C among cases of atopic glaucoma (7 of 62 eyes, 11.3%) was higher than the reported incidence of bleb-related infections in POAG (2.1-5.7%). [12] [13]

We found significantly higher IL-8 and CCL2 expression in the aqueous humor samples obtained from atopic glaucoma patients than in those from patients with senile cataracts (Figure 1). We excluded all the samples from the patients with a history of glucocorticoid use, which may have affected the results of cytokine analysis. Since two previous studies showed elevated IL-8 protein in the aqueous humor of POAG patients compared to the control samples, [14] [15] elevated IL-8 and CCL2 expression may represent a common pathological pathway between atopic glaucoma and POAG. However,

considering inflammatory nature of atopic glaucoma, it was our surprise to find no significant differences of IL-6, IL-8 and CCL2 expression between atopic glaucoma patients and POAG patients (Figure 1). The large variations of IL-6 and CCL2 concentrations among the atopic glaucoma samples suggested that the IL-6 and CCL2 levels might be fluctuate depending on the disease stages (Figure 1). The limitations of our cytokine assay were the relatively small number of samples and the lack of age and gender matching between the cases and controls. In addition, there may have been effects of prior ocular surgery because three of the five atopic glaucoma cases had prior cataract and/or retinal detachment surgeries. Further cytokine assay is ongoing in our laboratory to clarify the effects of glucocorticoid use, and of flare-up and remission of atopic inflammation.

Ultrastructural analysis of trabecular meshwork tissue obtained from atopic glaucoma patients showed deposition of electron-dense fibers with a diameter of around 10-30 nm (Figure 2 and supplementary Figure 4, arrows). The same 10-30 nm fibers were found in JCT and trabecular beams of POAG eyes (Figure 3, arrows). The abnormal 10-30 nm fiber depositions in atopic glaucoma did not accompany the elastic fiber component, whereas the 10-30nm fibers observed in the subendothelial spaces and trabecular beams of the POAG samples accompanied elastic fibers (Figure 3B, open arrows). Originally

the 10-30nm filaments or fibers were called oxytalan filaments or electron-dense filaments associated with elastic fibers.[7] These 10-30nm fibers were also reported as "connecting fibrils" which connect between innerwall cells and ciliary muscle, and serving as the ciliary muscle tendon.[16] In the POAG eye, the 10-30 nm fibers also intermingled with granular materials in the POAG eye (Figure 3B, arrowheads), which are a component of the sheath of the elastic fibers and thought to be aging materials.[16] Although the 10-30nm fibers may not be specific to atopic glaucoma, their abnormal accumulation in the trabecular meshwork without an elastic fiber component might be related to some pathological feature of atopic glaucoma. It also should be noted that these '10-30 nm electron-dense fibers' were different from the 'fingerprint-like arranged material resembling basement membranes' observed in glucocorticoid-induced glaucoma.[17]

In conclusion, we would like to propose atopic glaucoma as a clinical entity. Although there is a spectrum of diseases from pure atopic glaucoma to a mixed/overlapping type with glucocorticoid induced-glaucoma (Figure 4), atopic glaucoma tends to be severe glaucoma associated with inflammatory responses.

Acknowledgements: The authors thank Prof. Julian M. Hopkin (Swansea University,

UK) for his invaluable continuous support.

Figure Legends

Figure 1. Cytokine analysis of aqueous humor

Parallel box plots of cytokine concentrations of aqueous humor are shown. Significantly higher IL-8 and CCL2 expression is observed in the aqueous humor samples obtained from atopic glaucoma patients (n=5) than in the samples obtained from senile cataracts (n=9) (Bonferroni-adjusted p-value: p<005), but no significant difference was observed between atopic glaucoma and POAG patients (n=6). No significant difference was observed for IL-6 expression among the three groups (Kruskal-Wallis multiple comparison: p-value=NS).

