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Increased expression of mucinous glycoprotein KL-6 in human pterygium

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Ocular Neovascularisation (VISION) treated 1186 patients with more than 9000 IV Macugen injections and reported no RPE tears during a 2 year follow up.³ As IV Avastin injections are an "off-label use of a FDA approved drug," several physicians established an internet register to track adverse events (https://www.formrouter.net/forms@PACEA/AvastinSafetySurvey05_A.aspx). This register so far contains no RPE tear (Phil Rosenfeld, Anne Fung, personal communication).

In conclusion, we present two patients with occult CNV and PED who developed a RPE tear early after the first IV injection of Avastin. The role of intravitreal Avastin therapy in the development of this RPE tear is not clear.⁶ As occult CNV are frequently accompanied by a PED, we may face a higher incidence of acute RPE tears after intravitreal antiangiogenic injections compared to classic CNV after PDT.¹ Patients need to be informed about this possible complication in this novel off-label use drug.

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Increased expression of mucinous glycoprotein KL-6 in human pterygium

Pterygia represent growth onto the cornea of fibrovascular tissue continuous with the conjunctiva.¹ KL-6 (Krebs von den Lunge-6) is a high molecular weight mucinous glycoprotein, and the monoclonal antibody reacts with the sugar moiety of MUC-1.^{2,3} We have reported that measurement of serum KL-6 levels is useful for the diagnosis and management of uveitis patients with sarcoidosis.^{4,5} The aim of this study was to examine the expression of KL-6, and Ki-67, a proliferation marker, in normal human conjunctiva, pterygium, and pseudopterygium tissues.

Methods

Five samples consisting of one normal conjunctiva, three pterygia, and one pseudopterygium were surgically collected. Formalin fixed and paraffin embedded tissue sections were incubated with anti-KL-6 and anti-Ki-67 monoclonal antibodies, and then examined immunohistochemically.

Results

Immunoreactivity for KL-6 was detected on the apical membrane of the wing and basal cells in the normal conjunctiva. In the human pterygium head, immunoreactivity for KL-6 was observed on the apical membrane and in cytoplasm of the epithelium (fig 1A–E). In the pterygium body, immunoreactivity for KL-6 was strongly detected in cytoplasm and/or circumferential membrane of epithelial cells (fig 1G–K). Many KL-6 positive cells were observed in the superficial layer, while the immunoreactive cells were not detected in the subepithelial layer. Although KL-6 immunopositive cells were detected in the basal layer of the pseudopterygium, superficial cells did not express KL-6. The number

of KL-6 immunopositive epithelial cells was lower than those in pterygia and the normal conjunctiva. Table 1 summarises immunopositive rate of KL-6.

Nuclear immunoreactivity for Ki-67 was detected in each epithelium (fig 1F, L). The number of Ki-67-positive nuclei was higher in pterygium head (labelling index: 13.6%) than that in the body (3.3%).

Comment

There was no significant difference in KL-6 immunopositive rate of basal and suprabasal layers between pterygia and normal conjunctiva. This suggests that pterygia seem to show no obvious change in mucin secretion compared with normal conjunctiva. In contrast, KL-6 was downregulated in the pseudopterygium, implicating advanced loss of the conjunctival epithelium's ability to produce mucin. Although it is sometimes hard to distinguish pterygia from pseudopterygia histopathologically, pseudopterygia clearly differ from pterygia with regard to KL-6 expression.

In this study, we showed the diversity of subcellular immunolocalisation of KL-6 in pterygia and the normal conjunctiva. As recently demonstrated, the cytoplasm/circumferential membrane staining pattern of KL-6 in colorectal carcinoma contributed to unfavourable prognosis when compared with apical membrane patterns.⁶ Moreover, the number of Ki-67 positive nuclei was higher in the pterygium head than in the body, indicating that proliferation activity was high in the pterygium apex. Taken together, subcellular reactivity of KL-6 in human pterygia might be correlated with pathobiological behaviour such as corneal invasion.

It has been demonstrated that pterygium body fibroblasts play an important part in the pathogenesis and development by expressing gene products.^{1,7,8} As recently reported, KL-6 molecules had pro-proliferative and anti-apoptotic effects on lung fibroblasts,⁹ which are correlated with epithelial-mesenchymal interactions in interstitial lung disease.⁹ The upregulation of KL-6 expression might be associated with the proliferation of pterygium fibroblasts and invasion of the cornea.

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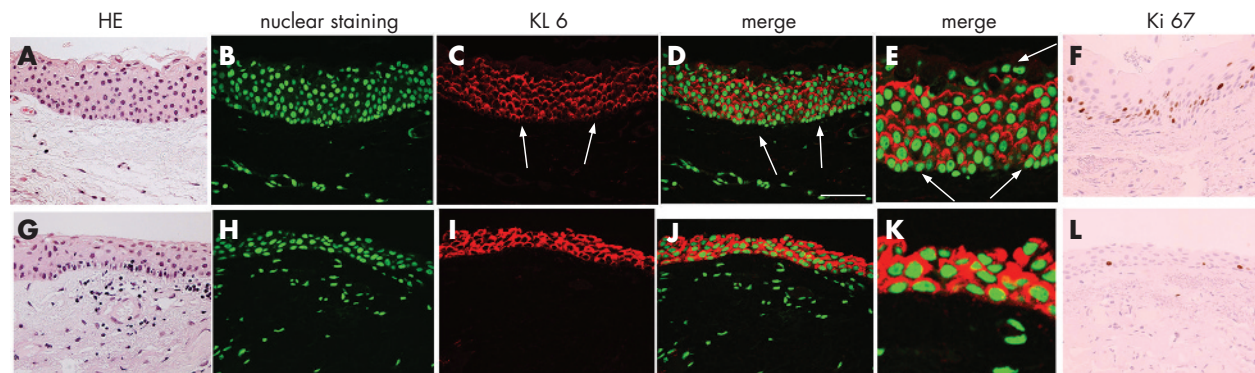


