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- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma
- To increase the understanding of such disorders through reporting of educational activities
- To publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders
- To work closely with Asian and international researchers to achieve these aims
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- To maintain and promote relationships with any organisation with similar goals.

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PUBLICATION SCHEDULE 2014-2015:

2014	
September 2014	**14-1**
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October 2014	**14-2**
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2015	
February 2015	**14-4**: *Special issue on Generic Medications*
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Asian Journal of Ophthalmology is the peer-reviewed journal for The Asian Pacific Glaucoma Society (APGS), The Asia Pacific Ophthalmic Trauma Society (APOTS) and all others with an interest in Ophthalmology.

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Focus and scope

As new technologies and therapeutic interventions are continually being developed, Ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. Asian Journal of Ophthalmology was established in 1998 with the aim of disseminating information relevant to Ophthalmology and glaucoma throughout Asia and to interested groups worldwide.

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- To provide a platform for the publication of information with a focus on Ophthalmology in Asia.
- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma.
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- To work closely with Asian and international researchers to achieve these aims.
- To provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform.
- To maintain and promote relationships with any organization with similar goals.

Although the focus of Asian Journal of Ophthalmology mainly was on glaucoma with close ties to the South-East Asian Glaucoma Interest Group (SEAGIG) in the past, the journal now focuses on the entire spectrum of Ophthalmology. This resulted in collaboration with the Asia Pacific Ophthalmic Trauma Society (APOTS).

The Asian Journal of Ophthalmology and Kugler Publications have started to collaborate since mid 2012 on the publication of the journal. A new website has been launched (www.asjoo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

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Asian Pacific Glaucoma Guidelines 3

The Asia Pacific Glaucoma Society (APGS) is moving ahead with preparation of the 3rd Edition of our popular Glaucoma Guidelines that are distributed and read widely across the Asia-Pacific Region. The last edition (then known as the SEAGIG Guidelines was published 6 years ago), this version was downloaded thousands of times per year since 2003. The APGG are a very important educational tool for the Asia-Pacific region and are widely used.

This latest edition of the Guidelines will be co-chaired by Profs. Aung Tin (Singapore) and Jonathan Crowston (Melbourne). Currently the Working party is researching and preparing the necessary updates. It is estimated that the e-book version will be ready in February 2015, with an official publication launch planned during the World Glaucoma Congress 2015 (Hong Kong June 6-9, 2015)

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Ultrasound biomicroscopic comparison of primary open-angle glaucoma and primary angle-closure glaucoma eyes in dark and light conditions

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Abstract

Background: *With the use of ultrasound biomicroscopy, we aim to look at differences in anterior segment parameters of eyes with primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) in dark and light conditions.*

Methods: *Ultrasound biomicroscopy was performed for 30 subjects with PACG and 30 subjects with POAG at initial presentation before any treatment. Measurements of angle opening distance (AOD-500 and AOD-750) and trabecular-iris space area (TISA-500 and TISA-750) 500 and 750 mm from the scleral spur in both dark and light conditions were made. Anterior chamber depth (ACD) and axial length (AL) were also measured.*

Results: *The mean age of PACG patients was 67.6 ± 9.6 years and POAG patients 62.1 ± 13.9 years. The mean ACD (2.70 ± 0.53mm) in PACG patients was significantly different from that (3.32 ± 0.52mm) of POAG patients ($p<0.0001$). There were also significant differences ($p=0.0004$) in the mean AL of PACG (22.91 ± 0.86mm) and POAG (24.47 ± 1.67mm) patients. Significant differences between POAG and PACG eyes were found for TISA-500, TISA-750, AOD-500 and AOD-750 in both light and dark conditions ($p<0.001$ for all). The light-dark differences in PACG eyes were smaller than that of POAG eyes for all AOD and TISA values in the inferior, superior, nasal and temporal quadrants. However, with the exception of AOD-750 in the inferior quadrant ($p=0.0524$), there were no significant differences in light-dark changes between POAG and PACG eyes for all parameters in the 4 quadrants.*

Conclusions: *Ultrasound biomicroscopy is a useful tool in the diagnosis and management of glaucoma. We found significant differences in mean AL, ACD, TISA-500, TISA-750, AOD-500 and AOD-750 between PACG and POAG eyes. However, there were no significant differences between PACG and POAG eyes in terms of light-dark difference in anterior segment parameters, except for AOD-750 in the inferior quadrant. Further evaluation of the above findings could be done in future with a larger population*

Key words: *Imaging, Ultrasound biomicroscopy, PACG, POAG*

Introduction

Ultrasound biomicroscopy (UBM) is a useful tool in the diagnosis and management of glaucoma, and has revolutionized the evaluation of the anterior segment of the

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eye.[1] It has the capacity to produce high-quality images of anterior segment parameters, and readily images the ciliary body and other structures behind the iris, thus contributing greatly to our understanding of glaucoma and other anterior segment disorders.

The reproducibility of anterior chamber angle measurements of UBM has been shown to be comparable with anterior segment optical coherence tomography (ASOCT).[2] There have been numerous articles describing and comparing these anterior segment imaging tools.[3-5] The analysis of angle closure eyes with ASOCT and UBM has also been described, showing them to be highly sensitive in detecting angle closure when compared with gonioscopy.[6-9] However, there have not been any studies comparing anterior segment parameters of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) patients at initial presentation with UBM.

Our study aims to look at differences in anterior segment parameters of eyes with POAG and PACG in both dark and light conditions.

Methods

This was a prospective comparative study of new patients with POAG or PACG, who presented to the National University Health System, a tertiary eye care center in Singapore, from January 2002 to June 2009. These were newly-diagnosed patients, with no previous treatment or laser therapy done. The patients, who presented with unrelated eye conditions, were found to have clinical signs suggestive of glaucoma. They were referred from general ophthalmology clinics and community screening programs for diabetes mellitus and glaucoma, as they were found to have suspicious discs or raised intraocular pressure (IOP).

Ethics approval was obtained from the ethical review board of the National University Hospital Singapore, and written informed consent was obtained from all subjects. The work was carried out in accordance with the World Medical Association's Declaration of Helsinki.

Thirty consecutive patients with PACG, and 30 consecutive subjects with POAG were recruited. PACG was defined as visual field defect, glaucomatous optic neuropathy and at least one recorded IOP > 21 mmHg (among three readings taken) in the presence of an occludable angle and peripheral anterior synechiae (PAS). An occludable angle was defined as one in which the posterior, usually

pigmented, trabecular meshwork was not seen over 270 degrees or more of the angle without indentation.[10,11]Patients were asymptomatic at the time of presentation with no symptoms of acute attacks such as headache, nausea, vomiting and eye pain. Visual field defect consisted of either two points reduced by > 5 dB or one point reduced by > 10 dB below the age-specific threshold.[10-12] Secondary causes for angle closure, including iris neovascularization, lens intumescence, posterior segment mass, prior penetrating trauma and previous cataract or other ocular surgery, were excluded. Patients with serious medical conditions were also excluded from the study. POAG was defined as visual field defect, glaucomatous optic neuropathy and at least one recorded IOP > 21 mmHg (among the three

readings taken) in the presence of an open angle.

All subjects recruited underwent UBM imaging of the eye(s) with either the Humphrey P40 or the Sonomed UBM. After instilling 2% tetracaine drops in the eye, a plastic eyecup was placed on the sclera and sterile normal saline placed in the eye cup to form a water bath, taking care not to exert pressure on the globe. The UBM probe was placed in the saline reservoir perpendicular to the ocular surface and scanning was performed in the supine position. The contralateral eye was fixated on a distant target on the ceiling to maintain accommodation. The gain was set between 60 and 80 dB to maximize the view of the imaged structures and minimize noise. Images of the central anterior chamber, as well as the superior, inferior, nasal and temporal angle quadrants were captured. Imaging of all quadrants was performed in both light and dark conditions (Figs. 1 and 2).

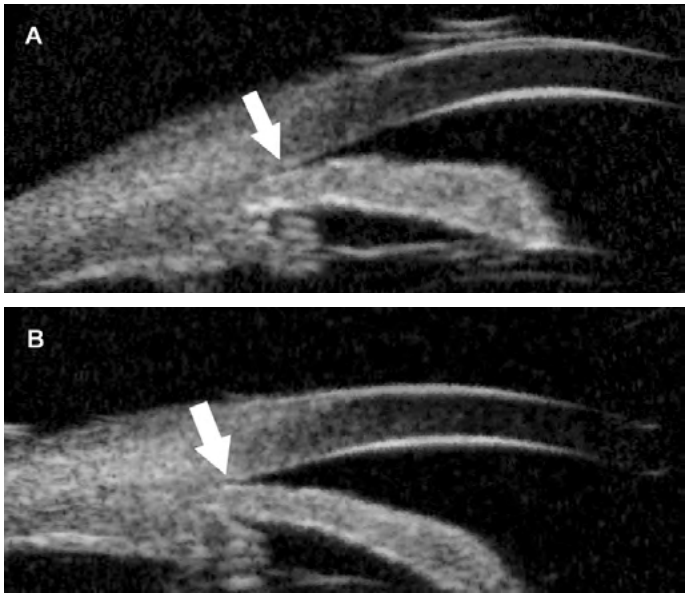

Fig. 1. Ultrasound biomicroscopic images of the superior angle of a patient with PACG in dark(A) and light(B) conditions. Angle posterior to scleral spur (white arrow) shows iridocorneal contact in dark (A); Angle posterior to the scleral spur (white arrow) shows slight opening in light but the angle recess is still closed (B).

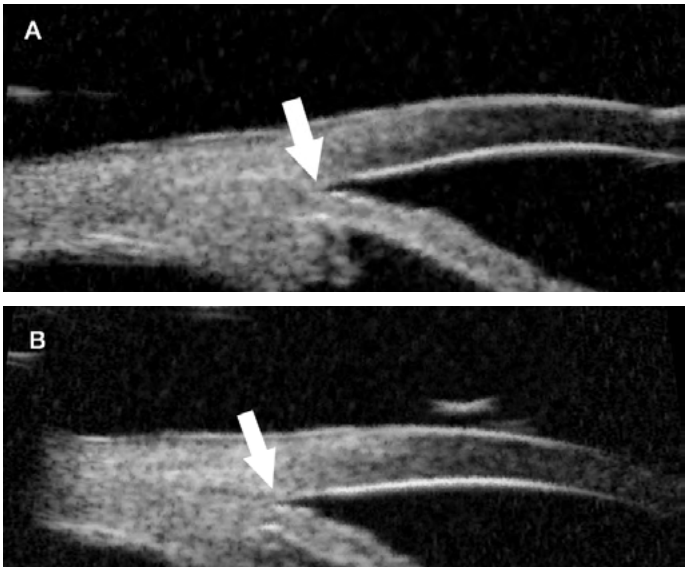

Fig. 2. Ultrasound biomicroscopic images of the inferior angle of a patient with POAG in dark(A) and light(B) conditions. Angles posterior to scleral spur (white arrow) are open.

A customized software (Anterior Segment Analysis Program, ASAP, National University Health System, Singapore) was used in this study. This was coded as a plug-in software under ImageJ (version 1.38x), which is a public domain Java program (available at ***http://rsb.info.nih.gov/ij***; National Institutes of Health, Bethesda, MD). ASAP automatically calculated anterior segment parameters using the scleral spur as reference point by a single observer.

