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EDITOR'S MESSAGE

Dr Aliza Jap, Editor

Antifibrotic agents of various forms have been used in an attempt to improve the success rate of glaucoma filtration surgery since the 1990s. However, they are still not good enough, partly because we are not able to adjust their dose very accurately according to the individual patient's wound healing response. This in turn is partly due to the method of application of these agents. Currently the 2 commonly used antifibrotics, Mitomycin C (MMC) and 5-fluorouracil (5-FU) are delivered via sponge applications intra-operatively. There is considerable variation in the amount of agent released as well as absorbed by the subconjunctival tissues following a sponge application. They may also be administered as subconjunctival injections, but again there is no good consensus on the concentration to be used.

Perhaps the real issue though is not the antifibrotic agents and their mode of delivery but the whole concept of the trabeculectomy itself. Following a trabeculectomy, the aqueous bypasses the normal outflow channels and is diverted into the subconjunctival space. However this in turn leads to the problems with wound healing.

More "physiological" alternatives, which are less dependent on the formation of a conjunctival bleb, include the non-penetrating surgeries and shunts such as the Gold microshunt and the Eyepass implant.

Although the non-penetrating surgeries have lower complication rates as compared to trabeculectomy, at present, they are unable to achieve the same amount of pressure lowering and have a higher failure rate overtime.

The shunts are said to show promise... and if all else fails there's always pneumatic trabeculoplasty?

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OVERVIEW OF STRABISMUS IN SINGAPORE CHILDREN

Presented by Dr Quah Boon Long on 2 May 2007
Written by Dr Zena Lim

The reported prevalence of strabismus ranges from 0.3% to 7.87%. In Western populations, esotropia is 1.5 to 4 times more common than exotropia. In Asia, exotropia forms the majority of childhood strabismus (65-86%).

For the period January 2000 to June 2002, an audit of 850 children presenting with possible squint to Singapore National Eye Centre and KK Women's and Children's Hospital showed that true squints comprised 59.1% of cases, and pseudosquints the remaining 40.9%. Of the 502 children with true squints, the majority had intermittent exotropia (61.2%), followed next by accommodative esotropia (13.3%), infantile esotropia (6.4%), non-accomodative esotropia (6.2%), constant exotropia (6.2%) and others (6.8%).

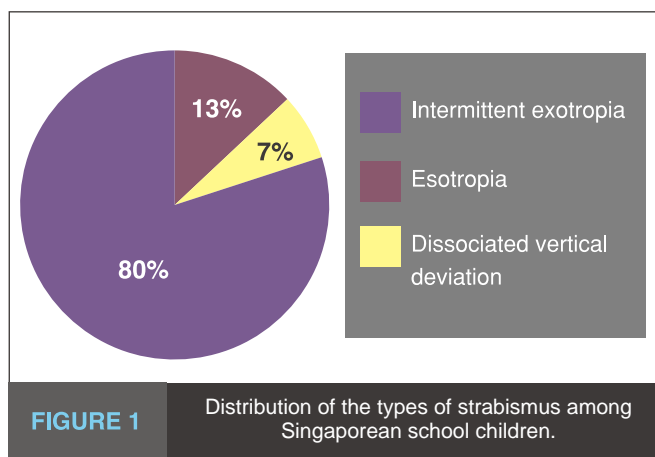
In a cross-sectional study to further determine the prevalence and types of strabismus in Singapore schoolchildren, 668 participants aged 12-14 years from 2 schools in Singapore were screened. These children were participants of the Singapore Cohort study Of the Risk factors for Myopia (SCORM). Parents were given a questionnaire on the child's history of strabismus. Visual acuity tests and eye screenings for strabismus and ocular motility disorders were carried out at school premises by trained orthoptists and ophthalmologists. Referral was made to a paediatric ophthalmologist for confirmation of diagnosis if there was a positive or suspected case of strabismus, limitation of eye movement or a positive history of strabismus.

Of the 30 children found positive for strabismus at the schools, 25 were re-assessed by a paediatric ophthalmologist with 15 finally diagnosed with strabismus. The prevalence of strabismus was found to be 2.2% with no gender or racial predilection. Twelve (80%) had intermittent exotropia, 1 each had accommodative and non-accomodative esotropia and 1 had dissociated vertical deviation. Figure 1 shows the distribution of the types of strabismus found. In addition, between strabismic and non-strabismic children, there was no difference in mean spherical equivalent and axial lengths. Comparing high

and low myopes, there was no statistically significant difference in strabismus rates ($p=0.27$). None were found to have strabismic amblyopia.