Figure 2. Ultrastructural analysis of a trabeculectomy specimen from the atopic glaucoma patient

Transmission electron microscopy photographs of inner-wall cells of Schlemm's canal and the juxtacanalicular meshwork (JCT). A tissue sample obtained during a trabeculectomy (TLE) operation (case no. 7 in Table 2) was analyzed. Toluidine blue staining of the TLE specimen (A) and transmission electron microscope (TEM) images (B, C, D) of the trabecular meshwork tissue are shown. Increased magnifications of the

boxed area are shown in the order A to D. 10-30nm microtubules are indicated by arrows (D). S: Schlemm's canal.

Figure 3. Ultrastructural analysis of a trabeculectomy specimen from a POAG patient

Ultrastructural analysis of a trabeculetomy specimen from a POAG patient (61 years old, male) Transmission electron microscopy photographs of Schlemm's canal (S) and the trabecular meshwork. Figure 3B is a large magnification of the boxed area in Figure 3A. Elastic fibers (open arrows in Figs. A and B) are observed in the juxta-canalicular meshwork and the trabecular beams in the corneoscleral meshwork. In higher magnification (Figure B), 10-30nm fibers (small arrows) are clearly seen adjacent to the elastic fibers (open arrow) and granular materials (arrowheads).

Figure 4. Concept of atopic glaucoma and overlapping with glucocorticoid-induced glaucoma

Atopic glaucoma can appear as pure atopic glaucoma to mixed atopic/glucocorticoid-induced glaucoma. In the pure form of atopic glaucoma, the atopic dermatitis tends to be severe, often accompanied by atopic cataract and retinal detachment, and no history of glucocorticoid usage.

References

1. Foster CS, Calonge M. Atopic keratoconjunctivitis. Ophthalmology 1990; 97:992-1000.
2. Hori K, Matsuda A, Ebihara N et al. Involvement of plasminogen activator inhibitor-1 in the pathogenesis of atopic cataracts. Invest Ophthalmol Vis Sci 2012; 53:1846-1851.
3. Hida T, Tano Y, Okinami S et al. Multicenter retrospective study of retinal detachment associated with atopic dermatitis. Jpn J Ophthalmol 2000; 44:407-418.
4. Harris JL. Glaucoma associated with steroid therapy and atopic dermatitis. Am J Ophthalmol 1960; 49:351-353.
5. Katayama I, Kohno Y, Akiyama K et al. Japanese guideline for atopic dermatitis. Allergology international : official journal of the Japanese Society of Allergology 2011; 60:205-220.
6. Hamanaka T, Takei A, Takemura T et al. Pathological study of cases with secondary open-angle glaucoma due to sarcoidosis. Am J Ophthalmol 2002; 134:17-26.
7. Ghadially F. Elastic fibers, elaunin fibers, and oxytalan fibers. In: Ultra Structural Pathology of the Cell and Matrix. Boston: Butterworth-Heinemann; 1997: 1352-1359.
8. Iwase A, Suzuki Y Araie M et al. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 2004; 111:1641-1648.
9. Jonas JB, Degenring RF, Kreissig I et al. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology 2005; 112:593-598.
10. Ritch R. Exfoliation syndrome. In: The Glaucomas. St. Louis: Mosby-Year Book; 1996: 993-1022.
11. Iwao K, Inatani M, Tanihara H. Success rates of trabeculotomy for steroid-induced glaucoma: a comparative, multicenter, retrospective cohort study. Am J Ophthalmol 2011; 151:1047-1056.
12. DeBry PW, Perkins TW, Heatley G et al. Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. Arch Ophthalmol 2002; 120:297-300.
13. Bindlish R, Condon GP, Schlosser JD et al. Efficacy and safety of mitomycin-C

in primary trabeculectomy: five-year follow-up. Ophthalmology 2002; 109:1336-1341.
14. Kuchtey J, Rezaei KA, Jaru-Ampornpan P et al. Multiplex cytokine analysis reveals elevated concentration of interleukin-8 in glaucomatous aqueous humor. Invest Ophthalmol Vis Sci 2010; 51:6441-6447.
15. Takai Y, Tanito M, Ohira A. Multiplex cytokine analysis of aqueous humor in eyes with primary open-angle glaucoma, exfoliation glaucoma, and cataract. Invest Ophthalmol Vis Sci 2012; 53:241-247.
16. Rohen JW, Futa R, Lutjen-Drecoll E. The fine structure of the cribriform meshwork in normal and glaucomatous eyes as seen in tangential sections. Invest Ophthalmol Vis Sci 1981; 21:574-585.
17. Johnson D, Gottanka J, Flugel C et al. Ultrastructural changes in the trabecular meshwork of human eyes treated with corticosteroids. Arch Ophthalmol 1997; 115:375-383.

