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A denileukin diftitox (Ontak) associated retinopathy?

Two patients with haematological malignancies presented with visual symptoms during therapy with denileukin diftitox. Both experienced loss of central and colour vision, coarse pigmentary macular changes, and decreased electroretinographic amplitudes. These cases raise the possibility of a novel drug associated retinopathy.

Case 1

A 58 year old man with chronic lymphocytic leukaemia was enroalled in a clinical trial of denileukin diftitox (Ontak, Ligand Pharmaceuticals) receiving 10 standard cycles of therapy with good response.[1] Eight months later his disease progressed and he received four further cycles. During this treatment he noted blurred vision, photopsias and difficulty adjusting to bright lights. Acuity was 6/12 bilaterally and coarse macular pigment changes were present (fig 1). Automated fields showed paracentral scotomas and electroretinograms (ERG) revealed delayed and diminished photopic wave forms with preserved scotopic responses. Brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) were normal.

After 1 month of visual symptoms high serum levels of retinal α-enolase antibodies were detected. Antibodies to recoverin were absent. Denileukin diftitox was stopped, he received plasmapheresis, pooled human immunoglobulin, and high dose prednisolone. There was no visual improvement though anti-enolase testing became negative. Nine months later he was diagnosed with metastatic adenocarcinoma of unknown primary from which he died 2 months later.

Case 2

A 62 year old man with relapsed primary cutaneous T cell lymphoma (CTCL) was enrolled into a trial of denileukin diftitox and received four cycles.[2] His lymphoma responded to treatment; however, he noted gradual blurring of vision. Visual acuity was 6/18 bilaterally and coarse macular pigmentary changes were present (fig 2). Brain MRI and CSF were normal. Electrophysiology revealed reduced photopic and scotopic amplitudes. Retinal antibodies against 30 kDa, 35 kDa, and 46 kDa (enolase) retinal proteins were detected. He died 2 months later from liver failure.

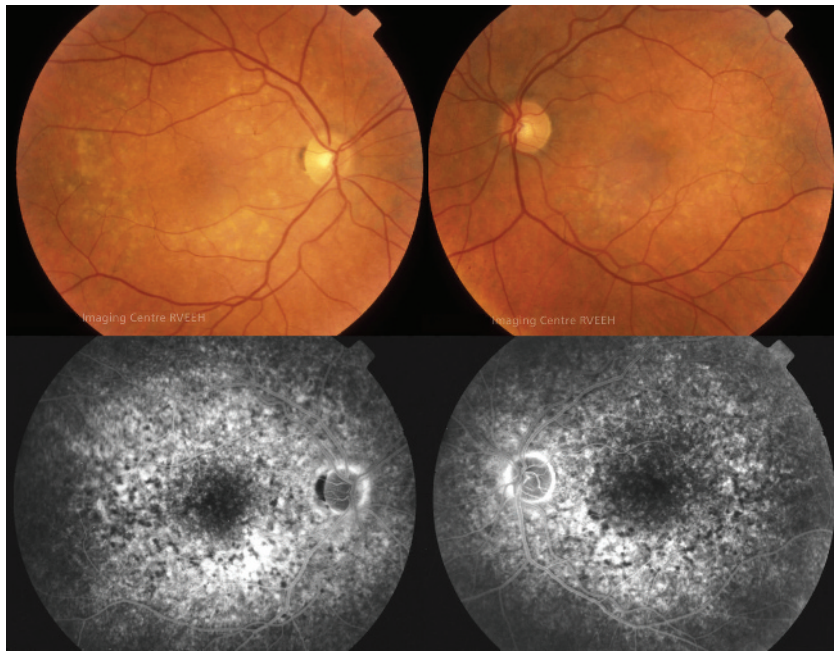

Figure 1 Colour fundus photographs and mid-phase fluorescein angiogram reveals marked macular pigmentary change in patient 1.

Comment

Denileukin diftitox is a fusion protein of portions of diphtheria toxin and interleukin 2. It targets IL-2 receptors on malignant cells and induces cell death. It is approved for the treatment of CTCL and trials in other malignancies continue. Both patients experienced visual symptoms concurrent with their denileukin diftitox therapy and were receiving no other chemotherapy agents. They had strikingly similar macular changes, ERG loss, and anti-enolase in their sera.