Eight children (53%) were aware of having strabismus prior to screening. The largest angle exotropia that went unnoticed by parents was 45 prism dioptres. The largest angle esotropia that went unnoticed was 30 prism dioptres. The smallest angle exotropia that was recognized was 25 prism dioptres.

In conclusion, the overall prevalence of strabismus in 12 to 14 year olds in Singapore is 2.2%. This is in concordance with reported strabismus prevalence rates. Intermittent exotropia is by far the most common type of strabismus in Singapore. Only half of parents surveyed were aware of the presence of strabismus prior to screening.



Key Learning Points:

1. Prevalence of strabismus among the school-going cohort of children in Singapore is 2.2%.
2. Intermittent exotropia is the most common type of strabismus locally.
3. Parental awareness of strabismus is not high, with only 50% aware of pre-existing strabismus in the child prior to screening.

WOUND HEALING AND BLEB FAILURE

Presented by Dr Tina Wong on 22 August 2007
 Written by Dr Anshu Arundhati

Wound healing is a subject of great interest because abnormal healing is the main reason for failure in glaucoma surgery. As surgical treatment is the most successful method to preserve vision in the long term, the ability to control the wound healing response to maximize surgical success is therefore vitally important. In addition, it is essential to understand why some filtration operations fail despite the use of conventional antifibrotics like Mitomycin C (MMC), 5-fluorouracil (5-FU) and beta-radiation.

A fine balance exists between subconjunctival wound healing and bleb survival. A cascade of events occurs following conjunctival injury that in normal circumstances leads to appropriate wound healing responses and bleb success (figure 1). This involves activation of platelets and the coagulation cascade, leading to inflammation, extracellular matrix remodeling, apoptosis and wound healing (figure 2). Inflammation is however, a two-edged sword; on the one hand it removes the injurious stimuli and promotes healing, while on the other hand excess of it can lead to scarring and surgical failure.