Figure 1
Click here to download high resolution image

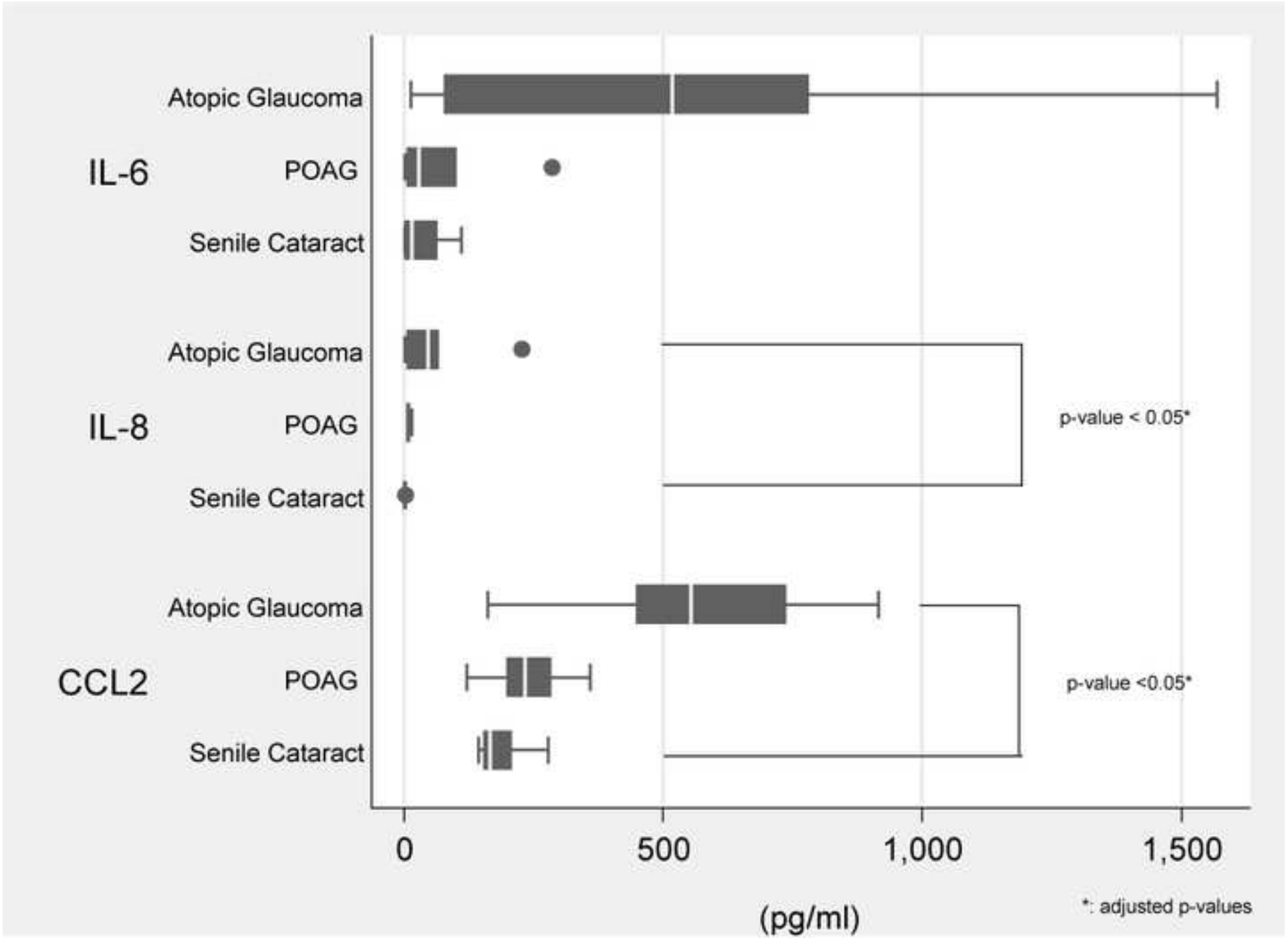

Figure 2
Click here to download high resolution image

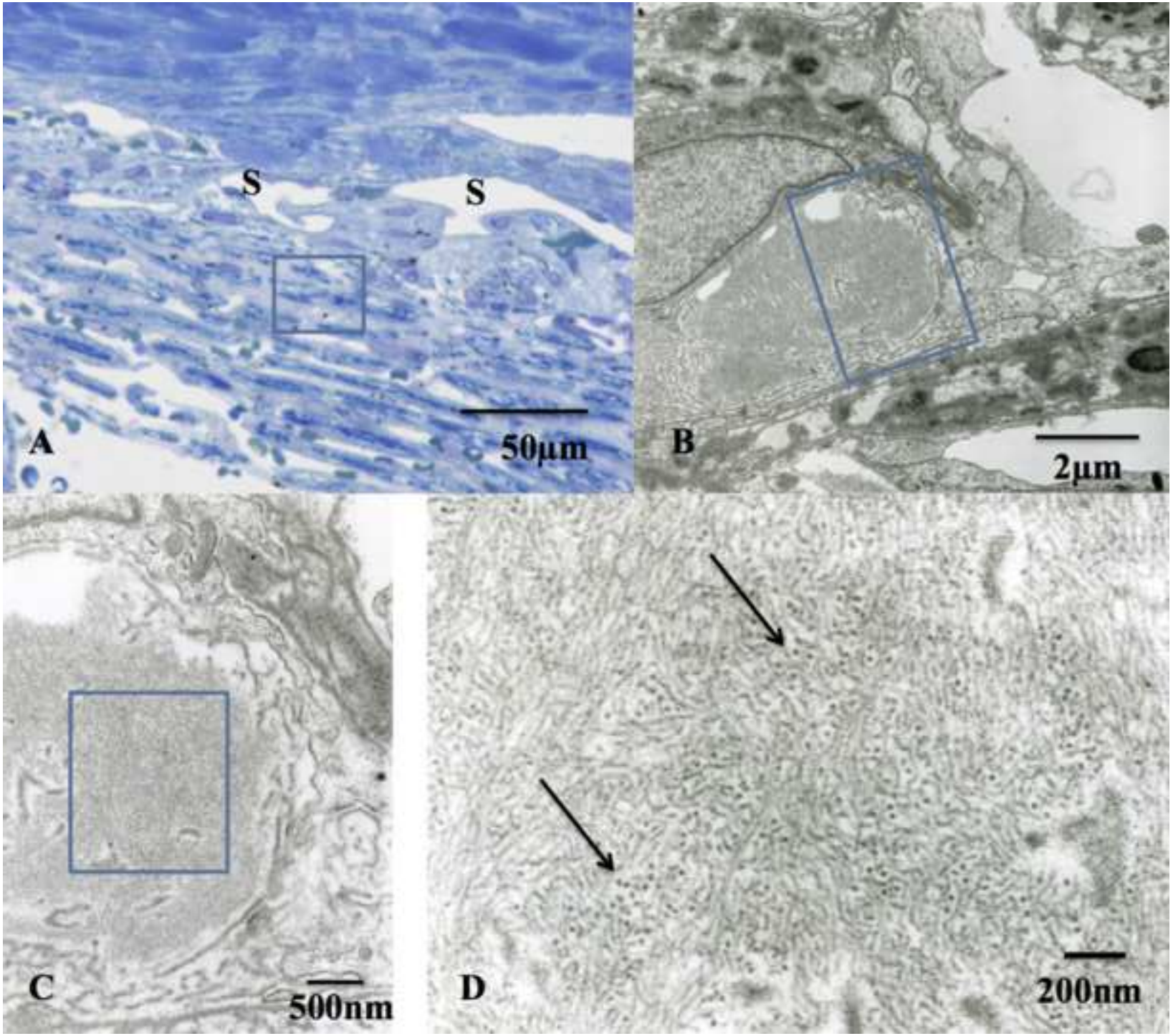

Figure 3
Click here to download high resolution image

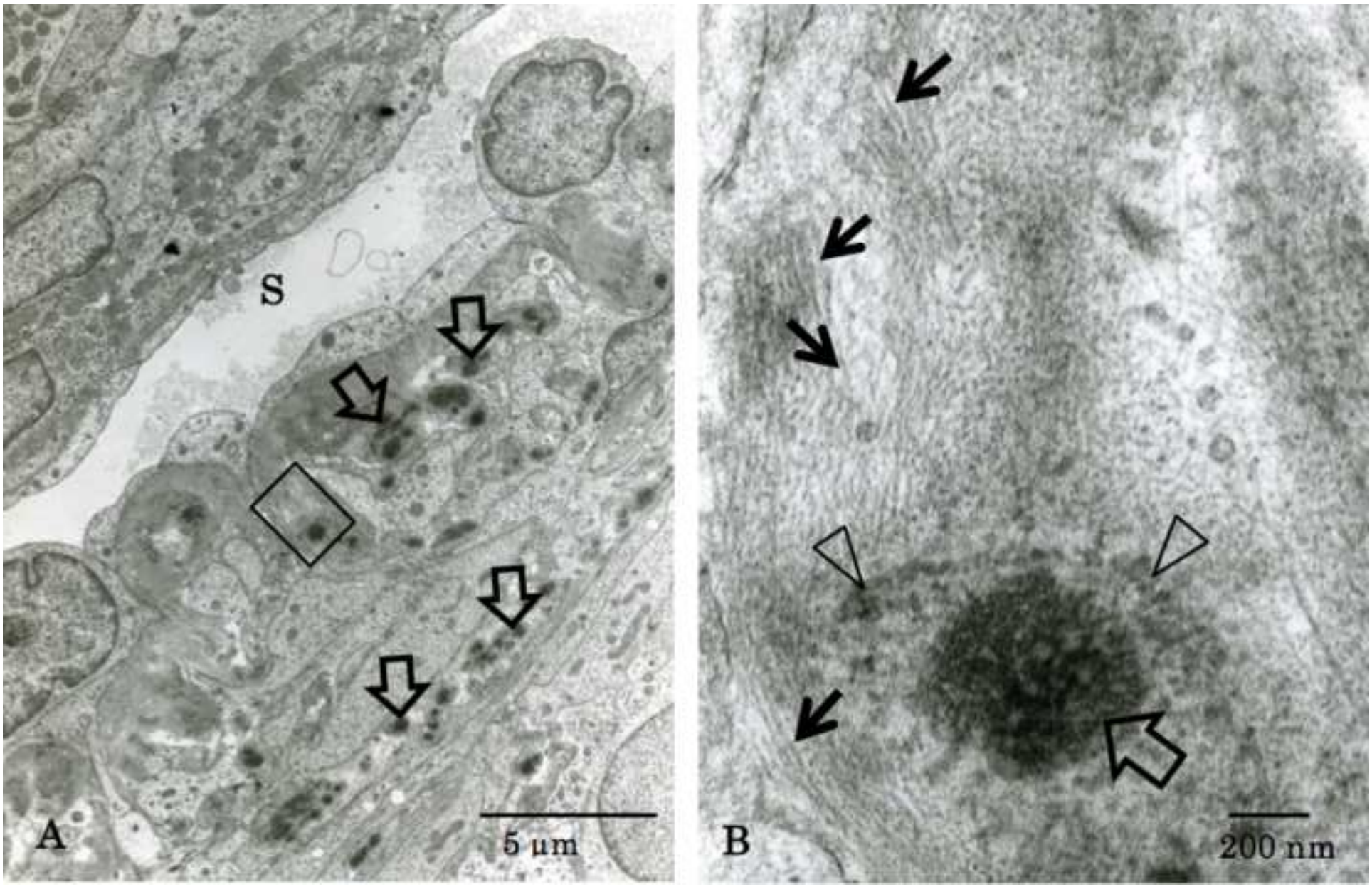

Figure 4
Click here to download high resolution image

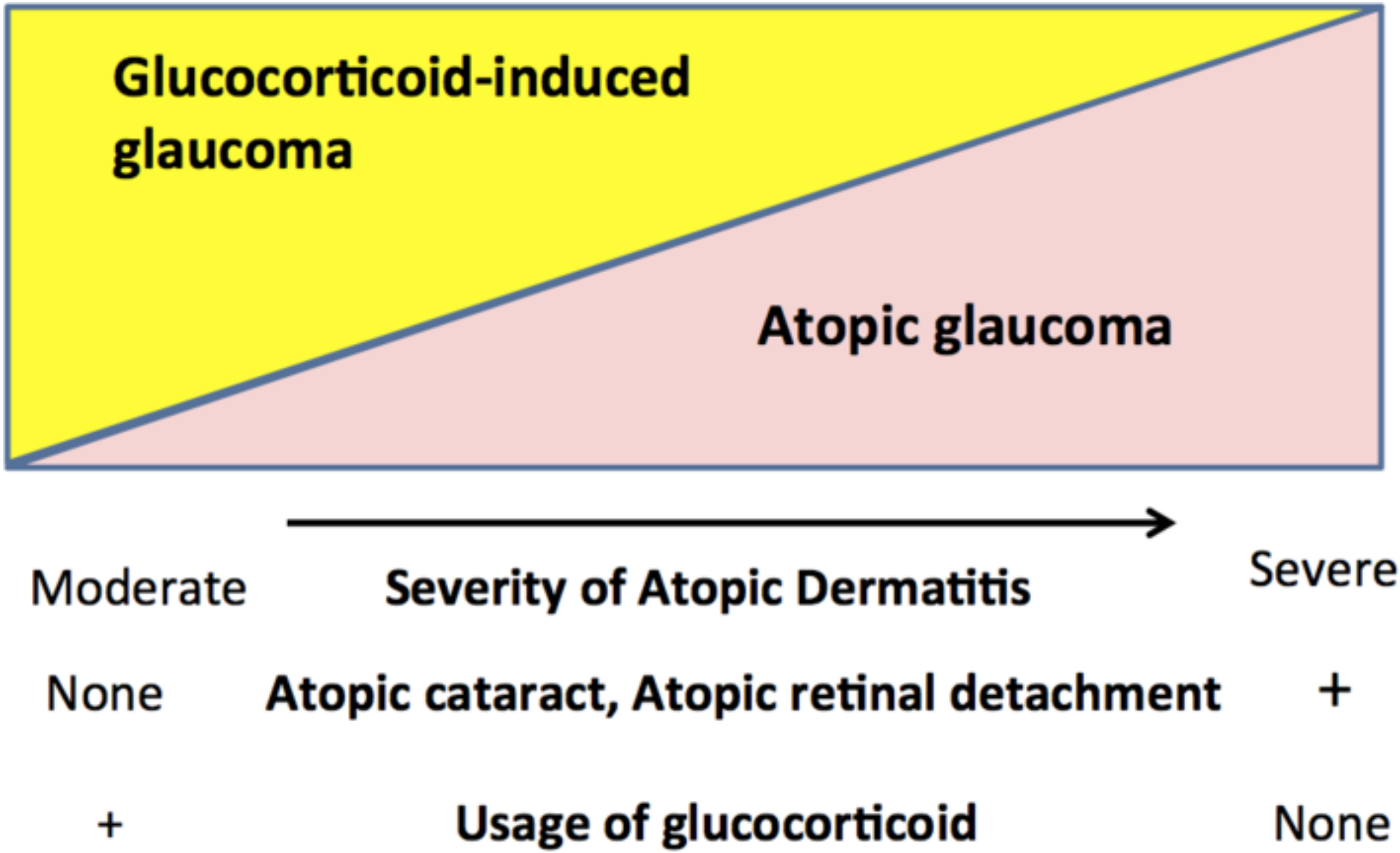

Table 1