There exists a theoretical link between denileukin diftitox and autoimmune retinal disease. A subset of regulatory T cells crucial in suppressing autoimmune disease also express the IL-2 receptor subunit known as CD25.[3] In a proportion of mice depleted of this regulatory subset of T cells, loss of self tolerance to retinal antigens has been reported.[4]

We considered other possible causes of these retinal changes including malignant infiltration and paraneoplastic retinopathy. Infiltration was excluded on the clinical fundus appearance, and the absence of progressive disease in CSF. Both fit the phenotype of cone loss that Weleber found in seven of 12 patients with presumed anti-enolase retinopathy,[5] but our patients' macular changes are distinctive. In the three reported cases of paraneoplastic retinopathy associated with haematological malignancy,[6–8]

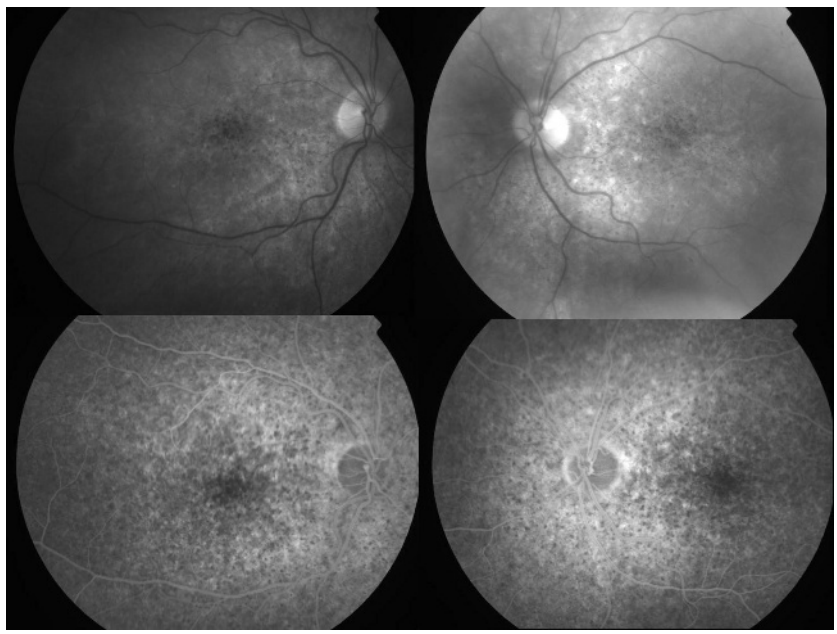

Figure 2 Red free photographs and mid-phase fluorescein angiogram of patient 2.

none was associated with CLL or CTCL. Some pigmentary changes were described in these cases, but in a pattern quite different from that seen in our patients.

To date of approximately 6000 patients treated with denileukin diftitox the manufacturer has only nine reports of visual disturbance including these patients (data on file at Ligand Pharmaceuticals). Formal review of these reports has not revealed a clear pattern of ocular involvement. However, the similarity of the two cases reported here is striking, and raises the possibility of a novel toxic retinopathy.

Acknowledgements

We gratefully acknowledge the assistance of Ligand Pharmaceuticals in providing information from their database and reviewing the manuscript.

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doi: 10.1136/bjo.2006.091165

Accepted for publication 1 April 2006

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NOTICES

Macula of Paris

This meeting will take place on 6th September 2006 at the InterContinental Paris Le Grand Hôtel, 2 Rue Scribe, 75009 Paris, France. For further information, please contact Gisèle Soubrane, MD, Department of Ophthalmology, University Créteil-Paris XII, Avenue de Verdun, 40, 94010 Creteil, France. Or email Anne-Sophie Caron at:
as.caron@colloquium.fr

Back of the eye

The latest issue of *Community Eye Health* (No 57) assesses treatments for age related macular degeneration and other back of the eye conditions. For further information please contact: Journal of Community Eye Health, International Resource Centre, International Centre for Eye Health, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (tel: +44 (0)20 7612 7964; email: Anita.Shah@lshtm.ac.uk; online edition: www.jceh.co.uk). Annual subscription (4 issues) UK £28/US$45. Free to developing country applicants

Managing human resources

The latest issue of *Community Eye Health* (No 56) assess the use of human resources in the delivery of eye care. For further information please contact: Journal of Community Eye Health, International Resource Centre, International Centre for Eye Health, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (tel: +44 (0)20 7612 7964; email Anita.Shah@lshtm.ac.uk, url: ; online edition: www.jceh.co.uk). Annual subscription (4 issues) UK £28/US$45. Free to developing country applicants.