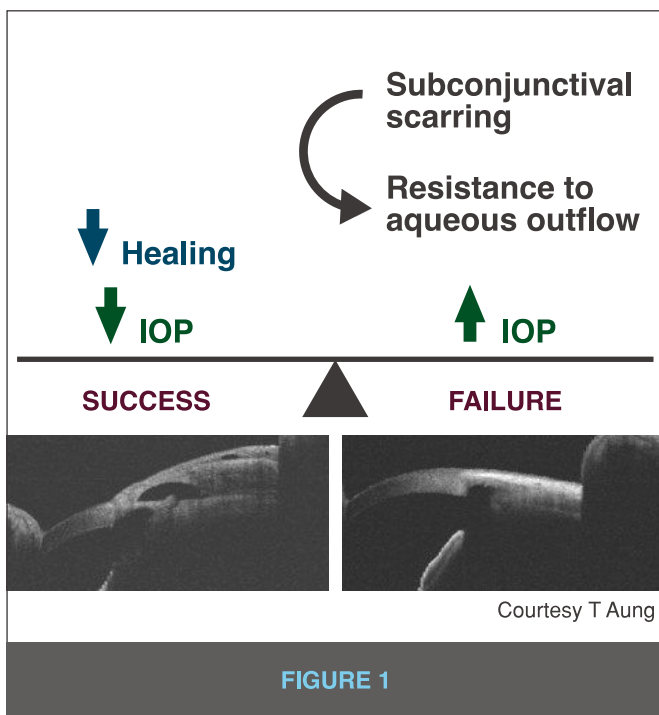


FIGURE 1

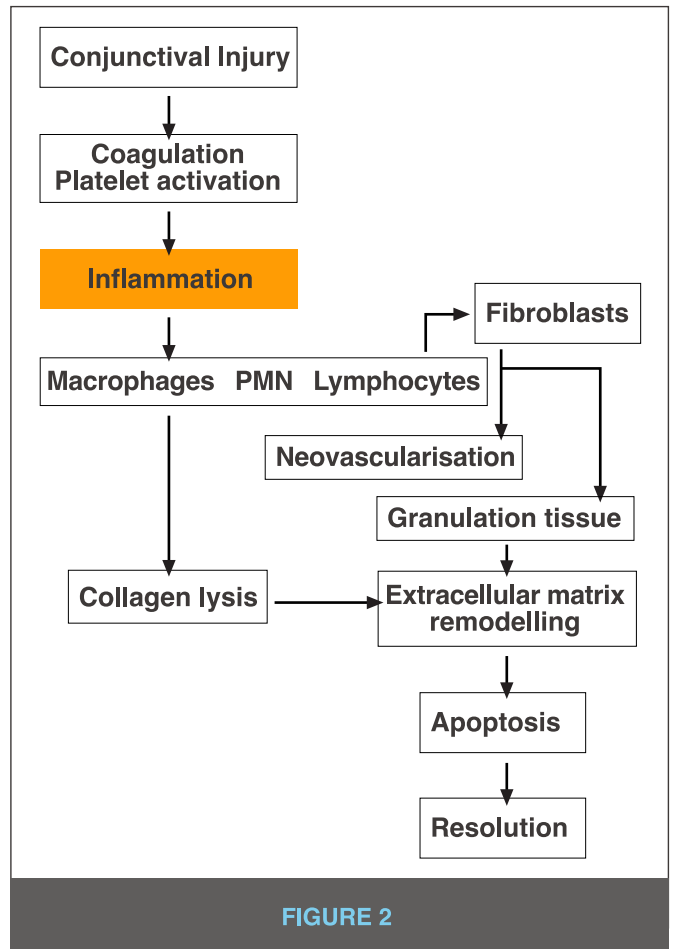


FIGURE 2

Following surgical trauma and local bleeding, a variety of inflammatory mediators that increase vascular permeability and recruit leucocytes and macrophages are released. In the first week following conjunctival injury, macrophages and stimulated T-cells increase the production of growth factors such as TGF beta, which in turn leads to fibroblast proliferation, granulation tissue formation and replacement of provisional matrix with collagen.

In week 2, collagen and fibronectin synthesis occurs. This is dependent on tissue oxygen tension and adequate perfusion. High lactic acid levels promote collagen synthesis. Hypoxia and increased lactic acid levels induce tissue ischemia that stimulates the release of angiogenic factors eg VEGF.

This results in endothelial cell proliferation and capillary bud formation and bleb vascularity. Increased production of TGF beta stimulates subconjunctival scarring and fibrosis.

Inflammation is followed by a phase of extracellular matrix (ECM) remodeling that begins 3 weeks after surgery and lasts several months. Wound remodeling is a dynamic process and involves conversion of granulation tissue and collagen type 3 to mature collagen type 1. During this phase of wound remodeling, a fine balance exists between collagen synthesis and crosslinking and collagen and ECM breakdown. Clinically, this can manifest as subconjunctival scar tissue (apposition of scleral flap to its bed and loss of subconjunctival space) and Tenon's encapsulation – "Ring of steel". Subconjunctival scarring leads to increased resistance to aqueous outflow, raised intra-ocular pressure (IOP) and bleb failure (figure 3a,b).



FIGURE 3a

Subconjunctival scar tissue formation with apposition of scleral flap to bed and subsequent loss of subconjunctival space

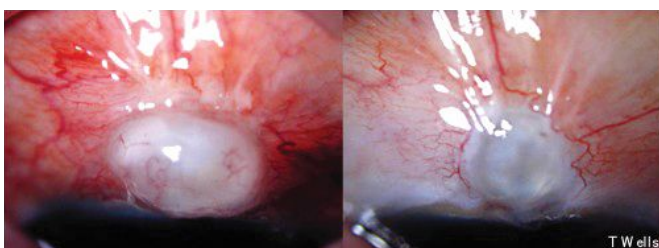


FIGURE 3b

Tenon's encapsulation - 'Ring of Steel'

Currently, treatment for bleb encapsulation and scarring involves needling that physically removes scar tissue and re-establishes aqueous outflow and injection of 5-FU or dexamethasone that alter fibroblast activity and hence wound healing via release of cytokines like TGF-beta, TNF alpha, IL-1, and IL-6.

Inflammation and ECM remodeling are followed by resolution and restoration of normal tissue morphology and function. This requires immune homeostasis coupled with apoptosis.

