We conclude that metastatic disease should be considered in the differential diagnosis of eyelid lesions. The present case emphasises the need for a good medical history in cases of persistent eyelid swelling. Even in the case of a history of an atypical primary tumour, like pleural mesothelioma, histopathological examination is necessary if those lesions fail to respond to treatment.

E K Tsina

Department of Ophthalmology, Hygeia Hospital, Athens, Greece

D Papaioannou

Histopathology Department, Hygeia Hospital, Athens, Greece

F O Matsouka, P A Kosmidis

2nd Medical Oncology Department, Hygeia Hospital, Athens, Greece

Correspondence to: Efthymia K Tsina, MD, PhD, Department of Ophthalmology, Hygeia Hospital, 35 Kifisias Street, Athens, 11523, Greece; etsina@hotmail.com

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Does intravitreal injection of bevacizumab have an effect on the blood-aqueous barrier function?

Bevacizumab (Avastin), a humanised monoclonal anti-VEGF antibody originally developed for intravenous therapy of metastatic cancer, is now being used as off-label therapy in age related macular degeneration.¹ The cost effective drug promises not only anti-angiogenic capabilities in neovascular eye disease, but has also anti-exudative effects by lowering transendothelial permeability of blood vessels.²

Blood-aqueous barrier (BAB) breakdown has been reported after intraocular application of lyophilised rhuFab formulations.³ Anterior chamber inflammation is one of the most frequently reported adverse events (19%) after pegaptanib injections.⁴ We wanted to post these safety issues for bevacizumab by objective detection of aqueous protein concentration.

Methods

The anterior chamber reaction was analysed in 60 patients receiving 1.25 mg of bevacizumab for age related macular degeneration. All patients opted for treatment after being given detailed information about the limited

Figure 1 Aqueous flare as photon counts per millisecond at baseline and after 1 day, 1 week, and 1 month for patients after intravitreal bevacizumab injection. The bar within the box plots represents the median, the edges the 25th/75th percentiles and the whiskers extend from the ends of the box to the outermost data point within quartile-1.5 *(interquartile range).

experience of the drug, its side effects and off-label character. Mean age was 73 years. 38.3% were male. Postoperatively, gentamicin/dexamethasone ointment was applied once.

Aqueous humour flare was measured with the laser flare meter (FC-2000, Kowa Co Ltd, Tokyo, Japan) 30 minutes after pupil dilatation. Routine testing was performed at baseline, on the first postoperative day, after 1 week, and after 1 month. Flare values were expressed as photon counts per millisecond (ph/ms). Descriptive statistics were used to detect the difference in flare values (JMP 5.0.1.2; $\alpha = 0.05$).

Results

The mean flare values were 9.71 ph/ms (95% CI 8.41 to 11.03) at baseline and 9.87 ph/ms (95% CI 8.41 to 11.03) on the first postoperative day, declining to 8.39 ph/ms (95% CI 7.57 to 9.22) after 1 week and 8.25 ph/ms (95% CI 7.40 to 9.09) after 1 month (fig 1).

An increase in anterior flare on the first postoperative day was seen in 51.7% (31 of 60) of cases (mean change +0.14 ph/ms, 95% CI -0.91 to 1.21, $p = 0.84$). The decrease of flare after 1 month was significant (each pair, Student's t , $p < 0.05$). Presence (seven of 60) and quantity of cells in the anterior chamber did not change during the observation period.

Comment

Measurements by flaresmeter have been shown to be accurate and reproducible and more sensitive in quantifying BAB damage than anterior chamber fluorophotometry.⁵ Flare values are known to significantly increase with age. The values at baseline in this study showed a similar distribution as in age matched control groups.⁶

A single injection of bevacizumab caused only slight flare increase on the first day. Incidence of cells did not differ from occasional findings in normal eyes.⁷ The injection itself or non-specific inflammation could explain the temporary BAB reduction. In our experience even repeated injections of the potentially immunogenic full length antibody bevacizumab have not caused inflammatory or allergic reactions.

The reduction of flare in the course of time might be related to direct pharmacodynamic

effects of the drug lowering the permeability of intraocular blood vessels.² Further investigation is necessary to assess whether flare could be used as a non-invasive indicator of bevacizumab concentration or drug efficiency. Stabilisation of BAB over 28 days is consistent with the assumed half life, longer than that of ranibizumab or pegaptanib.

Further studies with longer follow up should be undertaken to assess tolerability and safety, also in respect of repeated application.