Figure 1 Haematoxylin and eosin staining (A, G), and expression of KL-6 (B–E, red) and Ki-67 (F, L) in the human pterygium head (A–F) and body (G–L). KL-6 immunoreactivity is detected in the pterygium tissue (B–D). At high magnification, immunoreactivity for KL-6 is located in the cytoplasm and on the cell membrane of many epithelial cells (E). KL-6 expression is not detected in superficial cells (E, arrows), nor in the basement membrane (C–E, arrows). Immunoreactivity for KL-6 is strongly noted in pterygium body epithelium (H–J), especially in the cytoplasm (K). Nuclear immunoreactivity for Ki-67 is detected in several pterygium epithelial cells (F, L). Green: nuclear staining with YO-Pro-1. Bar = 50 μ m.

Table 1 Summary of KL-6 immunopositive pattern in normal human conjunctiva, pterygia, and a pseudopterygium

| | Total (%) | Cytoplasmic/ circumferential membrane | Apical |
|--------------------|-----------|---|--------|
| Normal conjunctiva | | | |
| Superficial | 0 | 0 | 0 |
| Wing | 100 | 7.3 | 92.7 |
| Basal | 100 | 3.0 | 97.0 |
| Pterygium head | | | |
| Superficial | 25 | 0 | 25.0 |
| Suprabasal | 100 | 9.4 | 90.6 |
| Basal | 90 | 5.0 | 85.0 |
| Pterygium body | | | |
| Superficial | 83.3 | 35.7 | 47.6 |
| Suprabasal | 100 | 62.5 | 37.5 |
| Basal | 100 | 65.5 | 34.5 |
| Pseudopterygium | | | |
| Superficial | 16.7 | 8.4 | 8.3 |
| Suprabasal | 58.2 | 9.5 | 48.7 |
| Basal | 65.5 | 3.4 | 62.1 |

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A simple technique for indirect gonioscopy for patients who cannot be examined at the slit lamp

Gonioscopy, the visualisation of the anterior chamber angle, is central to the examination during the initial and subsequent evaluation of a glaucoma patient.¹ In the infirm or immobile patient it can present a challenge to the examining ophthalmologist when patients are unable to position adequately for slit lamp microscopy. Here we present a valuable technique for indirect gonioscopy utilising a mirrored lens and the direct ophthalmoscope. To our knowledge this method has not previously been described.

Technique

Instead of using the slit lamp for magnification, we use a direct ophthalmoscope with the internal lens set to +15 dioptres or +20 dioptres. The gonioscopy lens is applied in the usual way, with the examiner holding the lens in one hand and the direct ophthalmoscope in the other (fig 1). Using a four mirrored lens in this way, indentation gonioscopy is possible. With practice, this technique can be performed in patients who are supine (for example, in bed) or seated (for example, in a wheelchair).

Comment

This simple technique allows for gonioscopy in patients who cannot be examined at the slit lamp. It uses equipment that should be readily available in the glaucoma clinic. For clinicians who are experienced at slit lamp gonioscopy, it is a relatively easy procedure to learn and yields comparable views of the iridocorneal angle enabling detection of configuration variants and angle anomalies. We find the technique very useful in the evaluation of many patients who might otherwise be impossible to examine fully.

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Figure 1 Demonstration of the technique of indirect gonioscopy utilising a four mirrored contact lens and the direct ophthalmoscope.

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Reference

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Haemorrhagic vitreoretinal complications associated with combined antiplatelet agents

Antiplatelet agents are increasingly encountered in combination¹⁻³ or taken with non-steroidal anti-inflammatory drugs (NSAIDs), which potentiate their action. We present four cases of intraocular haemorrhage associated with these combinations.

Case 1

An 83 year old man presented with visual acuity reduced to hand motions in both eyes as a result of dense vitreous haemorrhage. He had hypertension, which was being treated, but was not diabetic. Medications included 75 mg clopidogrel once daily and diclofenac.

He underwent a right vitrectomy with cryotherapy and gas tamponade. There was copious intraocular and extraocular bleeding that was difficult to control, significantly prolonging surgery. Postoperatively the acuity was still hand motions with persistent vitreous haemorrhage. Clopidogrel and diclofenac were discontinued before left eye surgery.

At left vitrectomy dense vitreous blood and peripheral disciform lesions were found. Final acuity was 6/12 left eye. The right eye required further surgery for retinal detachment with a final acuity of hand movements.

Case 2

A 72 year old man with inferior retinal detachment under silicone oil, was scheduled for vitrectomy and retinectomy. He was taking aspirin 75 mg once daily and clopidogrel 75 mg once daily, following myocardial infarction (MI). Retinectomy was performed under oil after bipolar diathermy. Extensive and persistent haemorrhage from the cut retina was difficult to control, prolonging surgery. At follow up he had a hyphaema, which cleared over 1 month. The retina redetached under oil.

We have encountered two further cases of spontaneous vitreous haemorrhage associated with combination antiplatelet agents, requiring surgery. No obvious source of bleeding was identified (table 1).