An aggravated inflammatory response, increased fibroblast proliferation and activity, coupled with enhanced collagen lysis results in a chronic wound healing response with subconjunctival scarring and fibrosis.

In conclusion, the last remaining barrier to surgical success is the post-operative wound healing response. Knowledge of the mechanisms and stages of wound healing aid in institution of specific treatment, which is not "one size fits all" technique. Current antifibrotic agents like MMC and 5-FU are however not good enough and several new methods are currently being evaluated for prevention of bleb failure which include amongst others, anti-angiogenic agents, drug delivery systems and spacers.

Key Learning Points:

1. The postoperative wound healing response following filtering surgery is the last barrier to surgical success and IOP control. Despite the use of conventional anti-fibrotics like MMC and 5-FU, bleb failure still occurs.
2. Optimal inflammation, fibroblast proliferation, extracellular matrix remodeling and apoptosis lead to resolution and return of normal tissue morphology and function.
3. Knowing the signs of active scarring process and the mechanisms involved is useful in tailoring individualized treatment.

NEW CONCEPTS AND TECHNIQUES IN THE TREATMENT OF SEVERE CORNEA AND OCULAR SURFACE DISEASE

Presented by Dr Leonard Ang on 3 October 2007

Written by Dr Cheng Jin Fong

A new grading system for ocular surface disease

Limbal stem cell deficiency can occur as a result of a variety of diseases including Stevens - Johnson syndrome (SJS), chemical injury and Ocular Cicatricial Pemphigoid. The corneal changes include corneal ulceration, vascularisation, opacification, scarring, thinning and perforation. Conjunctival damage includes keratinization, scarring, symblepharon and fornix shortening. Lid changes that may be seen include ectropion, entropion, damage to lashes and keratinisation. Lastly, severe dry eyes can result from decreased tear production.

Despite the potentially devastating nature of these severe diseases and the increasing indications for ocular reconstructive surgery, there is currently no standardized method for evaluating the spectrum and severity of ocular complications.

A study published in Ophthalmology 2007, on a new grading system for the evaluation of chronic ocular manifestations in patients with Stevens - Johnson syndrome (SJS) attempts to address these issues, so

as to allow for objective monitoring of the disease, predicting treatment and visual outcome and it creates a common platform for the discussion and management of the disease.

This prospective multicentre case series involving the Kyoto Prefectural University of Medicine, Keio University and National Tokyo Medical Centre had 73 patients (138 eyes) with SJS seen between April 2003 and March 2005. SJS was diagnosed based on a history of acute onset of high fever, serious mucocutaneous illness with skin eruption and involvement of at least 2 mucosal sites including the ocular surface. They had chronic ocular complications that persisted for at least one year from the onset of SJS. Patients with previous history of ocular surface surgery were excluded.

Ocular involvement was categorized into cornea, conjunctiva and eyelid complications and 13 components in the above categories were assessed and graded from 0-3 with 0 being the least severe and 3 being the most severe. The maximum total score was 39 for each eye.

Corneal Complications

Score	0	1	2	3
Superficial punctuate keratopathy	A1D1	A1D2	A1D3, A2D2 or A3D1	A2D3, A3D2 or A3D3
Corneal epithelial defect	nil	<1/4	1/4-1/2	>1/2 corneal surface
Loss of Palisades of Vogt	nil	<1/4	1/4-1/2	Total circumference loss
Conjunctivalization	nil	<1/4	1/4-1/2	>1/2 corneal surface
Corneal neovascularisation	nil	Confined to corneal periphery	Extend to pupil margin	beyond pupil margin into central cornea
Corneal opacification	clear	Partial obstruction of iris details	Iris details poorly seen. Pupil margin just visible	Complete obstruction
Corneal keratinization	nil	<1/4	1/4-1/2	>1/2

A=area. A0= no punctuate staining A1= less than 1/3, A2=1/3-2/3, A3=>2/3
D= density. D0=no staining, D1=sparse D2=moderate, D3=high