Click here to download high resolution image

Table 1. Clinical characters of the atopic glaucoma patients

Total subjects	45 (62 eyes)
Mean age	38.13 (17-68y)
Male:Female ratio	4:1
Affected eyes	Bilateral:17, Right only: 18, Left only:10
Cataracts	43 eyes (both eyes, 18; unilateral, 7)
Retinal Detachment	19 eyes (both eyes, 5; unilateral, 9)
Atopic Dermatitis	Very Severe: 35 cases, Severe: 10 cases
Glucocorticoid usage	27 cases: Topical glucocorticoid
	12 cases: No history of glucocorticoid usage
	6 cases: More than 6 months of wash period

Table 2
Click here to download high resolution image

Table 2. Diagnostic criteria of Atopic glaucoma

1. Presence of severe or very severe atopic dermatitis, including on their face
2. Glaucomatous cupping having a vertical cup ratio of > 0.7 and/or notching or saucerization
3. Presence of compatible visual field loss
4. IOP>21mmHg
5. No apparent relation between glucocorticoid usage and intraocular pressure

Table 3
Click here to download high resolution image

Table 3. Clinical information of aqueous humor analysis

	Sex	Mean age	
Atopic glaucoma	5 males	41.2 (27-50y)	(Patients 30, 31, 32, 42, 44)
POAG	3 males and 3 females	63.0 (46-91y)	
Senile cataract	3 males and 6 females	69.3 (58-77y)	

