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Acute retinal pigment epithelial tear following intravitreal bevacizumab (Avastin) injection for occult choroidal neovascularisation secondary to age related macular degeneration

Retinal pigment epithelium (RPE) tears are well recognised complications of pigment epithelial detachments (PED) in age related macular degeneration (AMD) and may arise spontaneously after trauma, photocoagulation, or photodynamic therapy (PDT).[1] Rosenfeld *et al* recently reported favourable results after intravitreal (IV) bevacizumab (Avastin) injection in neovascular AMD.[2] We present two patients, who developed an RPE tear after an intravitreal Avastin injection.

Case reports

The first case was a 64 year old man with an occult CNV with a PED in the right eye (fig 1A–C). His visual acuity (VA) gradually declined from 20/30 to 20/60. Four days after an uneventful IV injection of 0.05 ml Avastin, the patient noted a sudden drop in VA. His VA was 20/80 while fluorescein angiography (FA) and optical coherence tomography revealed a large RPE tear (fig 2A–C). The second case was a 84 year old woman with an occult CNV with a PED. Her VA was 20/60 when she required an IV Avastin injection. When she returned for her second IV injection, we noticed a fresh RPE tear in the inferotemporal quadrant. Both patients developed an RPE tear after their first IV injection. Both RPE tears were observed also among the first 50 intravitreal Avastin injections at our institution.

Comment

Four possible mechanisms may have induced the development an acute RPE tear in our patients. Firstly, a spontaneous rupture of a PED may occur. Secondly, the deformation of the globe during the insertion of the needle may cause a tearing of the RPE. Thirdly, the IV injection may induce a syneresis and vitreous incarceration at the insertion site, leading to a consecutive vitreoretinal traction.[3] Fourthly, the antiangiogenic drug itself can modulate the permeability and activity of the CNV, thus inducing a contraction of the CNV. As the RPE tears in our patients occurred soon after the IV injection, they developed presumably as a direct consequence of the therapy, rather than the natural progression of the lesion.

For more than 10 years at our institution we performed several hundred intravitreal injections with a variety of different drugs for numerous vitreoretinal diseases including AMD.[4] Also the VEGF Inhibition Study in

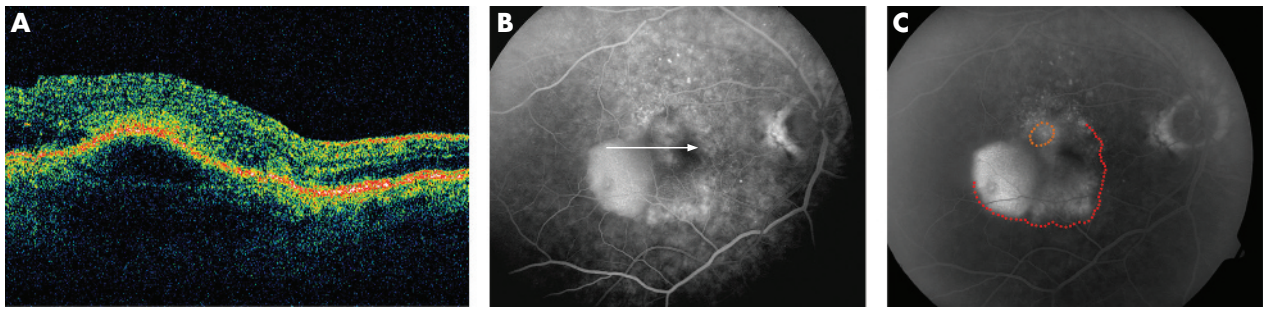

Figure 1 (A) Optical coherence tomography (OCT) before an intravitreal injection. The horizontal OCT scan shows a curved hyper-reflective band under the retina, corresponding to a shallow pigment epithelial detachment. (B, C) Fluorescein angiography (FA) before an intravitreal injection. The early frames of the FA demonstrate a hyperfluorescence temporal to the fovea. This round PED has a connection to an occult CNV, superior to the fovea. The white arrow indicates the length, location, and direction of the corresponding OCT scan. (C) In the late phase of the FA there is a moderate pooling of dye in the PED. The RPE tear will later occur at the margin between attached and detached RPE. The red dots indicate the edge of the RPE tear, the brown dots indicate the location of the contracted RPE.