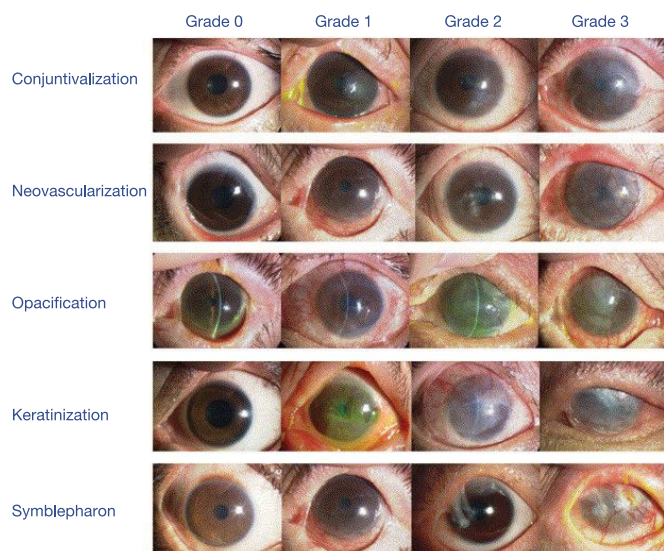


FIGURE 1

Classification of corneal complications

Conjunctival Complications

Score	0	1	2	3
Conjunctival hyperemia	nil	Mild or Sectoral	Moderate/diffuse	Severe
Symblepharon formation	nil	Involving conjunctiva surface	<1/2 corneal surface	>1/2 corneal surface

Eyelid Complications

Score	0	1	2	3
Trichiasis	nil	<1/4 of lid margin	1/4-1/2 of lid margin	>1/2 of lid margin
Mucocutaneous junction involvement	normal	Mild irregularity	Moderate	Severe
Meibomian gland involvement	Clear oily fluid expressed	Yellowish white oily fluid	Thick cheesy oily fluid	Inability of express fluid
Punctual involvement	Normal patent	Iatrogenic punctual occlusion	Either superior or inferior punctual occlusion by scarring	Both puncta occluded by scarring

The study showed that meibomian gland involvement and loss of palisades of Vogt were the most common ocular complications of SJS. Patients with the best visual acuity of >20/20 had the best mean score of 5.86 and patients with the worst visual acuity of <20/2000 had a mean score of 27.45. The total score for each eye was significantly correlated with its visual acuity. When the score increases the visual acuity decreases.

All 13 complications were significantly correlated with visual acuity. On multivariable regression analysis, cornea neovascularization, cornea opacification and cornea keratinization correlated most with severe visual loss. Conjunctivalization being a sequela of limbal stem cell deficiency was also correlated with poor vision in the series. This study showed that eyes with higher scores had poorer vision.

In summary, we have described a new method of classifying chronic ocular surface disease which will help in objective monitoring of the disease, prognosticate treatment and visual outcome and provide a common platform for discussion and management of the disease.

Management concepts of severe ocular surface disease

Currently, there are many types of surgical treatment performed for severe ocular surface disease. The commonly performed procedures include: limbal stem cell transplantation with allografts or autografts, keratoepithelioplasty which is the transplantation of a lenticule of peripheral cornea, and amniotic membrane transplant. Where there is a significant scar, cornea transplant with optical, tectonic, lamellar or penetrating keratoplasty may be used although lamellar surgery is preferred as this preserves the endothelium and when all else fails a keratoprosthesis is used. These have met with limited success.

Limbal autograft transplants have been used in patients with unilateral chemical injury with good results. Allografts from cadaver tissue will have to be used if the injury is bilateral. However despite the initial good results, many of these transplants eventually fail. Studies by Tugal-tutkin et al. and Solomon et al. have shown that limbal transplant of patients with SJS fails after 3 years.

Cultured epithelial transplantation was first described by Pellegrini G et al. 1997, where he grew cornea epithelial cells from normal tissue on a fibrin sheet and subsequently transplanted these cells onto the eye. This cultivated tissue sheet is similar in nature to the structure of in vivo cornea, demonstrating a normal cornea phenotype with desmosomal attachments. This combined with a lamellar keratoplasty can be used to treat patients with chronic scarring from SJS. Patients have demonstrated stable ocular surface several years after such a procedure.

Previously the bulky oral mucosa had been used to reconstruct the forniceal region but not the bulbar conjunctiva. However when the oral mucosal cells are cultivated, they can be modified to form smooth, stratified multi-layered epithelium sheets which are similar to cornea epithelium. This epithelial sheet may be used not only to reconstruct the cornea surface, but may also be used to reconstruct the fornices and bulbar conjunctiva.