Measurements made included anterior chamber depth (ACD), axial length (AL), and angle opening distance (AOD-500 and AOD-750), defined as linear distance between trabecular meshwork and iris at 500μm and 750μm anterior to the scleral spur (Fig. 3). In addition, trabecular-iris space area (TISA-500 and TISA-750) was measured, defined as a trapezoidal area with the following boundaries: anteriorly as the AOD 500 or AOD 750; posteriorly as a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the opposing iris; superiorly as the inner corneosceral wall; inferiorly as the iris surface.

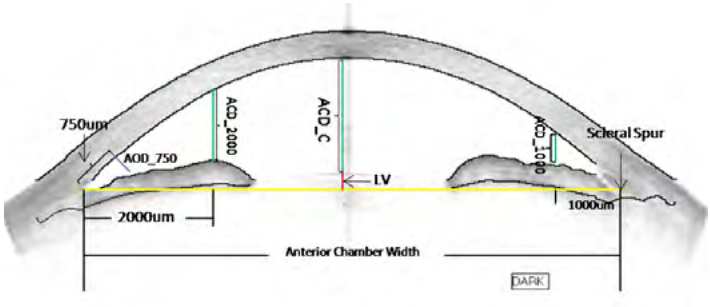

Fig. 3. Diagrammatic representation of anterior segment cross section.

Results

The mean age of PACG patients was 67.6 ± 9.6 years and POAG patients 62.1 ± 13.9 years. The proportion of male and females among PACG patients was 40.0% and 60.0%, and among POAG patients 68.8% and 31.2%, respectively. Among our patients, 8.2% had a family history of glaucoma. The IOP at presentation (mmHg) was 24.50 ± 3.30 for POAG eyes and 26.90 ± 6.90 for PACG eyes. Best-corrected visual acuity (logMAR) for POAG and PACG eyes were 0.15 ± 0.19 and 0.17 ± 0.16 respectively. Corneal thickness (mm) was 0.45 ± 0.23 and 0.57 ± 0.40 for POAG and PACG eyes correspondingly. The mean ACD (2.70 ± 0.53 mm) in PACG patients was significantly different from that (3.32 ± 0.52 mm) of POAG patients ($p < 0.0001$). There were also significant differences ($p = 0.0004$) in the mean AL of PACG (22.91 ± 0.86 mm) and POAG (24.47 ± 1.67 mm) patients.

Table 1 shows the difference in anterior segment parameters of POAG and PACG in dark condition, while Table 2 shows that in light condition. Significant differences between POAG and PACG eyes were found for TISA-500, TISA-750, AOD-500 and AOD-750 in both light and dark conditions ($p < 0.001$ for all).

Table 1. Difference in anterior segment parameters of POAG and PACG in dark condition.

	PACG	POAG	Mean difference (C.I)	p
TISA-500 (10^{-3}µm)	3.0 (9.01)	41.8 (38.10)	-38.87 (-45.94, -31.79)	< 0.001
TISA-750 (10^{-3}µm)	16.7 (87.10)	94.9 (72.75)	-78.15 (-98.72, -57.58)	< 0.001
AOD-500 (10^{-3}µm)	24.9 (62.65)	205.4 (137.10)	-180.56 (-207.79, -153.33)	< 0.001
AOD-750 (10^{-3}µm)	71.3 (206.41)	368.8 (204.90)	-297.42 (-350.06, -244.78)	< 0.001

Table 2. Difference in anterior segment parameters of POAG and PACG in light condition.

	PACG	POAG	Mean difference (C.I)	p
TISA-500 (10^{-3}µm)	4.2 (12,27)	44.8 (41.26)	-40.60 (-48.44, -32.77)	< 0.001
TISA-750 (10^{-3}µm)	19.9 (89.13)	104.6 (80.57)	-84.73 (-106.53, -62.94)	< 0.001
AOD-500 (10^{-3}µm)	28.4 (67.36)	210.0 (139.69)	-181.59 (-209.77, -153.41)	< 0.001
AOD-750 (10^{-3}µm)	71.0 (139.82)	404.4 (204.88)	-333.41 (-378.43, -288.39)	< 0.001

The univariate analyses for anterior segment parameters in dark and light conditions are shown in Tables 3 and 4, respectively. The β coefficient of age was negative and significant ($p < 0.05$) for all parameters, indicating that increasing age was associated with decreasing TISA-500, TISA-750, AOD-500 and AOD-750 values. The β coefficient of AL and ACD were positive and significant for all parameters, implying that increasing AL and ACD led to increasing TISA-500, TISA-750, AOD-500 and AOD-750 values. Similarly, the last column of diagnosis revealed that patients with POAG had larger TISA-500, TISA-750, AOD-500 and AOD-750 compared with PACG patients. In contrast, the p-values of gender showed that gender did not have a significant influence on TISA-500, TISA-750, AOD-500 and AOD-750.

Table 5 shows the light minus dark difference for anterior segment parameters in POAG and PACG eyes. The light-dark differences in PACG eyes were smaller than that of POAG eyes for all AOD and TISA values in the inferior, superior, nasal and temporal quadrants. However, with the exception of AOD-750 in the inferior quadrant ($p = 0.0524$), there were no significant differences in light-dark changes between POAG and PACG eyes for all parameters in the four quadrants.

Table 3. Univariate analysis for anterior segment parameters in dark condition.

	Univariate Linear regression analysis β coefficient (p-value)*									
	Age		Gender		AL		ACD		Diagnosis	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
TISA-500	-0.001	0.031	0.009	0.231	0.007	0.011	0.022	< 0.001	0.038	< 0.001
TISA-750	-0.002	0.029	0.011	0.530	0.016	0.014	0.045	< 0.001	0.076	< 0.001
AOD-500	-0.003	0.015	0.059	0.048	0.023	0.047	0.076	< 0.001	0.168	< 0.001
AOD-750	-0.006	< 0.001	0.042	0.424	0.048	0.017	0.131	< 0.001	0.282	< 0.001

Table 4. Univariate analysis for anterior segment parameters in light condition.

	Univariate Linear regression analysis β coefficient (p-value)*									
	Age		Gender		AL		ACD		Diagnosis	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
TISA-500	0.000	0.274	0.010	0.230	0.008	0.013	0.023	< 0.001	0.040	< 0.001
TISA-750	-0.001	0.169	0.029	0.125	0.020	0.004	0.045	0.013	0.079	< 0.001
AOD-500	-0.002	0.163	0.046	0.134	0.025	0.041	0.072	0.011	0.177	< 0.001
AOD-750	-0.004	0.081	0.088	0.109	0.053	0.012	0.147	0.003	0.319	< 0.001

Table 5. Light minus dark difference for anterior segment parameters in PACG and POAG eyes.

		Light minus dark difference for PACG	Light minus dark difference for POAG	p
		Mean ± sd	Mean ± sd	
Inferior (µm)	**TISA500**	0.0003468 ± 0.005891	0.005264 ± 0.03829	0.514
	AOD500	0.002738 ± 0.05647	0.05234 ± 0.1922	0.1949
	TISA750	0.00001724 ± 0.01280	0.01194 ± 0.08463	0.4708
	AOD750	0.001566 ± 0.09141	0.1008 ± 0.2488	0.0524
Superior (µm)	**TISA500**	-0.0004967 ± 0.0124	0.005264 ± 0.03829	0.6928
	AOD500	-0.01060 ± 0.04441	0.02037 ± 0.1530	0.2914
	TISA750	0.0008567 ± 0.2424	0.01860 ± 0.06145	0.7122
	AOD750	-0.03687 ± 0.3998	0.04158 ± 0.2033	0.3668
Nasal (µm)	**TISA500**	-0.001036 ± 0.005803	-0.002475 ± 0.03350	0.8193
	AOD500	0.003453 ± 0.02903	-0.02670 ± 0.1519	0.2959
	TISA750	-0.0007300 ± 0.01319	-0.003983 ± 0.06541	0.7916
	AOD750	-0.002480 ± 0.1207	0.01481 ± 0.2553	0.7312
Temporal (µm)	**TISA500**	0.005980 ± 0.01677	0.006687 ± 0.04489	0.9274
	AOD500	0.01935 ± 0.09473	-0.02573 ± 0.1546	0.1216
	TISA750	0.01276 ± 0.03275	0.01242 ± 0.09082	0.9834
	AOD750	0.03873 ± 0.1607	-0.01445 ± 0.2528	0.3103

Discussion

Assessment of the anterior segment plays a major role in the diagnosis and treatment of glaucoma. Traditional tools for the assessment of the angle and anterior segment are the slit-lamp and gonioscopy.[13] Several newer technologies now exist for imaging of the anterior segment, including scanning Scheimpflug and scanning slit-lamp systems.[5,14] While these visible light systems are undoubtedly useful, especially for screening for narrow angles, OCT and UBM systems allow imaging of the full-angle anatomy and, in the case of UBM, visualization of retro-iridal structures and the ciliary body. Thus, these technologies provide optimal means for the assessment of the anterior segment in glaucoma.[3]

There are some advantages of OCT, especially in the case of spectral-domain systems, owing to its superb resolution, high speed and non-invasive character.[2] Compared to OCT, UBM has several limitations. A coupling medium is required

such that scanning must be performed through an immersion bath. As it requires contact with the globe, it may be unpleasant for the patient, induce artifacts, and cause a risk of infection or corneal abrasion.[15] The procedure also requires trained and experienced technicians and is time consuming.

Despite the above, UBM is advantageous in that it provides better penetration through opaque or cloudy media than OCT, allowing improved depiction of the ciliary body, retro-iridal structures and the anterior chamber in the presence of corneal edema, scars or hyphema.[7,8] In a study by Radhakrishnan *et al*., OCT and UBM provided similar mean values for various anterior segment parameters, with equal reproducibility between the two.[2] UBM showed excellent discriminative value for the detection of narrow angles that was comparable to OCT.[2]

There have been reports on the use of UBM and OCT to characterize PACG eyes alone or comparing them to normal subjects.[6-9] However, to our knowledge there has been no previous study comparing the anterior segment parameters of POAG and PACG eyes with UBM. Over the last decade there has been much research investigating the early diagnosis and treatment of PACG in Asian populations, including the use of potential screening tests.[16-18] Both POAG and PACG have important clinical significance in many populations, and our study complements the information available by looking at the differences between POAG and PACG eyes with UBM, a useful and reliable anterior segment assessment tool. In addition, there has yet been any study on differences between POAG and normal eyes. This study could spearhead future studies looking at UBM differences between POAG and normal eyes, which would allow better understanding of the significance of the UBM data.

In our study, as expected, POAG and PACG eyes had significant differences in both dark and light conditions for all parameters: TISA-500, TISA-750, AOD-500, AOD-750, each representing the mean of a four quadrants measured. This was true for both dark and light conditions. While this is not an unexpected finding, it confirms our knowledge that the anatomical structures for patients with the two different types of glaucoma are significantly different. If we get more UBM data for both POAG and PACG eyes, the range of data available could serve as a guide for each condition, and could be used in future for either for screening or diagnostic purposes.