Table 4

Click here to download high resolution image

Table 4. Clinical information of the atopic glaucoma patients

									Glucocorticoid				
Case	Age at Diagnosis	Sex	Maximum IOP	Visual Field	Affected Eyes	Cataract	Retinal Detachment	Blebitis	Glucocorticoid Usage	Part of Usage	Frequency	Wash out period	Glaucoma Operation
NO-1	33	M	R31 L24	R2	R	-	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	Every 3days		R TLO, R TLE
NO-2	20	M	R41 L23	R1	R	-	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	Occasional		R TLO, R TLE
NO-3	41	M	R31 L23	R1	R	R+ L+	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	Occasional		R TLE
NO-4	44	F	R42 L16	R2	R	-	-	+	Topical	Face	Occasional		R TLE
NO-5	34	M	R41 L23	R2, L1	B	-	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	Occasional		R TLE
NO-6	26	M	R50 L20	R5	R	R+	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	Occasional		R TLE
NO-7	44	M	R48	R5, L1	B	-	-	-	Topical	Face, eyelid (Ophthalmic Ointment)	No recent useage	16 years	R TLE
NO-8	46	M	R30 L55	R5, L6	B	R+	-	-	Topical	Body trunk	No recent useage	2 years	R TLO, R TLE, L TLE, LTLE
NO-9	27	M	R45 L30	R5	B	-	-	-	Topical	Head only	Occasional		R TLE L TLO
NO-10	43	M	Unknown	R5	R	R+	R+, L+ (PVR)	-	Topical	Face, eyelid (Ophthalmic Ointment)	No recent useage	6 years	R TLE
NO-11	31	M	L50	L5	L	L+	L+	-	Topical	Face	No recent useage	6 month	L TLE
NO-12	68	M	R41	R6	R	R+	R+	-	Topical	Face	No recent useage	11 years	R TLO, R TLE
NO-13	41	M	R38	R1	R	-	-	-	None (Tacrolimus)				R TLO, R TLE
NO-14	39	M	R46, L40	R6, L5	B	R+, L+	L+	R+L+	Topical	Face	Occasional		R TLO (2times), R TLE, L TLO, L TLE (5times)
NO-15	47	M	L31	R3, L4	B	R+, L+	-	-	Topical	Face	Occasional		R TLO (2times), L TLO (5times), L TLE
NO-16	32	M	R44,L47	R6, L4	B	-	-	-	Topical	Body trunk	Occasional		R TLO (2times), R TLE, L TLO, L TLE
NO-17	61	M	R51	R6, L5	B	R+, L+	-	-	Topical	Face	Occasional		R TLE
NO-18	24	M	R38,L35	R6, L6	B	-	-	-	Topical	Face	Daily		R TLO, L TLO
NO-19	33	F	R34	R4, L5	B	R+, L+	-	-	Topical	Body trunk	Occasional		R TLE