Cultivated conjunctival transplantation involves a conjunctival stem cell biopsy from the fornix. Ex vivo expansion is used to form the conjunctival epithelial equivalent. This conjunctival sheet is then transplanted onto the ocular surface. It has been used for pterygium surgery especially in patients with extensive, recurrent or aggressive pterygium. We have used cultivated conjunctiva to resurface the cornea in 13 eyes of 11 patients with chemical injuries, recurrent pterygia, SJS and acne rosacea. The visual acuity improved by 2 lines or more in 42.9 % of these eyes. The reasons for poor vision in the remaining eyes include amblyopia, pre-existing glaucoma and stromal scarring.



FIGURE 2a Cultivated conjunctival transplant – pre-op

In all cases of cultivated oral or conjunctival epithelial transplant, autologous tissue is preferred because there is no need for immunosuppression. The procedure could be repeated multiple times and rejection rates would still be low as autologous tissue is used. When allogenic tissue is used, there may be clarity in the initial stages but the survival of future transplants may be jeopardized due to sensitization.

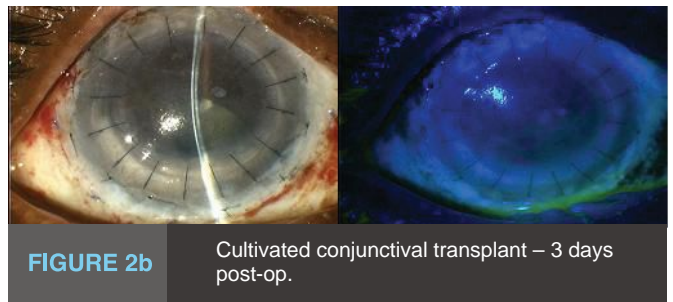


FIGURE 2b Cultivated conjunctival transplant – 3 days post-op.

Conventional treatments of chronic ocular surface disease with limbal stem cell transplantation, keratoepithelioplasty and amniotic membrane transplants have met with limited success. We are exploring the possibility of using sheets of cultivated cornea, conjunctiva and oral mucosal to replace the cornea in such cases.

Advances - Cultivated Epithelial Transplantation

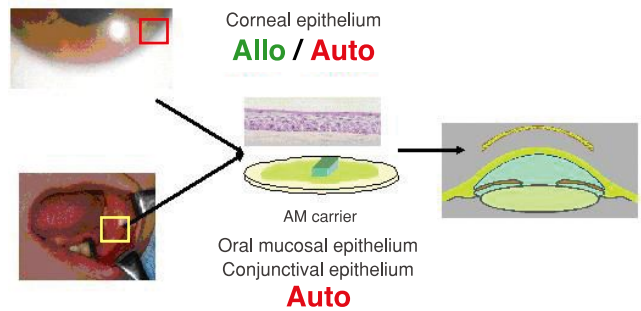


FIGURE 3 Summary of recent advances in the management of ocular surface disease.

Key Learning Points:

1. A new method of classifying chronic ocular surface disease where ocular involvement is categorized into cornea, conjunctiva and eyelid complications.
2. Cultivated epithelial transplant had been used successfully to treat chronic ocular surface disease.

CMV INFECTION IN THE IMMUNOCOMPETENT

Presented by A/Prof Chee Soon Phaik on 24 October 2007
Written by Dr Elaine Chee

Cytomegalovirus (CMV) infections of the eye are usually thought of as an infection occurring in the immunocompromised patients. In these patients, CMV usually manifests as CMV retinitis with the typical findings of haemorrhages and patches of retinitis along the blood vessels, giving a “tomato ketchup and cheese” appearance. In recent years, CMV infections have been identified with increasing frequency even among the immunocompetent individuals.

CMV infections in the immunocompetent individuals can manifest in the following ways:

1. Chronic anterior uveitis with raised intraocular pressures (IOP)
2. Acute episodic iritis with high IOP
3. Sectorial iris atrophy with high IOP
4. Corneal endotheliitis

The different manifestations as mentioned above are illustrated in 3 of our immunocompetent patients who were initially misdiagnosed as other clinical entities.