Our univariate analyses for anterior segment parameters in dark and light conditions showed age having an inverse association with TISA-500, TISA-750, AOD-500 and AOD-750. This correlates with previous studies which showed older patients to have significantly lower values of various quantitative parameters.[19-22] It has been postulated that increments in lens thickness and a forward shift of the lens position induced by zonular weakness may cause these changes during aging.[20] These findings suggest that old age may be a significant risk factor for PACG, because narrow anterior chamber angle parameters are associated with angle closure.

As expected, univariate analysis showed AL and ACD to have a positive correlation with TISA-500, TISA-750, AOD-500 and AOD-750 values. This was not unpredicted, as a similar association was found in another study.[23] However, the univariate analysis for gender showed it did not have a significant influence on all parameters.

This was similar to findings in other studies,[19,22,24] although literature has reported that female subjects display a smaller ACD than male subjects in almost all age groups, but these differences were minor and not statistically significant.[21]

Unsurprisingly, TISA-500, TISA-750, AOD-500 and AOD-750 were smaller in PACG than POAG patients. According to the classic view , the anterior chamber in patients with PACG is shallow, due to a combination of several factors, namely, a smaller cornea,[25] a shorter eye,[25-27] and, above all, a thicker lens,[27,28] located more anteriorly than normal.[29,30] This gives rise to 'crowding' of the anterior segment in PACG patients and results in the decreased anterior chamber angle parameters in PACG, as confirmed in our study.

Finally, our study looked at light-dark differences in PACG and POAG eyes and compared these differences. Other studies have investigated the differences in anterior chamber angle measurements in light and dark conditions with UBM and ASOCT, and found these parameters to be significantly greater in the dark compared to light.[31-33] In addition to these known findings, we were interested in examining if there were any significant differences in light-dark changes between POAG and PACG eyes, which has not been investigated previously with UBM. We found that light-dark differences in PACG eyes were smaller than that of POAG eyes for all AOD and TISA values in the inferior, superior, nasal and temporal quadrants. However, with the exception of AOD-750 in the inferior quadrant ($p = 0.0524$), there were no significant difference in these light-dark differences for all parameters in the four quadrants between POAG and PACG eyes. Based on these findings, more research on a larger population would be useful for future detection and characterization of the different types of glaucomas.

Conclusion

Our study showed significant differences in mean AL and ACD between PACG and POAG eyes. TISA-500, TISA-750, AOD-500 and AOD-750 were significantly different for POAG and PACG eyes in both light and dark conditions. Light-dark difference in PACG eyes was smaller than that of POAG eyes for all AOD and TISA values in all four quadrants. However, except for AOD-750 in inferior quadrant, there was no significant difference between PACG and POAG eyes in terms of light-dark difference in anterior segment parameters. Further evaluation of the above findings could be done in future with a larger population, for better characterization of differences in anterior segment parameters in POAG and PACG eyes.

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A family with Von Hippel-Lindau disease with different presentations

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Abstract

Objective: *To report three cases of Von Hippel-Lindau (VHL) disease from a family with different presentations.*

Method: *Case series.*

Results: **Case 1**, *a 14-year-old Malay boy with a history of gradual blurring of vision in both eyes presented with sudden deterioration of right vision. Fundus examination revealed bilateral retinal capillary hemangioma with exudative retinal detachment. His right eye underwent combination therapy of laser photocoagulation, cryotherapy, intravitreal anti-VEGF and photodynamic therapy, but failed to improve vision. His left vision deteriorated and eventually required surgical intervention.* **Case 2** *was the sister of case 1. She was a 17-year-old Malay girl who presented with sudden onset of left eye pain and redness. Diagnosis of left eye rubeotic glaucoma with closed funnel retinal detachment secondary to a huge retinal hemangioma was made. She underwent left eye external drainage of subretinal fluid plus anterior retinal cryopexy. The rubeotic vessel regressed postoperatively and IOP reduced.* **Case 3** *was the eldest sister of case 1; a 19-year-old Malay girl who came for eye screening after two of her siblings were diagnosed with VHL. She was, however, asymptomatic. Fundus examination revealed right retinal capillary hemangioma. She was treated with laser photocoagulation and her condition remained stable. Systemic investigations identified midline cystic masses in the brain, spine and pancreas.*

Conclusions: *This case series highlight different clinical pictures of Von Hippel-Lindau disease. As marked visual loss is a dreadful sequela of VHL, it is important to screen the family members as early detection and management of ocular and systemic lesions save sight and life.*

Key words: *Von Hippel-Lindau, retina capillary hemangioma*

Introduction

Von-Hippel Lindau (VHL) disease is a rare hereditary disorder that results from an inherited mutation in the VHL tumor suppressor gene and is characterized by retinal and central nervous system hemangioblastoma. It is panethnic, and inherited in an autosomal dominant manner and occurs in one in 36,000 births per year. It is also associated with renal cell carcinoma, phaeochromocytoma, renal, pancreatic and epididymal cyst.[1] Retinal capillary hemangioma (RCH) is the most frequent

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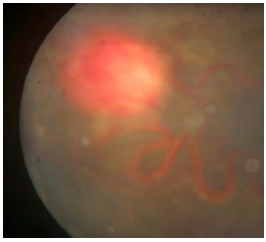
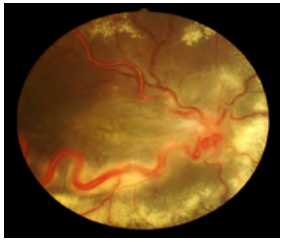
and often the earliest manifestation of VHL disease. It occurs in about 37% of patients with clinically definite and genetically confirmed VHL.[2] Forty-two percent of patients have unilateral RCH and 58% of have bilateral RCH.[3] Most RCH enlarge progressively; and the retinal changes can be various.

We report three cases of VHL from a family with different presentations.

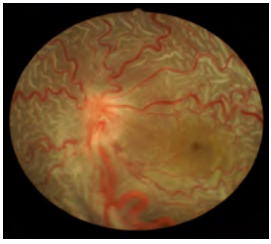
Case 1

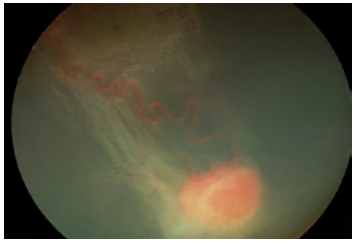
A 14-year-old Malay boy presented with gradual reduction of vision in both eyes over two years prior to presentation. On examination, his best-corrected visual acuity (BCVA) was 6/60 in the right eye and 6/15 in the left eye. Both eyes had normal anterior segments. Fundus examination of the right eye revealed a solitary RCH at the temporal region. Dilated and tortuous retinal vessels present were associated with subretinal lipid deposition and exudative retinal detachment involving the macular (Figs. 1a &1b). A similar fundus finding was noted in the left eye with the solitary RCH in the infero-temporal peripheral retina (Figs. 2a & 2b). Systemic examination was unremarkable. Screening tests for other systemic associations were negative.





Figs. 1a & 1b. Fundus photos of the right eye show dilated and tortous feeder vessel with marked retinal edema and lipid exudates. An orange red solitary RCH is located at the temporal periphery retina.





Figs. 2a & 2b. Fundus photos of the left eye show extensive exudative retinal detachment. RCH at the inferotemporal peripheral retina associated with exudative and tractional retinal detachment.

Both eyes were treated with a combination of laser indirect ophthalmoscopy, peripheral retinal cryopexy, intravitreal Ranibizumab 0.5 mg (Lucentis, Genetech) and subtenon injection of triamcinolone (40 mg). There was an initial responce to treatment in the right eye with partial resolution of the exudative detachment and BCVA improved to 6/18 (Fig. 3). However, the exudative detachment then recurred (Figs. 4a & 4b). The left eye did not show any response with progressive exudative retinal detachment. A repeat of the treatment regime in both eyes was unsuccessful. He was then given photodynamic therapy to the RCH in both eyes, which unfortunately was accompanied by extensive exudative retinal detachment and choroidal effusion.

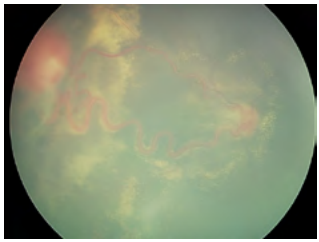
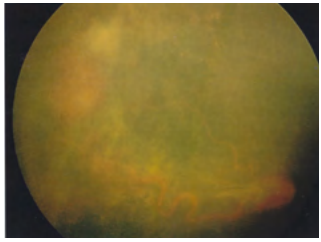
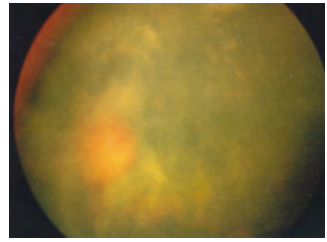


Fig. 3. Fundus photo of the right eye shows reduction of subretinal lipid exudation over the posterior pole.





Figs. 4a & 4b. Fundus photos of the right eye show increased gliosis and posterior pole exudation.

Oral Prednisolone 15 mg OD (0.5mg/kg) was started in addition to another intravitreal injection of Ranibizumab 0.5 mg and subtenon triamcinolone (40 mg). The exudation became less in the right eye and the retina was flat six weeks later. However, his right eye vision remained poor. His left eye developed cataract with total retinal detachment (Fig. 5). He underwent left eye lens aspiration with scleral buckling, pars plana vitrectomy, subretinal fluid drainage, C3F8 gas tamponade combined with cryotherapy and endophotocoagulation. Unfortunately, his vision deteriorated to no perception of light due to extensive fibrosis and tractional retinal detachment (Figs. 6a & 6b).

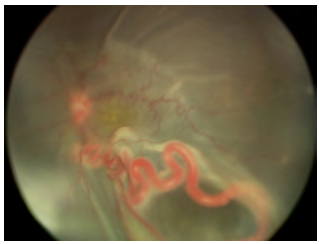
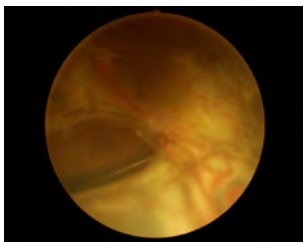
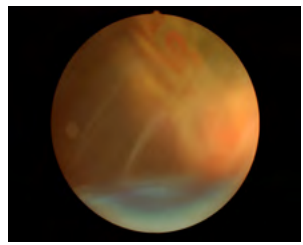


Fig. 5. Fundus photo of the left eye shows total funnel retinal detachment.





Figs. 6a & 6b. Fundus photos of the left eye show extensive fibrosis and tractional retinal detachment.

Case 2

A 17-year-old Malay girl, a sister of case 1, presented with sudden onset of left eye pain and redness for two days. She complained of left eye blurring of vision for many years. BCVA of the right eye was 6/9 and perception of light in the left eye. Ocular examination showed left circumciliary injection with edematous cornea. There was 360-degree of rubeosis iridis and ectropion uveal with intraocular pressure (IOP) of 58 mmHg. Fundal examination of the left eye revealed closed funnel retinal detachment. Examination of the right eye was normal. Her IOP was controlled with systemic and topical antiglaucoma medication preoperatively. She underwent left eye transcleral subretinal fluid drainage with anterior retinal cryopexy. A huge retinal hemangioma was discovered (Fig. 7) after the retina was flattened intraoperatively (Fig. 8). She was diagnosed to have left rubeotic glaucoma with retinal detachment secondary to VHL. Post operatively, IOP was reduced and the rubeosis regressed (Fig. 9). Systemic examination and investigations were unremarkable.