NO-20	26	M	R44	R5, L2	R	-	-	-	Topical	Face	Occasional		R TLE
NO-21	37	F	L39	R2, L5	B	R+, L+	R+, L+	-	Topical	Body trunk	Occasional		L TLO (2times), L TLE
NO-22	40	M	L28	R3, L3	B	R+, L+	L+	L+	Topical	Face	Occasional		L TLO (2times)
NO-23	45	M	R37 L17	R6, L1	R	-	-	-	Topical	Face	Occasional		R TLO
NO-24	23	F	R39, L40	R5, L4	B	-	-	-	Topical	Face	Occasional		R TLO, L TLO
NO-25	35	M	R51, L19	R6	B	R+	-	-	Topical	Body trunk	Occasional		RTLO, RTLE (2times)
NO-26	45	F	R23, L38	L3	L	R+,L+	-	-	Topical	Body trunk	Rare		LTLO, LTLE
NO-27	48	M	R22, L42	R5, L2	B	-	-	-	Topical	Face	Occasional		RTLE, LTLO
NO-28	37	M	R15, L33	L6	L	-	-	-	Topical	Face	Occasional		LTLO
NO-29	42	M	R18, L47	L3	L	-	-	-	Topical	Face	Daily		LTLO
NO-30	50	M	R38	R5	R	R+, L+	R+, L+ (PVR)	-	None				RTLO, R Tube implant, R TLE
NO-31	45	M	L52	L5	L	R+, L+	-	-	None (Tacrolimus)				L TLO (2times)
NO-32	27	M	R40	R5	R	-	-	-	Topical	Face	Occasional		
NO-33	17	M	R33	R4	R	R+, L+	L+ (PVR)	-	None				R TLE (2times)
NO-34	37	M	R36	R6	R	R+, L+	L+ (PVR)	-	None				
NO-35	31	M	Unknown	R6, L1	R	R+, L+	R+,L+	-	None				
NO-36	24	M	R32	R6	R	R+, L+	-	-	None				
NO-37	60	M	R32	R2	R	R+	-	-	Topical	Face	Occasional		R TLO
NO-38	37	M	L32	L2	L	R+, L+	L+	-	None				L TLO
NO-39	34	F	Unknown	R5, L5	B	-	L+	-	None				RTLE, L TLE
NO-40	33	F	L38	L3	L	-	-	-	Topical	Body trunk	Occasional		L TLO
NO-41	45	F	L30	L4	L	R+, L+	-	-	Topical	Fluorometuronne eye drops for VKC	No recent useage	20years	L TLO, L TLE
NO-42	43	M	R50, L33	R5, L1	B	-	-	-	None				R TLO, R TLE
NO-43	33	M	L46	L2	L	R+, L+	L-	L+	Topical		Occasional		L TLO, L TLE, L Tube implant
NO-44	41	M	R60	R4	R	R+, L+	R+ L-	R+	None				R TLO , R TLE, R Tube implant
NO-45	51	F	Unknown	L5	L	-	-	L+	None				L TLE

Supplemental Data File (tif, pdf, etc., PDF Preferred)
Click here to download Supplemental Data File (tif, pdf, etc., PDF Preferred): Supplementary Figures 1-4.docx

*LWW Copyright Transfer and Disclosure Form
Click here to download LWW Copyright Transfer and Disclosure Form: copyrightTransfer-akira matsuda.pdf