Case 1

This 39 year old Chinese gentleman was initially diagnosed with Fuch’s heterochromic iridocyclitis. (FHI) He had persistent episodes of uveitis with raised intraocular pressures; hence an anterior chamber (AC) tap was done to exclude infections. The AC tap turned out to be positive for CMV DNA. Figure 1a shows the iris heterochromia. Figure 1b shows the stellate keratic precipitates which are often seen in FHI.



FIGURE 1a

Iris heterochromia



FIGURE 1b

Stellate keratic precipitates

Case 2

This 48 year old Chinese male presented 3 months after Lasik with redness and a drop in vision. It was initially thought to be a diffuse lamellar keratitis. However the presence of fluid in the interface and high intraocular pressures raised the possible diagnosis of herpetic uveitis. The patient however had repeated relapses of uveitis, despite treatment with acyclovir. Hence an anterior chamber tap was done, which was also positive for CMV DNA.

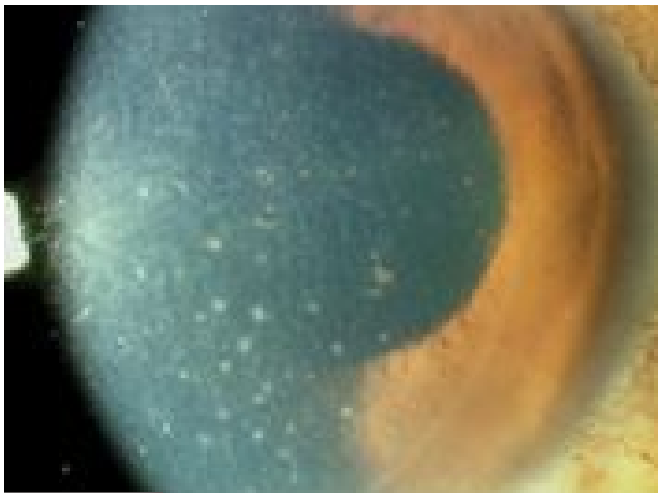


FIGURE 2a

Edematous lasik flap

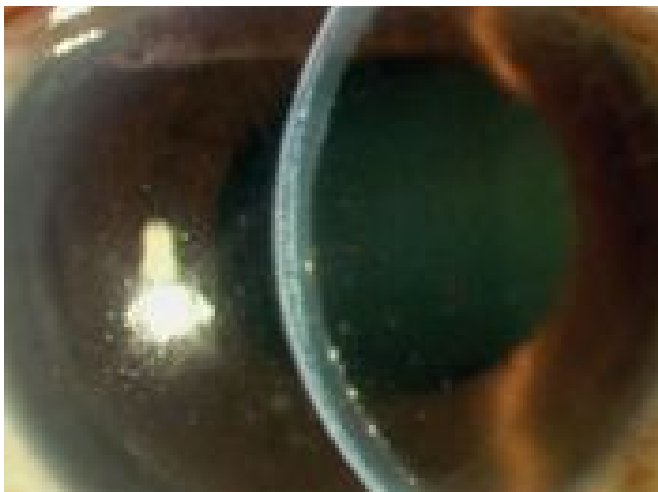


FIGURE 2b

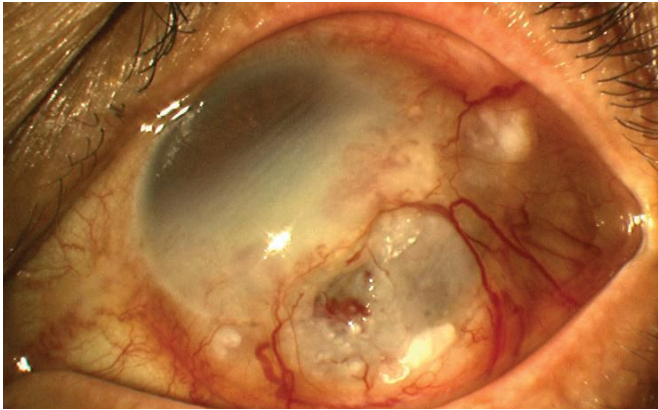
Fluid seen in the flap interface
with Keratic precipitates

As illustrated, CMV infections in the immunocompetent patient can be missed initially as they are often diagnosed as other more common conditions, such as Fuch's heterochromic iridocyclitis or Posner Schlossman syndrome. (PSS) In a study done among our SNEC patients with hypertensive uveitis, 37.5% of those presumed to have Posner Schlossman (PSS), and 31.1% of those presumed to have Fuch's heterochromic iridocyclitis (FHI) were found to be CMV positive from anterior chamber taps. CMV infections therefore can have a spectrum of manifestations, ranging from PSS to sectorial iris atrophy with iritis, FHI and finally retinitis. These clinical manifestations probably manifest according to the immune response of the patient and the eye, with the most severe manifestation of retinitis occurring in the immunocompromised patients.