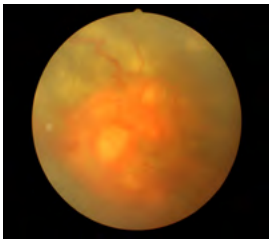


Fig. 7. Huge RCH post scleral drainage.

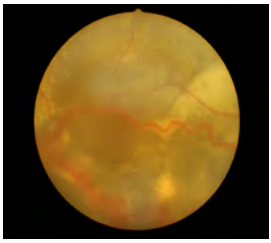


Fig. 8. Flattening of funnel retinal detachment.

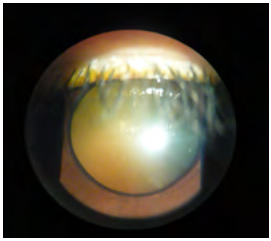


Fig. 9. Regression of rubeosis iridis.

Case 3

A 19- year-old Malay girl, eldest sister of case 1, came for eye screening after two of her siblings were diagnosed to have RCH. She was asymptomatic. Her BCVA was 6/6 both eyes. Anterior segments for both eyes were normal. Fundus examination

showed a right solitary retinal capillary hemangioma about two-disc diameter at nasal peripheral retina (Fig. 10). She was treated with argon laser photocoagulation. After two sessions of laser photocoagulations, the lesion shrunk and became whitish in color (Fig. 11). MRI brain, spine and abdomen identified midline cystic masses in the brain, lesion at spine and pancreas. She was then referred to neurosurgery and a medical team for further management.

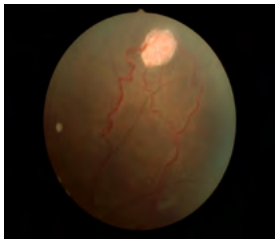


Fig. 10. RCH located at the nasal peripheral retina.

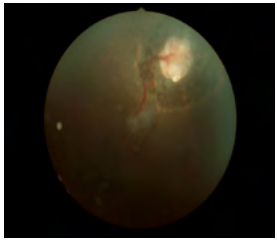


Fig. 11. RCH appeared whitish in colour post laser treatment.

Discussion

Von-Hippel Lindau disease is a blinding disease and RCH is the most frequent and the earliest manifestation. Von-Hippel Lindau gene mutation carriers have a 35% probability of visual loss by age 50.

The natural course of untreated RCH is uncertain. Most eyes with RCH show progression over time, although some may remain stable or regress spontaneously. The exudate tends to accumulate in the macular region when the tumor increases in size. The initial cystoid macular edema often progresses to a distinct star-shaped exudative maculopathy. It may further complicate with macular gliosis; from which the angioma could extend through a break in the internal limiting membrane into the vitreous. If left untreated; the serous and lipid exudation from the hemangioma can lead to total retinal detachment. Although rare, retinal and iris neovascularisation can follow, and potentially lead to secondary glaucoma and phthisis bulbi.[4 5]

Retinal changes due to RCH can be divided into various stages by Vail's classification:[6]

Stage I: Early stage with dilation of feeding artery and draining vein and angioma formation;

Stage II: Development of hemorrhages and exudation;

Stage III: Massive exudation and retinal detachment;

Stage IV: Uveitis, absolute glaucoma, and loss of the eye.

There are two possible mechanisms contributing to visual loss: Subretinal exudation due to leakage from the hemangioblastoma and traction retinal detachment due to fibrovascular proliferation at the vitreoretinal interface.[7] Causes of visual loss in VHL are cystoid macular edema, subretinal exudates, exudative or tractional retinal detachment, vitreous hemorrhage or neovascular glaucoma[4] as presented in this series. In view of the progressive nature of subretinal exudation in VHL, most authorities agree that treatment should be initiated as soon as a RCH is detected.

The choice of treatment method is dictated by media clarity, lesion size, location and the retina changes. Various treatment modalities including observation, laser photocoagulation, cryotherapy and vitreoretinal surgery, have been described.[8] The possibility that the upregulation of downstream genes, such as VEGF leading to the formation of vascular tumors has prompted the exploration of anti-angiogenic therapies as a possible treatment modality for ocular VHL.[9] Recent case reports have also suggested that anti-VEGF agent, delivered either systemically[10] or via intravitreal injection may be useful.[11, 12]

Management of RCH is mainly orientated toward reducing the destructive exudation associated with these lesions. For early-detected cases like our Case 3 direct Argon laser photocoagulation showed a response rate of 91-100%. Laser photocoagulation is most effective in tumors that are 1.5 mm or smaller and is effective in RCH up to 4.5 mm in size. It can be applied directly to the tumor, to the feeder artery or to both. Change of color of the tumor from bright red to pale pink, and narrowing of vessels are indicative of adequate response to treatment; which normally show in four to six weeks. Usually more than one treatment session is required to be effective.[13]

Visual prognosis is often poor and management is difficult when patients come in advanced stages like the case 1 in these case series. We used combined laser photocoagulation and cryotherapy in view of the huge size and the anterior locality of the RCH with a significant amount of subretinal fluid. Cryotherapy was applied until the ice ball completely enclosed the RCH as described by Welch.[14] Cryotherapy can be repeated two months after the previous application.[15] Complex vitreoretinal surgery including vitrectomy, endolaser and combined scleral buckling is usually required for a larger RCH complicated with retinal detachment. However treatment of huge tumor could be hazardous and the visual outcome is often disappointing. Marked increase in subretinal exudation and a total retinal detachment has resulted in this patient's left eye after treatment.

Clinical studies also reported elevated intraocular levels of VEGF in patients with VHL disease leading to the formation of vascular tumors.[7,9] This has substantiated the use of anti-VEGF to achieve regression of the RCH and subretinal exudation.[11] However it did not work so well in our patient although there was some evidence of resorption of subretinal exudation. We suggest more prospective clinical trials to evaluate the efficacy of this treatment modality.

Photodynamic therapy (PDT) with verteporfin has been reported as a treatment for RCH in VHL. It has been hypothesized that as verteporfin targets vascular endothelial cells, there may be selective affinity for verteporfin in the leading

pathological capillaries of hemangioma. There are several cases of retinal angiomas having encouraging results after being treated with PDT.[16,17] Bakri *et al*. reported one case where retinal hemangioma was successfully closed after verteporfin PDT along with argon laser and TTT. However, the patient developed a combined rhegmatogenous and exudative retinal detachment with proliferative vitreoretinopathy that needed subsequent vitrectomy, scleral buckling and silicone oil tamponade.[18] Our case 1 patient had extensive exudative retinal detachment with choroidal effusion post PDT treatment could possibly explained by upregulation of VEGF caused by PDT. PDT may not be an effective treatment and further investigations are required to determine the indications and parameter for effective treatment of RCH with PDT.

Rubeosis iridis and neovascular glaucoma are uncommon anterior segment complications of VHL; only 2% cases are reported.[1] It usually leads to painful and phthisical eyes that require enucleation. The aim of the treatment was to save the eye and provide some symptomatic relieve. In our case 2, the rubeosis did regress and IOP reduced following treatment.

RCH could be the only manifestation of VHL disease. Therefore, patients with an isolated hemangioma should be screened for VHL disease. A systemic workup should include MRI or CT of the head, upper cervical spinal cord, and abdomen, as well as a urinalysis to investigate for the presence of catecholamines in the urine. Genetic testing was not done. Ideally it should have been done to detect the genetic mutation in this family with subsequent genetic counselling.

Conclusion

This case series highlight the different presentations and different stages of VHL and the complexity in clinical management. Treatment of RCH is difficult when the patient presents late and the visual prognosis is usually poor. We also highlight the importance of screening the family members for early treatment in order to save sight and save life.

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Ocular metastasis from a rare thyroid carcinoma

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Abstract

Objective: *To report a case of primary thyroid carcinoma with ocular metastasis.*

Methods: *This is a case report of a 39-year-old male, who initially presented with a sudden painless loss of vision in the left eye and an anterior neck mass. He was initially diagnosed to have retinal detachment with vitreous hemorrhage based on ocular ultrasound. Fine Needle Aspiration Biopsy of the neck mass initially revealed medullary thyroid carcinoma. Computed topography of the chest and abdominal ultrasound revealed lung and liver metastasis. Whole body bone scintigraphy also revealed bone metastasis.*

Results: *Patient underwent total thyroidectomy with bilateral modified radical neck dissection of the neck mass and vitreous biopsy of the left eye. Histopathology report revealed malignant carcinoma of the thyroid, medullary type while vitreous showed malignant cells from the thyroid. Patient was scheduled to undergo chemotherapy for the widespread metastasis.*

Conclusions: *Ocular malignancy can present in many ways, thus it is necessary to consider it as a differential for cases of retinal detachment and vitreous hemorrhage. Choroidal metastasis from malignant thyroid carcinoma is rare, more so the medullary type.*

Key words: *Thyroid cancer, ocular metastasis, choroidal metastasis*

Introduction

Choroidal metastasis originating from thyroid carcinoma is very rare. In a survey of 227 cases of uveal metastasis, Ferry and Font found only one case from thyroid cancer.[1] Shields *et al*. found only two out of 520 cases of uveal metastases from thyroid cancer of follicular origin (papillary and follicular).[2] Choroidal metastasis from medullary thyroid carcinoma has been reported in a patient who had multiple endocrine neoplasia (MEN) type 2B.[3] This report is of a young male patient with primary sporadic thyroid carcinoma with choroidal and vitreous metastasis confirmed by biopsy.

Case description

A 39-year-old male presented for evaluation of unilateral painless vision loss and an anterior neck mass. He was initially diagnosed to have retinal detachment with

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vitreous hemorrhage on the left eye based on ocular ultrasound in another institution. Vision at the right eye was 20/20, while the left eye was light perception. Fundus of the right eye showed clear media with distinct disc borders and multiple retinal pigment epithelium detachments. The left eye had no view due to vitreous hemorrhage. Ocular ultrasound of the left eye showed a dome-shaped, homogenous mass in the retina with moderate reflectivity on A-scan (Fig. 1).

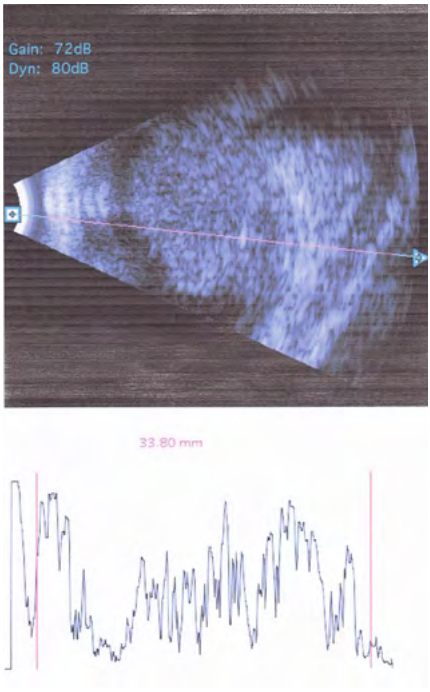

Fig. 1. Ocular ultrasound shows a hyper-echoic homogenous mass in the retina with moderate to high reflectivity in A scan.