8th EUNOS Meeting – 2007

The 2007 European Neuro-ophthalmology Society meeting (EUNOS; www.eunos.web.org) will be taking place in Istanbul, Turkey on 26-29th May 2007. For further information please visit www.eunos2007.org or contact Pinar Aydin aydinp@eunos2007.org

Teaching courses on Retinal and Vitreous Surgery

Several teaching courses on Retinal and Vitreous Surgery have been organised throughout 2006 and 2007 around the world in association with the International Faculty. For further information on each of these courses please contact Ingrid Kressig, Univ.-Augenklinik Theodor-Kutzer-Ufer 1-3, 68164 Mannheim, Germany; email: Ingrid.kreissig@augen.ma.uni-heidelberg.de; website: http://kressig.uni-hd.de/.

EVER 2006

The EVER 2006 meeting will take place in Vilamoura, Portugal on 4-7th October 2006. For further information please contact the EVER Office, Kapucijnenvoer 33, 3000 Leuven, Belgium; website www.ever.be

Recruitment halted on ESCRS study on antibioltic prophylaxis of endophthalmitis following clear beneficial result

THE ESCRS has terminated recruitment for their two year study of antibiotic prophylaxis of endophthalmitis following cataract surgery. Quarterly analysis of the figures to date by the study's statisticians at the University of Strathclyde clearly indicates a beneficial treatment effect. In January 2006 the Data Montioring Committee recommended that the study be unmasked and found the result to be so clear that they recommended to the Study Chairman that recruitment be halted.

The study has found that the risk of contracting endophthalmitis following phacoemulsification cataract surgery is significantly reduced by an intracameral injection of cefuroxinme at the end of surgery.

The escrs Study, a partially masked, randomized, placebo controlled, multi-national study conducted at 24 ophthalmology centres across Europe commenced recruitment in September 2003. a preliminary report on the primary results will be published in the march 2006 issue of the Journal of Cataract and Refractive Surgery. Complete follow-up data and analyses will be reported at the XXXIV Congress of the ESCRS in London in September 2006 and will subsequently be published in the Journal of Cataract and Refractive Surgery.

For further information contact Caroline Fitzpatrick European Society of Cataract and Refractive Surgeons, tel: +353 1 209 1100, caroline.fitzpatrick@escrs.org.

Prevention of Blindness Fellowship Programme

Application are invited for BCPB Fellowships to start in 2007. The aims of the Fellowships are to fund research and training in prevention of blindness for high caliber clinicians and scientists from the UK and overseas. Projects must further the goals of VISION 202: THE RIGHT TO SIGHT, the elimination of avoidable blindness. In 2007, BCPB seeks to fund one Fellow from the UK and one Fellow from a low-income country to undertake projects that focus on Africa.

Priority will be given to applicants who:

- Demonstrate that their project is innovative and increases knowledge of the causes of blindness and/or its prevention in line with the priorities of VISION 2020
- Demonstrate the ability and ambition to pass on their skills in blindness prevention

The fellowships will be worth up to £60,000pa for 2 or 3 years. Applications must be submitted jointly by the Fellowship candidate and the supervisor at the host institution in the UK.

For full information and an application form, see www.bcpb.org or contact Jackie Webber at BCPB, 59-60 Russell Square, London WC1B 4HP or by email: info@bcpb.org. Closing date for applications is 30 September 2006.

CORRECTION

doi: 10.1136/bjo.2005.074955corr1

In the Scientific report titled, Incidence and severity of keratoconus in Asir province, Saudia Arabia (*Br J Opthalmol* 2005;**89**: 1403–6) figure 2 was incorrect. The original legend printed for figure 2 has also changed. The authors apologise for this error. A full corrected figure is available on the BJO website at http://www.bjophthalmol.com/supplemental.