Key Learning Points:

1. CMV anterior uveitis in the immunocompetent individuals is increasingly being recognized as a separate clinical entity.
2. CMV infections should be suspected in patients with persistent hypertensive uveitis or corneal endotheliitis.
3. With a high prevalence of CMV infections being recognized, there should be more judicious use of steroids in these patients.

ANSWER TO PHOTOQUIZ 12



The figure shows opacification and vascularization of the inferotemporal $\frac{3}{4}$ of the left cornea. The surface is irregular, with an inferior paracentral thinned area and other well circumscribed white areas suggesting keratin formation. Although the inferotemporal vessels appear to have enlarged calibers, the eye does not otherwise appear very inflamed.

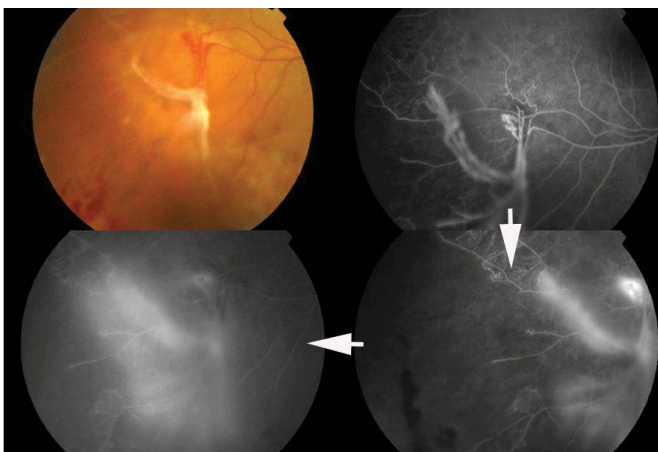
The diagnosis is ocular surface squamous cell carcinoma (OSCC). As opposed to conjunctival/corneal carcinoma in situ (CIN) which does not invade beyond the epithelial basement membrane, this lesion clearly involves corneal stroma with opacification and erosion of an ovoid area in

the inferior paracentral region. Risk factors for ocular surface squamous neoplasia (OSSN) include ultraviolet light exposure, increasing age, exposure to petroleum products and exposure to the human papillomavirus.

Patients with OSCC require an oncologic referral and screen to exclude metastases. Further management may then include medical therapy, surgery, or a combination of both. In general, most cases of CIN may be treated with topical medications. These include antimetabolites such as mitomycin C and 5-fluorouracil, and immunomodulators such as interferon alfa-2b. Surgery for more extensive cases involves wide excision, with a 4mm tumour free conjunctival margin and 2mm corneal epithelial margin. Adjunctive intra-operative therapy includes cryotherapy and/or localized application of absolute alcohol to the margins.

The patient described had an extensive OSCC with marked corneal thinning which unfortunately progressed and necessitated left deep lamellar keratoplasty with wide excision of tumour margins and adjunctive cryotherapy. Post-operatively he was also commenced on G interferon alfa-2b qds.

QUESTION TO PHOTOQUIZ 13



A 25-year-old Indian gentleman presents complaining of sudden onset blurring of vision in the right eye. He is systemically well with no known medical problems. The colour picture and fundus fluorescein angiograms are presented as follows.

What do the figures show and what is the most likely diagnosis?

Please send your entries to: cmenewsletter@sneec.com.sg or fax to: (65) 6226 3395 Attention: Ms Chia Hui Yien. Winners will each receive a 1GB thumbdrive and will be notified by post. The answers will be published in the next issue.



Singapore National Eye Centre

11 Third Hospital Avenue
Singapore 168751

Tel: +65 6227 7255
Fax: +65 6227 7290

www.snec.com.sg
Reg No: 198900840W

ips

International Patient Service
24 hour Hotline

Tel: +65 6100 9393
Fax: +65 6222 9393
email: ips@snec.com.sg

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