Physical examination of the patient showed a large, firm, multi-nodular anterior neck mass measuring around 10 x 10 cm with multiple, bilateral, cervical lymphadenopathy measuring 5 x 5 cm. Fine Needle Aspiration Biopsy (FNAB) of the neck mass initially revealed medullary thyroid carcinoma (Fig. 2).

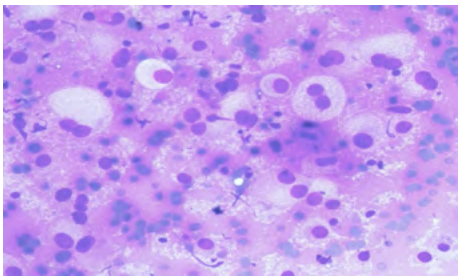

Fig. 2. Fine Needle Aspiration Biopsy of the neck mass shows binucleated large dispersed cells; plasmocytoid cells; amyloid-like material; and salt and pepper chromatin that are consistent with a medullary carcinoma variant of the thyroid.

On further examinations, blood pressure was in normal range for age. Complete blood count, blood chemistry (sodium, potassium, calcium, magnesium, phosphorus), fasting blood sugar, liver enzymes, thyroid function test (TSH, FT3, FT4), and prothrombin time were all within normal range. On further workup, computed topography (CT) of the cranium showed a layering hyper-density in the posterior chamber of the left globe which is consistent of posterior vitreous hemorrhage (Fig. 3); the brain is essentially normal. There is a trace finding of possible extraocular spread of the lesion in the left eye.

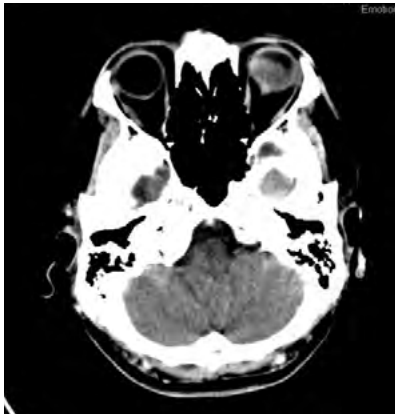

Fig. 3. Cranial CT (axial cut) of the patient showed a layering hyper-density in the posterior chamber of the left globe.

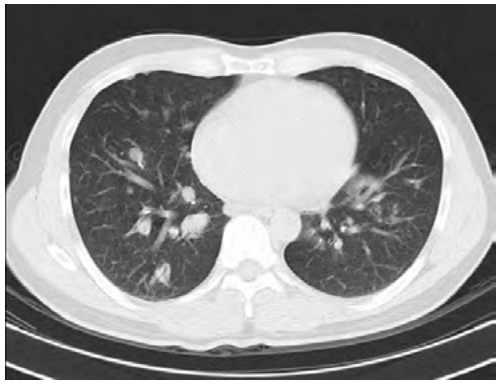

Fig. 4. Chest CT scan of the patient showed multiple various-sized opacities scattered in both lung fields consistent with lung metastasis.

Computed topography of the chest showed multiple varisized opacities scattered in both lung fields, and abdominal ultrasound showed multiple ill defined hypoechoic and hyperechoic foci consistent with lung and liver metastasis respectively (Figs. 4 and 5). Whole body bone scintigraphy also revealed lytic lesions in the ribs consistent with bone metastasis (Fig. 6).

Patient underwent total thyroidectomy with bilateral modified radical neck dissection of the neck mass and vitreous biopsy of the left eye. The vitreous biopsy of the left eye showed atypical cells characteristic of a metastatic lesion originating from the thyroid (Fig. 7). Histopathology of the neck mass revealed malignant medullary thyroid carcinoma (stage IVC).[4] Immunohistochemical staining of the specimen for calcitonin and carcinoembryonic antigen was done and stained positive. The patient was supposed to undergo chemotherapy, but he expired before starting any treatment.

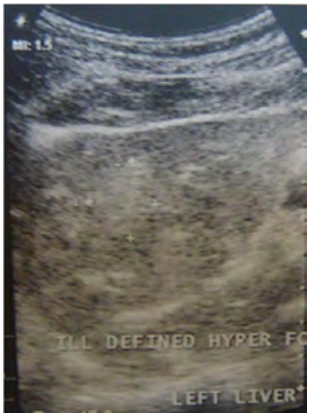

Fig. 5. Holoabdominal ultrasound of the patient showed multiple ill-defined hypoechoic and hyperechoic foci in the liver consistent with metastasis.

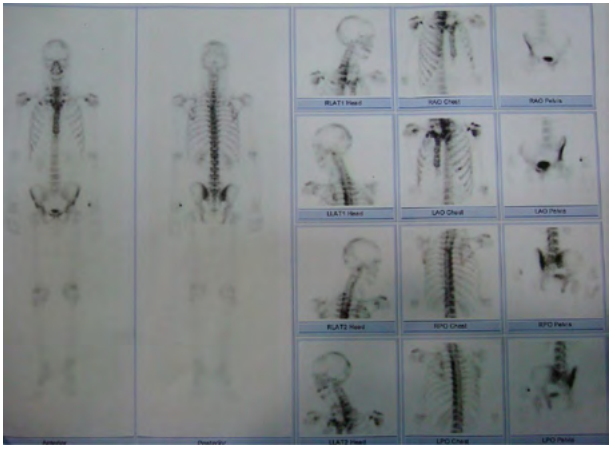

Fig. 6. Whole body scintigraphy of the patient showed osteoblastic foci in the anterior 2nd right and 6th left rib consistent with bone metastasis.

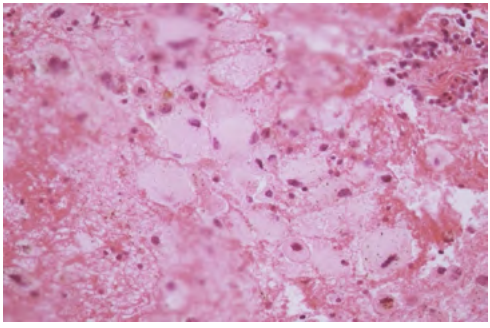

Fig. 7. Vitreous biopsy of the left eye showed large cell with eccentric nuclei and abundant cytoplasm that are similar to the thyroid aspirate.

Discussion

Thyroid mass or nodule is usually benign (90-95% of the time). Only a small percentage of thyroid masses are cancerous. There are five different types of thyroid cancers, namely: papillary thyroid cancer (80%); follicular thyroid cancer (10%); medullary thyroid cancer (5%); anaplastic thyroid cancer (2%); and thyroid lymphomas and sarcomas (< 2%).[5-6] Thyroid carcinomas arise from the two cell types present in the thyroid gland. The endodermally derived follicular cell gives rise to papillary, follicular, and probably anaplastic carcinomas. The neuroendocrine-derived calcitonin-producing C (parafollicular) cell gives rise to medullary thyroid carcinoma. Thyroid lymphomas arise from intrathyroid lymphoid tissue,[7] whereas sarcomas likely arise from connective tissue in the thyroid gland.

Papillary thyroid carcinomas are the most common type of thyroid cancer. They usually grow very slowly and often spread to regional lymph nodes. Distant spread to other organs is very rare. The follicular thyroid carcinomas, on the other hand, usually metastasize via hematogenous routes and rarely spread to regional lymph nodes. Medullary carcinomas are equally likely to spread to the regional lymph nodes or adjacent blood vessels. This type of thyroid cancer can run in families and may be part of a multiple organ neoplasia, namely the multiple endocrine neoplasia (MEN).[5] The anaplastic thyroid cancers are the least common form and the most aggressive. The majority of the thyroid lymphomas are non-Hodgkin's B cell lymphoma.

Medullary thyroid carcinoma is a form of thyroid carcinoma which originates from the parafollicular cells that produce the hormone calcitonin. It can be classified as sporadic if it occurs by itself, familial if there exist a thyroid cancer in the family history and gene mutation, or it can be part of the MEN type 2, which consist of tumors in the adrenal glands, parathyroid, and thyroid. It frequently metastasizes to the regional lymph nodes or distant organs, such as the lungs, liver, and bones.[8] Although ocular or orbital metastasis from thyroid is quite rare, it is still important to recognize that this situation can happen.

The most common intraocular and intra-orbital tumor in adult is metastasis, where in the most common primary site is the lungs for men, and breast for women.[9] The uveal tract is the most common part of the eye involved in ocular metastasis.[10] The choroid constitutes 80-90% of the metastasis to the uveal tract because of its rich vascular supply. Uveal metastasis begins asymptomatically; when patient becomes symptomatic, symptoms evolve quite rapidly. Blurring of vision still is the most common symptom in ocular metastasis which is the case in our patient.

Choroidal metastasis can present in many ways, thus it is necessary to consider it as a differential for cases of retinal detachment and vitreous hemorrhage so that appropriate management may be initiated.

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Isolated corneal squamous cell carcinoma in a patient with unilateral dry eye symptoms

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Abstract: *The aim of this study was to report a case of isolated corneal squamous cell carcinoma in a patient with unilateral dry eye symptoms. The case was a 48-year-old man with a history of thermal corneal injury on his left eye two years ago with decreased visual acuity and dry eye symptoms a short time after, which was treated for dry eye and had no improvement in symptoms. Examination revealed hypertrophy of near total corneal epithelium, without limbal and conjunctival involvement. The surface of the lesion was irregular with punctate epithelial erosions. The patient underwent excisional biopsy which revealed severe corneal dysplasia (carcinoma in situ). After excision, the patient was treated with Fluorouracil and there was no sign of recurrence till the time of the last follow-up examination six months after excision. Dry eye symptoms had disappeared completely. We conclude that, in the case of unilateral chronic dry eye which was resistant to the treatment with signs of corneal epithelial involvement, isolated corneal neoplasia should be considered even without limbal or conjunctival involvement.*

Key words: *Isolated corneal squamous cell carcinoma, cornea, dry eye*

Introduction

Corneal and conjunctival dysplasia and squamous cell carcinoma form a wide range of squamous neoplasia and together represent the most common tumor of the ocular surface.[1] Although various terms have been used to describe the disorder, ocular surface squamous neoplasia (OSSN) describes both intraepithelial dysplasia and squamous cell carcinoma of the cornea and conjunctiva.[2] Squamous lesions of the cornea and conjunctiva are uncommon; however, they are important because of their potential for causing ocular and even systemic morbidity and mortality. The clinical presentation of these lesions extends across a wide spectrum and differs based on the degree of pathologic involvement. The cause of OSSN is unclear and possibly multifactorial. This tumor is usually unilateral and often occurs in fair-skinned men in their mid-60s who have had a history of long-term sun exposure.[3] Ultraviolet (UV) light-induced mutations to the p53 tumor suppressor gene may play a role in this condition. In addition, other identified risk factors include heavy smoking, previous exposure to petroleum derivatives, xeroderma pigmentosum, and human papilloma virus (HPV). HPV has been identified in both benign (types 6, 8 and 11) and malignant (types 16 and 18) conjunctival epithelial growths. Because

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of a possible association, human immunodeficiency virus (HIV) testing is advised in patients younger than 50 years in whom OSSN is diagnosed. Isolated squamous cell carcinoma of cornea is very rare. To the best of our knowledge, only a few such reported cases have been found in litrature.[4,5] However, most of the reported cases in aforementioned cases involve the limbus. In this case report, a case of isolated squamous cell carcinoma of the cornea without involvement of the limbus was investigated.