F Ziemssen, M Wurga, I M Neuhann, M Leitritz, S Biester, S Grisanti, K U Bartz-Schmidt, Tuebingen Bevacizumab Study Group
University Eye Hospital, Tuebingen, Germany

Correspondence to: Dr Focke Ziemssen, University Eye Hospital, Schleierstrasse 12, D-72076 Tuebingen, Germany; focke.ziemssen@med.uni-tuebingen.de

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Bilateral ocular metastasis from an occult primary melanoma

The simultaneous occurrence of bilateral uveal and conjunctival melanocytic tumours is rare, and in the absence of any apparent cutaneous primary melanoma is a difficult diagnostic problem, with the differential diagnosis including multiple primary ocular tumours, metastases, and a paraneoplastic syndrome.^{1–4}

We report the clinical picture and management of a patient with bilateral ocular melanomas, highlighting the value of magnetic resonance imaging (MRI).

Case report

A 44 year old man with a scotoma in his left visual field was found to have tumours superior to the left macula and in the inferior conjunctival fornix of the right eye. Histopathology showed a malignant melanoma with high mitotic rate. The right fundus showed three pigmented choroidal tumours and in the left eye there was one choroidal tumour (fig 1A). Fluorescein angiography of the left eye is shown (fig 1B, C).

Brain MRI showed bilateral diffuse uveal lesions with low signal on spin echo T2

weighted images and high signal on the spin echo T1 weighted images and with enhancement following the intravenous administration of Gd-DTPA (fig 2A, B). These appearances are attributed to the paramagnetic effect by stable radicals in melanin. Widespread metastases were detected including in the brain. Chemotherapy and later radiotherapy were unsuccessful and the patient died 7 months after the onset of these visual symptoms. No autopsy was performed.

Comment

Bilateral uveal and conjunctival melanocytic tumours without a previous history of cutaneous melanoma and without visible sign of a primary cutaneous tumour are extremely rare.

Multiple ocular melanocytic tumours in the absence of a primary melanoma give rise to an interesting differential diagnosis, which included (a) multiple primary uveal and conjunctival melanomas, (b) bilateral diffuse uveal melanocytic proliferation (BDUMP),

and (c) metastases from an occult primary melanoma.

Eyes with ocular melanocytosis can develop more than one uveal melanoma, but melanocytosis was absent in our patient. Only isolated cases of bilateral primary uveal melanoma have been reported and the simultaneous bilateral occurrence of uveal melanoma is even more exceptional.¹ BDUMP is a rare paraneoplastic condition associated with visual loss.^{2,3} On the basis of the absence of red patches and diffuse early hyperfluorescence in the posterior poles and on the presence of conjunctival melanomas, BDUMP can be considered unlikely in our patient.

Uveal metastasis from cutaneous melanoma is rare and bilateral ocular involvement is even more exceptional.⁴⁻⁶ We believe that in our patient the metastatic disease arose either from an undetected primary visceral or cutaneous melanoma or from a primary tumour that regressed spontaneously. Both of these occurrences have been well documented in patients with metastatic cutaneous melanoma without apparent ocular involvement.^{7,8}

Figure 1 Red free (A), early (B), and late (C) fluorescence angiographic images of the left eye showing the supramacular mass with early central masking, pinpoint lesions at the borders and leakage over the surface of the mass and under the neurosensory detachment.

Figure 2 Axial T2 weighted (A) and gadolinium enhanced T1 weighted spin echo image (B) demonstrate the uveal masses on both sides. Note the characteristic signal of the melanin containing lesions.

D Verhulst, P Demaerel

Department of Radiology, University Hospitals Gasthuisberg, Leuven, Belgium

B Damato

Ocular Oncology Service, St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, UK

A Leys

Ophthalmology, University Hospitals Gasthuisberg, Leuven, Belgium

Correspondence to: Philippe Demaerel, MD, PhD, Department of Radiology, University Hospitals Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium; philippe.demaerel@uz.kuleuven.ac.be

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Thiopurine methyltransferase screening before azathioprine therapy

Azathioprine is used to treat various inflammatory eye conditions such as uveitis and dysthyroid orbitopathy. Despite good overall clinical response rates, particularly when used as steroid sparing agent, adverse effects such as severe myelosuppression can lead to early withdrawal in approximately a quarter of patients.^{1,2}

Thiopurine methyltransferase (TPMT) is a cytosolic enzyme that metabolises azathioprine in vivo. The risk of azathioprine induced myelosuppression may be predicted by detecting patients with intermediate or low TPMT activity. The human TPMT gene exhibits genetic polymorphism that is evident in all populations studied to date.³ Population studies have shown 89% of white people have high TPMT activity, 11% have intermediate, and 0.3% have low TPMT activity.^{2,4} People heterozygous for TPMT mutations have intermediate activity while those homozygous for the mutation have low activity and are therefore at a higher risk of thiopurine induced myelosuppression. Conversely, individuals with very high levels of TPMT activity are known to have the homozygous wild type phenotype, in which the clinical response to thiopurines is less likely.³ This in turn suggests that pretreatment TPMT levels may be used to titrate the starting dose of azathioprine.