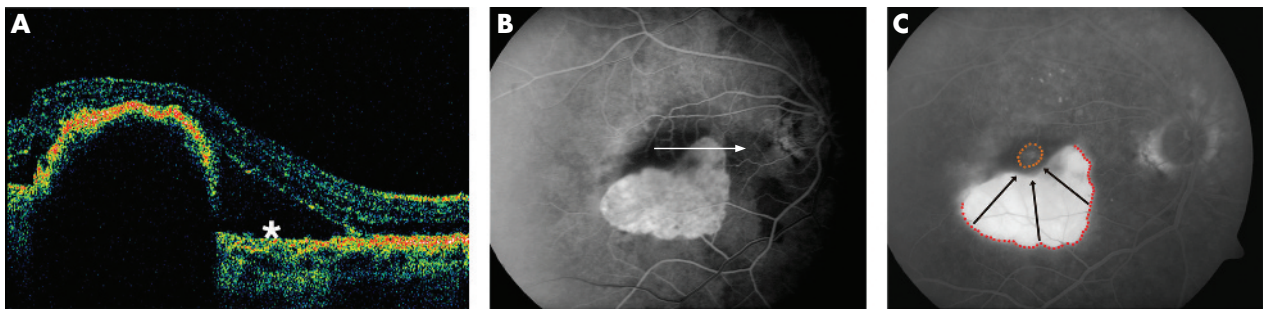

Figure 2 (A) Optical coherence tomography (OCT) after the intravitreal injection. On OCT, there is a dome-shaped hyper-reflective band of the contracted RPE. Nasal to the RPE tear is the missing RPE choriocapillaris-complex (asterisk). The hyper-reflective area under the retina corresponds to subretinal fluid. (B, C) Fluorescein angiography (FA) after the intravitreal injection. In the early FA, there is a large hyperfluorescent window defect in the area of the former PED including the adjacent occult CNV. A square dark, hypofluorescent band corresponds to the contracted and heaped up RPE. The white arrow indicates the length, location, and direction of the corresponding OCT scan. (C) The late phase of the FA demonstrates an increased fluorescence in the bed of the denuded RPE. The inferior edge of the RPE tear is marked by red dots. The RPE contracted from the inferior edge of the PED towards the superior location of the occult CNV (brown dots) in a radial fashion (black arrows).

Ocular Neovascularisation (VISION) treated 1186 patients with more than 9000 IV Macugen injections and reported no RPE tears during a 2 year follow up.[5] 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 (fig1G–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 (fig1F, 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 pteryiga 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.

Acknowledgements

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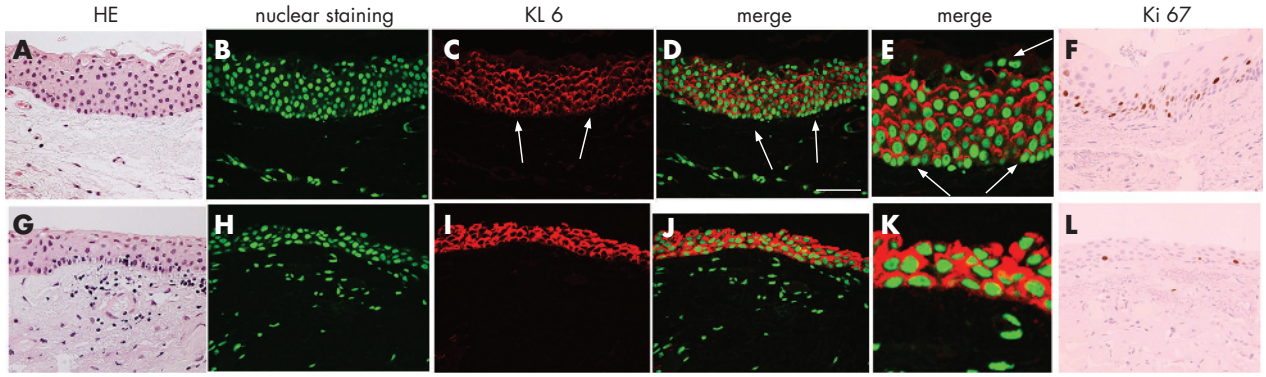

Figure 1 Haematoxylin and eosin staining (A, G), and expression of KL-6 (B–E, red) and Ki-67 (F, L) in the human pterygium head (A–F) and body (G–L). KL-6 immunoreactivity is detected in the pterygium tissue (B–D). At high magnification, immunoreactivity for KL-6 is located in the cytoplasm and on the 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 μm.