Case report

The reported case was a 48-year-old man with fair skin complained of the dry eye symptoms, and decreased visual acuity of his left eye. His past medical history was unremarkable. He mentioned a corneal thermal injury to his left eye two years ago and the symptoms started one month after then. With the diagnosis of the dry eye syndrome, he was treated with non-preservative artificial tear frequently, however, had no improvement of the symptoms.

At the final exam three months before referring to our specialized eye clinic, best corrected visual acuity (BCVA) was 10/10 and counting fingers at three meters in his right and left eyes, respectively. At slit-lamp examination of the left eye, epitheliopathy and filamentary keratopathy involving large areas of the cornea without limbal and conjunctival involvement was documented.

At the first follow-up examination in our clinic (Khatam-al-Anbia Eye Hospital), BCVA was 10/10 and counting fingers at six meters in his right and left eyes, respectively. Slit-lamp examination revealed hypertrophy of near total corneal epithelium with distinct and scalloped border, without limbal and conjunctival involvement (Fig. 1).

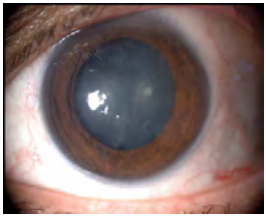

Fig. 1. Corneal epithelial hypertrophy with near total corneal surface involvement which has definite and scalloped border without involving the limbus.

The surface of the lesion was irregular with punctate epithelial erosions. Tear meniscus was normal in both eyes. Tear break-up time (TBUT) was ten and four seconds in his right and left eyes, respectively. There was no significant meibomian gland dysfunction. Other exams including ocular movements, relative afferent papillary defect (RAPD), intraocular pressure (IOP) and fundus examination were unremarkable in both eyes. Slit-lamp examination of the right eye revealed normal findings.

The patient underwent excisional biopsy (debridement) of the corneal epithelium. The smear and culture results of corneal specimen were negative for bacteria, fungi and amoeba. Histopathological investigation revealed severe corneal dysplasia including cells with irregular and hyper-chromatic nuclei and dyskeratosis

with diffuse mitosis on the entire epithelium. There was not any sign of underlying stromal involvement (Fig. 2).

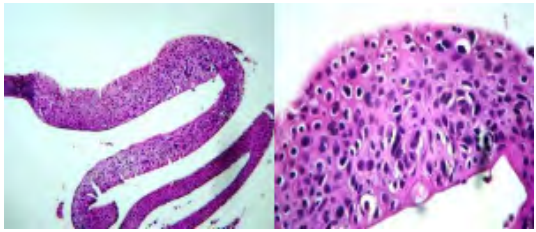

Fig. 2. Carcinoma *in situ*: Right: Severe dysplasia with cytonuclear atypy, involving full thickness of epithelium (H&E stain, x 100); Left: Cytonuclear atypy (H&E stain, x 400).

After excision, the patient was treated with Fluorouracil drop 50 mg/dl QID for two pulses of two weeks duration with one week pause between them. There was no sign of recurrence till the time of the final follow-up examination (45 days after the surgery). At the final examination, the visual acuity on his left eye was 9/10 and dry eye symptoms were disappeared completely (Fig. 3).

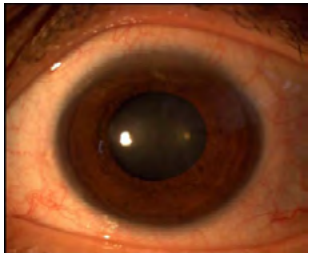

Fig. 3. Slit photograph of involved eye at last visit, with no sign of recurrence.

Discussion

Isolated squamous cell carcinoma of cornea is very rare and only few cases have been reported in the litrature.[4,5] Corneal intraepithelial neoplasia (CIN) is associated with the same risk factors as conjunctival intraepithelial neoplasia and presumably shares the same pathogenesis.

Corneal OSSN lesions typically are pre-invasive and appear as an opalescent ground-glass sheet with mottled surface. A main feature of many corneal lesions is that they have sharply defined and fimbriated borders and are avascular. Less frequently, the edges may be ragged or even smooth. The convex leading edge spreads away from the corneoscleral limbus in an advancing arc. In addition, fine white dots are often present over the gray epithelium. These lesions can sometimes appear as large, elevated, pearl-white mounds. Corneal OSSN lesions are slightly elevated in comparison with the adjacent normal epithelium. Rose bengal staining produces a diffuse punctate stain over the gray sheet. The virulence of these corneal lesions themselves is low. Early involvement of the cornea adjacent to a conjunctival lesion may manifest as a mild opacification of the cornea. Such areas have dysplastic corneal epithelium with a polycystic appearance which are best visualized by retro-illumination.[6] The etiology of these lesions is controversial, with some authors having proposed a *de novo* dysplastic process in the cornea,[7] while

others have suggested a centripetal sliding of subsequently neoplastic cells from the limbus.[8] These lesions are typically indolent and slow growing. They have a high tendency to recur.[7-9] Corneal neovascularization does not typically occur, which helps to differentiate CIN lesions from limbal stem cell failure.

The reported case in this study was a middle-aged man without any risk factors for OSSN, except the fair skin. It should be noted that thermal burn is a well-defined risk factor for squamous carcinoma of the skin, mouth and esophagus; however, there was no documented relation between OSSN and the thermal burn. Therefore, in our case, we could not state that either the thermal burn was the cause of corneal OSSN or it was a random relationship. In addition, one case of squamous cell carcinoma of the cornea and conjunctiva following thermal burn of the eye has been reported previously.[10] To the best of our knowledge, no other case of unilateral corneal SCC with initial presentation of dry eye symptoms has been reported in the literature. In the abovementioned case report,[10] the corneal schema demonstrated some signs of corneal surface squamous carcinoma. However, what mislead the mind from initial diagnosis was patient's younger age, lack of powerful risk factors, sparing of limbal and conjunctival area, symptoms and signs of dry eye specially filamentary keratopathy and lower tear break up time (TBUT) and higher incidence of dry eye than SCC.

In the ocular structure, there is a natural contraction between the tear film and the corneal surface epithelium. Any defect in the tear film or corneal epithelium could lead to filamentary keratitis. Disruption of the ocular surface epithelium is an important risk factor for filament formation which is produced by sliding of the epithelial cells around small areas of focal degeneration of the epithelium. Therefore, observation of filamentary keratopathy should not mean dry eye in any case, especially in the atypical cases such as this unilateral dry eye syndrome. This problem causes misleading of the diagnosis in our case; however, some factors helped an initial diagnosis such as: case gender, unilateral involvement, appropriate tear meniscus, the epithelial opacity and resistance to proper dry eye treatments.

Various treatment options have been previously discussed such as surgical excision with a two- to three-millimeter free margin, cryotherapy, brachytherapy, chemotherapy with mitomycine, 5- Flourouracil and interfrone α. Based on the current clinical experience, it is clear that mitomycin and 5-FU are effective options for complete eradication of pre-invasive OSSN. Use of 5-Flourouracil in the treatment of squamous carcinoma *in situ* was first introduced in 1986. This drug was used successfully with the dose of four times daily for one month in the treatment of squamous carcinoma *in situ* without combination of other therapeutic modalities.[11]

In this case study, we performed excisional biopsy of corneal epithelium for the diagnosis and treatment of the lesion. Almost all dysplastic lesions involving conjunctiva or cornea also involve the corneoscleral limbus, as this junction has the greatest mitotic activity, though isolated cases have been reported.[5,12] Although our patient had no limbal involvement, it is possible that the original abnormal cells had their origin at the corneoscleral limbus and subsequently became neoplastic after migration to the central cornea. Therefore, we have decided to treat the

patient with 5-Flourouracil (two pulses of two weeks duration with one week pause between them) after excision.

Conclusion

In the case of unilateral chronic dry eye which is resistant to the treatment with signs of corneal epithelial involvement (opacity and increasing corneal thickness), isolated corneal neoplasia should be considered even without limbal or conjunctival involvement.

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References: 1. Xalatan® (latanoprost) Prescription Information, Pfizer Corporation HK Ltd, version date: Oct, 2012. 2. Xalacom® (latanoprost /timolol maleate) Prescription Information, Pfizer Corporation HK Ltd, version date: Jun 2009. 3. Parrish RK et al. *Am J Opthalmol* 2003;135(5):688–703. 4. Drug Office, Dept of Health, HKSAR – Search Drug Database http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/search_drug_database.html

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XALACOM® ABBREVIATED PACKAGE INSERT. TRADE NAME: Xalacom® eye drops, solution 2.5mL, **PRESENTATION:** Each ml of Xalacom® contains 50mcg latanoprost and 5mg timolol. **INDICATIONS:** Reduction of intraocular pressure in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topic beta-blockers or prostaglandin analogues. **DOSAGE:** Instill 1 drop into the affected eye(s) once daily. **CONTRAINDICATIONS:** Hypersensitivity to any component in Xalacom®. Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, 2nd and 3rd degree atrioventricular block, overt cardiac failure, cardiogenic shock. **WARNINGS & PRECAUTIONS:** History of severe cardiac disease. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failures, have been reported following administration of timolol maleate. Caution in patients subject to spontaneous hypoglycemia or labile insulin-dependent diabetes. May mask signs of hyperthyroidism and worsen Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. Patients who are aphakic, pseudophakic with a torn posterior lens capsule or with known risk factors for macular oedema. May cause change in eye colour. Contact lenses should be removed before administration and maybe reinserted after 15 minutes **INTERACTIONS:** The use of two local beta-blockers or two local prostaglandins is not recommended. Epinephrine, oral calcium channel blockers, guanethidine or beta-blocking agents, antiarrhythmics, digitalis glycosides or parasympathomimetics, clonidine, antidiabetic agents **PREGNANCY AND LACTATION:** Should not be used during pregnancy since the potential risk for humans is unknown. Active substance and its metabolites may pass into breast milk and should not be used in women who are breast-feeding. **COMMON SIDE EFFECTS:** Increased iris pigmentation; Thickening and lengthening of eye lashes; Mild conjunctival hyperaemia; Transient punctuate epithelial erosions; Macular oedema, including cystoid macular oedema; Iritis/ uveitis; Corneal oedema and erosions; Eye irritation (including stinging, burning and itching) and eye pain. **REFERENCE:** HK PI (version date/LPD date) Jun 2009 **DATE OF PREPARATION:** July 2012 **IDENTIFIER NUMBER:** XALC0712

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A rare case of *Arthrographis kalrae* keratomycosis in a non-contact lens wearer

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Abstract

Purpose: *Keratomycoses secondary to Arthrographis kalrae are rarely reported. Previous cases involved patients with contact lens wear. Herein we report a rare case of severe fungal keratitis due to Arthrographis kalrae in a non-contact lens wearer.*

Methods: *Case report.*

Results: *A 52-year-old male presented with a left paracentral corneal ulcer with stromal infiltrates following contact with a foreign body while riding a motorbike. Initial treatment with intensive topical antibiotic drops failed. Antifungal therapy with hourly topical amphotericin B 0.15% and fluconazole 0.2%, as well as oral fluconazole was initiated. His ulcer progressed rapidly despite aggressive treatment. This led to a small, peripheral corneal perforation which was treated with corneal gluing and bandage contact lens. He also developed secondary glaucoma. Microbiological cultures of his corneal scrapings revealed Arthrographis kalrae. A single dose of subconjunctival amphotericin B 0.015% o.1mL was then given. At two months after presentation, he eventually underwent therapeutic penetrating keratoplasty (PK) for non-resolving keratomycosis. Following PK, he was maintained on topical amphotericin B 0.15%, fluconazole 0.2% and ciprofloxacin 0.3% four-hourly, together with fusidic acid ointment 2% twice daily. The graft failed three months post-transplant, albeit with no evidence of residual or recurrent infection.*

Conclusion: *Arthrographis kalrae-related keratitis may occur in non-contact lens wearer. Management remains clinically challenging because this organism causes severe, rapidly progressive keratitis.*

Key words: *Arthrographis kalrae, keratomycosis, fungal keratits, penetrating keratoplasty*

Introduction

Keratomycosis can lead to devastating ocular morbidity. According to the World Health Organization, corneal ulceration and ocular trauma may be responsible for 1.5 to 2 million new cases of corneal blindness each year.[1] In Asia, as many as 17-44% of corneal ulcers are due to fungal pathogens.[2] Of these, filamentous fungi like *Fusarium* and *Aspergillus* species represent the commonest etiologic agent.[3] Other filamentous fungi like *Arthrographis kalrae*, can rarely cause keratomycosis. To date, we found three reported cases.[4-6] These cases shared a striking similarity whereby all three patients developed the corneal ulcer while on contact lens use.

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To add to the literature on this rare human pathogen, we share our case of *A. kalrae* keratomycosis that occurred in a non-contact lens wearer.

Case report

A 52-year-old male with well-controlled diabetes mellitus presented with intense left eye pain, mild blurring of vision, redness, and epiphora four days following contact with a foreign body while riding motorcycle along the countryside. He denied a history of previous ocular trauma and contact lens use. His best-corrected visual acuity was 20/20 OD and 20/40 OS. There was a left paracentral corneal ulcer with stromal infiltrate measuring 4.0 x 3.8 mm. Associated with this was an intense anterior chamber reaction with 4+ cells. No corneal thinning or satellite lesions were present. Intraocular pressure (IOP) on presentation was 12 mmHg. Corneal scrapings were smeared for Gram stain, Giemsa stain and wet mount microscopy with potassium hydroxide (KOH) as well as inoculated directly onto the surface of blood agar, chocolate agar, MacConkey agar and Sabouraud dextrose agar.

He was initially treated with hourly topical gentamicin 0.9% and cefuroxime 5%. However, within five days, endothelial plaque and hypopyon formed. Based on these clinical features as well as the fact that the foreign body could contain organic material, antifungals were started. For this, hourly topical amphotericin B 0.15% and fluconazole 0.2 %, alongside systemic oral fluconazole were added. At this stage, results from Gram, Giemsa and KOH stains as well as microbiological cultures were all negative.

Despite the aggressive antimicrobial therapy, his ulcer further deteriorated over the next three weeks evidenced by enlargement of stromal infiltrates with fluffy, indistinct margins measuring 9.2 x 10.0 mm, formation of a dense stromal abscess and an anterior chamber fungal ball. This was further complicated by secondary glaucoma with an IOP of 31 mmHg, necessitating the use of three topical anti-glaucoma agents. At one month, a small, peripheral corneal perforation occurred with a positive Siedel test. Cyanoacrylate glue corneal patch was successfully performed and a bandage contact lens was placed. Intraoperative corneal swab yielded no growth.

Meanwhile, microbiological cultures of his initial corneal scraping revealed *Arthrographis kalrae* (Fig. 1). Subsequently, a single dose of subconjuntival amphotericin B 0.015% 0.1 ml was given on top of his topical and oral medications. Due to the protracted clinical course, our patient eventually underwent a therapeutic penetrating keratoplasty (PK) two months after presentation. Postoperatively he developed transient hyphema which resolved spontaneously. Following PK, he was maintained on topical amphotericin B 0.15%, fluconazole 0.2% and ciprofloxacin 0.3% four-hourly, as well as fusidic acid ointment 2% twice daily. Suture infiltrates developed a week after surgery which resolved with intensified topical ciprofloxacin 0.3%. His IOP post PK was maintained at 12-18 mmHg on four anti-glaucoma eye drops. However, the graft failed three months post-transplant (Fig. 2). Currently this patient is being maintained on topical chloramphenicol 0.5% and dexamethasone 0.1% six-hourly, fucidic acid 2% ointment twice daily as well as

three anti-glaucoma agents. He has been followed-up for eighteen months post-transplant with no evidence of residual or recurrent disease.

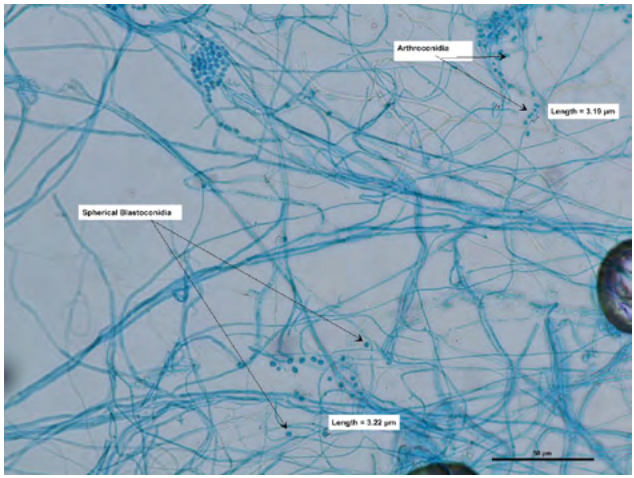

Fig. 1. *Arthrographis kalrae* isolates from corneal scrapings stained with lactophenol cotton blue showing typical morphological features. One-celled, smooth-walled, arthroconidia are seen.

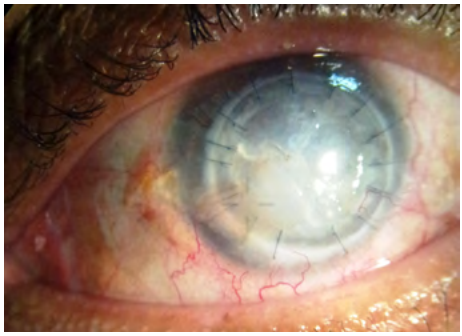

Fig. 2. Failed corneal graft.

Discussion

Arthrographis kalrae, although a rare opportunistic pathogen, has been isolated in a myriad of systemic diseases including pulmonary infection, endocarditis, knee joint infection, sinusitis, meningitis, cerebral vasculitis, panophthalmitis as well as keratomycosis.[4-12] Since it was first described in 1976 by Cochet ex Sigler and Carmichael, there have been less than 15 clinical case reports of *A. kalrae*-related human infections, including three keratomycoses.

In 1997, Perlman and Binns reported the first case of *A. kalrae* keratitis in a contact lens wearer who was exposed to soil and presented with intense photophobia and progressive infiltrate mimicking Acanthamoeba.[4] In 2004, Biser *et al*. highlighted another contact lens-related corneal ulcer that was empirically treated as Acanthamoeba keratitis before fungal culture results grew *A. kalrae*.[5] This patient received topical amphotericin 0.4% and miconazole 10% and oral itraconazole 200 mg twice daily. Recently, Thomas *et al*. reported the third case involving a healthy immune-competent soft contact lens user with rapidly progressing ulcer. Their

patient underwent three PK and was treated with topical and prolonged systemic voriconazole.[6]

Our patient shares similarities with the above cases in that he had intense eye pain, rapid progressive corneal infiltrate with eventual perforation and the need for PK to control the disease. However, unlike these cases, our patient had never worn contact lenses. Contact lens use has been associated with corneal ulcer via various mechanisms including direct and indirect corneal trauma.[13] Instead, risk factors for developing fungal keratitis in our patient included diabetes mellitus and possible exposure to organic material as he was traveling along the countryside.

A. kalrae is a slow-growing filamentous fungus found in soil and compost. Due to the rarity of cases, *A. kalrae* is often misdiagnosed as *Candida albicans* because of the initial cream-colored, yeast-like appearance.[9] However, on light microscopy, the characteristic of this species is the presence of one-celled, hyaline, smooth-walled, and cylindrical arthroconidia directly formed by fragmentation of undifferentiated hyphae or for the fresh cultures by disjunction and segmentation of hyaline fertile branches borne at the apex of the conidiophores.[11] Diagnosis can be challenging and may only be clinched after repeated testing. As such, when performing therapeutic penetrating keratoplasties, the host button should be divided into two parts: the first subjected to microbial analysis; and the other sent for histopathological evaluation. This helps in conforming the diagnosis. Additional testing like polymerase chain reaction may prove helpful.[6]

In terms of therapeutic options, previous sensitivity testing has shown susceptibility of this fungus to amphoterecin, itraconazole and voriconazole. Voriconazole, a noble broad spectrum triazole agent with good ocular penetration, has been effective in treating both common, as well as very rare fungal infections.[5,6] However, further *in-vitro* anti-fungal sensitivity testing of this uncommon organism is required for future reference.

In conclusion, this case illustrates that *A. kalrae* keratitis may occur in non-contact lens users. Clinicians should be aware of this rare pathogen when dealing with an intensely painful and rapidly progressive fungal ulcer.

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This paper and its contents were written with informed consent of our patient.
There is no financial interest to disclose.

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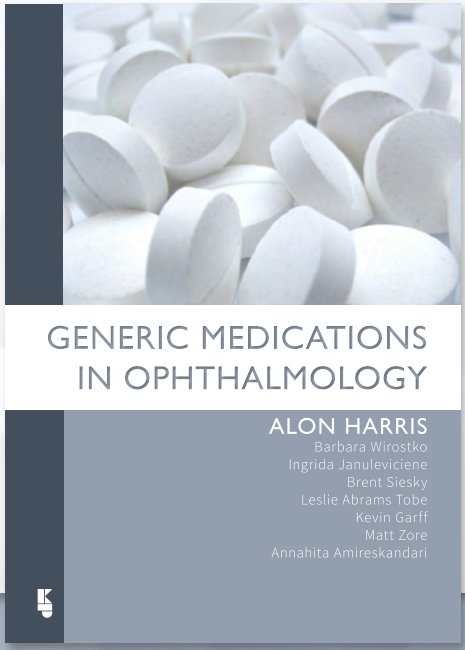

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Asian J Ophthalmol. 2014;14:043-047

Opacification of intraocular lens implant after uncomplicated cataract surgery: A case series

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Abstract: *Opacification of intraocular lens implant after successful cataract surgery is an important issue with the introduction of new intraocular lens. The complexity of the problem is not merely associated with visual impairment, but also lies in the difficulty in diagnosis and management of the case. We report 3 cases of late postoperative opacification of IOL implants warranted IOL exchange.*

Key words: *Opacification, intraocular lens*

Introduction

Transparency in an implanted intraocular lens (IOL) is essential for the maintenance of high-quality vision after cataract extraction. Although advancement in lens manufacturing and lens design have significantly improved lens clarity and ultimate visual outcomes of cataract surgery, loss of IOL transparency over time is still a potential problem that could end up with IOL explantation. Postoperative opacification of IOL has been reported in all varieties of lens including silicone, hydrophobic acrylic, hydrophilic acrylic, hydrogel and even in PMMA lens.[1] We report three cases of late postoperative opacification of IOL implants warranted IOL exchange.

Case 1

A 55-year-old Chinese female with diabetes and hypertension had undergone uneventful left phacoemulsification cataract surgery with posterior chamber Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed) in the left eye in April 2006 with best-corrected visual acuity (BCVA) of 6/24 post-operatively. She came back two years later with profound drop in vision to perception to light. Examination revealed homogenous white opacification of the optical component of IOL (Figs. 1 and 2). She underwent an eventful IOL explantation with anterior vitrectomy and anterior chamber IOL implantation (PMMA). However, her post-operative BCVA was not much improved, 6/60 due to her existing diabetic maculopathy.

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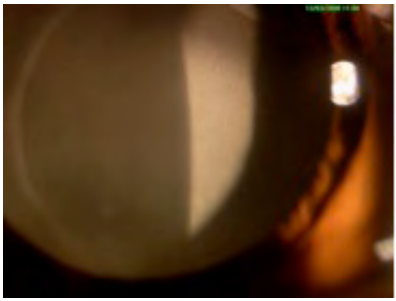

Fig. 1. Slit-lamp photo showing opacified Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed).

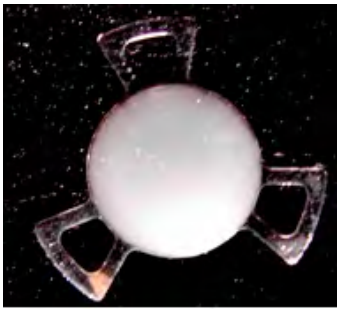

Fig. 2. Explanted single piece Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed).

Case 2

A 60-year-old Indian female, also a known case of diabetes, had right phacoemulsification cataract surgery with in-the-bag posterior chamber Hydroview H60M IOL (Bausch and Lomb Surgical; Rochester, NY, USA) implantation in August 1999. Her BCVA post-operatively was 6/6. She presented seven years later, with vision of counting finger! A diagnosis of non-resolving vitreous hemorrhage was made and she was referred to the Vitreo-retina team for vitrectomy. Further examination pointed to opacification of the implanted IOL (Fig. 3). The vitreous was confirmed clear on B scan. She underwent successful IOL explantation with secondary IOL implantation (hydrophobic-acrylic) in the sulcus (Fig. 4). Her postoperative visual acuity was best corrected to 6/6.

Fig. 3. Slit-lamp photos showing opacified Hydroview H60M IOL.

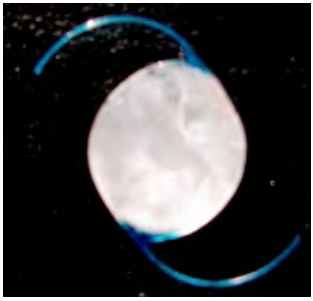

Fig. 4. Explanted single-piece Hydroview H60M IOL.

Case 3

In October 2007, a 72 year-old Chinese female diabetic, with hypertension and ischemic heart disease and suffering from open-angle glaucoma was referred to the Vitreo-Retina Team for further management of vitreous hemorrhage in the left eye. She had a history of uneventful phacoemulsification cataract surgery

with posterior chamber Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed) implantation one year before. Vision was hand-movement on presentation. Examination revealed an opaque IOL in the bag which warranted explantation. The release of the IOL was difficult due to fibrosed capsule with capture of IOL haptic. The IOL was maneuvered into the anterior chamber and delivered through a limbal wound. (The explanted IOL had a similar appearance as that in Case 1.) She was left aphakic in view of zonular dialysis. A secondary implantation of posterior chamber IOL in the capsular bag was performed in August 2008. Postoperatively, her BCVA was 6/12.

Discussion

Opacification of the intraocular lens (IOL) is an often overlooked cause of visual impairment following uneventful cataract surgery. It is often misdiagnosed as posterior capsule opacification or vitreous opacification and may unduly be subjected to Yag capsulotomy or vitreo-retinal surgery.

General factors contributing to postoperative IOL opacification could be IOL biomaterial and manufacturing, IOL packaging, surgical technique or patient's factors. IOL biomaterial like acrylic, hydrophilic, hydrogel and silicone had shown to have a higher incidence of IOL opacification post-cataract surgery among all the available IOL.[1] A packaging gasket containing silicone had been implicated in cases of IOL opacification.[2] Inadvertent damage of the optical surface by surgical instruments could promote calcium deposit postoperatively. The patient's pre-existing conditions, particularly her diabetes and glaucoma, have been postulated as a precipitating risk factor.[3]

Opacification of Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed) with resultant total recall of 239 patients, was reported by Andrew Lim and colleagues in Selayang Hospital, Malaysia. It involved 5.4% cases implanted with this hydrophilic acrylic lens. Analysis with scanning electron microscopy and energy dyspersive X-Ray spectroscopy of these cases revealed surface calcium and phosphorus deposits and intralenticular traces of calcium in the opacified IOL.[4] It is believed that the hydroxyhexyl methacylate present in Acriflex 50CSE Hydrophilic Acrylic IOL (Acrimed) has calcium affinity properties which were responsible for the lens calcification. The other type of hydrophilic acrylic IOL which had been reported with significant postoperative IOL opacification requiring IOL exchange was SC60B-0UV.[5]

Hydroview H60M IOL with significant lens opacification in 4.2% of post-cataract surgery cases warranting IOL exchange had been reported by Balasubramaniam *et al*.[3] Dorey *et al*. pointed out that opacified Hydroview H60M IOL was due to silicon acting as a nidus for calcium deposition; which was presumably derived from the Surefold packaging system.[2] Chemistry analysis on the surface deposits of the opacified Hydroview H60M IOL identified a mixture of calcium, fatty acid, salt and silicone.[1,6] Opacification of H60M IOL reported most commonly occurred between 12 and 25 months postoperatively. Our case was exceptional because of its late presentation.

Opacification of Silicon IOL was the most commonly reported cause of IOL opacification in patients who underwent vitreo-retina surgery with silicon oil tamponade. Silicon oil in a vitrectomized eye can also adhere to any hydrophobic, hydrophilic and even PMMA lens resulting in IOL opacification. Other reported cases of IOL opacification were PMMA IOL secondary to late biodegradation of PMMA and Acrysof™ 'glistening' with microvacuole formation in the lens.[1]

Patient factors like metabolic imbalance, breakdown of the blood-aqueous barrier and high level of calcium and phosphorus in the aqueous and serum had been implicated as causes of lens opacification in the diabetics;[1,2] which could be the case in the three patients in this series.

Opacified IOL is often misdiagnosed due to poor fundus view. Haymore *et al*.[7] reported eight cases of misdiagnosis of hydrophilic acrylic lens optic opacification. Four were misdiagnosed as having posterior capsular opacification and underwent Nd:YAG laser capsulotomy and the other four were misdiagnosed as having vitreous opacities and were subjected to vitrectomies. Failure to recognize the process of IOL opacification may lead to unwarranted surgical procedures.

Explantation and exchange of IOL is the only solution to IOL opacification. Nd:Yag laser treatment is not effective in clearing the opacification. Instead it could jeopardize implantation of a new IOL into the capsular bag. Nevertheless, explantation could be technically difficult and challenging. Posterior capsule rupture, zonular dehiscence, iridodialysis and vitreous loss are common complications seen in 10-48% of the IOL exchanges.[5]

Meticulous surgical technique is necessary in IOL removal. The anterior capsule should be carefully teased off the IOL. Careful visco-dissection and radial cuts on the anterior capsule can facilitate the procedure. It is important to caution that attempts to rotate the IOL out of the bag risk zonular dehiscence and rupture of the posterior capsule. Once the IOL is delivered into the anterior chamber, it can be delivered in one piece through a slightly bigger limbal incision the way in which it was done in our patients. Alternatively, it can be cut into two halves and retrieved through a 4-mm limbal incision. Very often the haptic was retained in the fibrosed capsule making complete explantation of IOL impossible.[5] In case of ruptured posterior capsule, the secondary IOL could be sulcus-fixated if in-the-bag implantation is not feasible. In the event of inadequate capsular support, anterior chamber IOL or scleral fixated IOL should be the alternatives. Besides the difficult surgical procedure in IOL explantation, the visual outcome after successful IOL exchange was not promising. Many patients developed post-operative cystoid macular edema after IOL exchange.[5] Therefore, prescription of topical NSAID, a form of 'off-label' treatment which is widely used is advisable after a complicated surgical procedure. Control of postoperative inflammation with steroids is equally important to minimize the risk of post-operative cystoid macular edema. Subtenon, infra-orbital or intravitreal triamcinolone could be given for severe inflammation. Medical therapy with systemic acetazolamide is one of the options besides intravitreal anti-VEGF injection. Surgical intervention is required for macular oedema secondary to vitreo-macular traction.[8]

Although IOL opacification postoperatively is a rare entity, careful selection of IOL should not be overlooked. It is particularly important for patients with present or potential vitreo-retinal disease such as diabetics and high myopic patients who may need silicone oil as tamponade to avoid having silicone IOL.

We recommend that new IOL should be rigorously tested for longer period by researchers before large-scale usage. Informed consent of cataract surgery should also include the possibility of postoperative IOL opacification. A proper reporting system is useful to highlight the issue and to alert the other clinicians of the potential hazard of postoperative opacification of particular IOL. Adverse-event reporting systems have been implemented in some countries to allow early reporting of problems with IOL.[4] Further investigations should be carried out to identify the cause of the IOL opacification and a notice or recommendation should be issued to withhold the use of the particular IOL or to alert caution in using it. This is to prevent repetition of the same problems of opacification of the particular IOL; especially in the under-privileged area where expertise is less available to handle this type of visual loss.

Conclusion

Careful testing and selection of new IOL for cataract surgery is important to minimize the incidence of IOL opacification postoperatively for it is a potential cause of significant visual impairment after cataract surgery. Furthermore, IOL exchange is a challenging procedure and may have an unpredictable surgical outcome.

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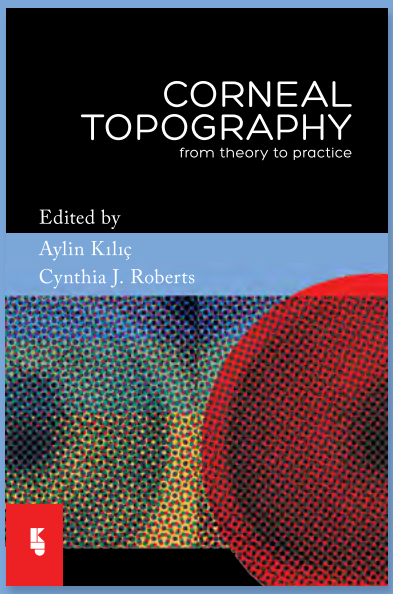

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