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Demonstration of identical clonal derivation in a case of "oculocerebral" lymphoma

Primary intraocular lymphoma (PIOL) is a high grade malignant non-Hodgkin's lymphoma (NHL) usually of B cell type, involving the retina and vitreous. PIOL can occur independently or together with primary central nervous system lymphoma (PCNSL; the combination termed "oculocerebral lymphoma"). Because of its slow onset and ability to simulate other conditions, the diagnosis of PIOL remains challenging. A number of techniques, including conventional cytology, immunocytology, flow cytometry, polymerase chain reaction (PCR), and biochemical analysis of vitreous samples, are recommended to aid the diagnostic procedure.¹⁻⁸ We report a case of oculocerebral lymphoma, whereby IgH-PCR and GeneScan analysis confirmed the histological diagnosis by demonstration of the identical clonal B cell populations in both the vitreous and stereotactic biopsy.

Case report

A 51 year old systemically healthy man presented in March 2002 with an epileptic fit. Cranial magnetic resonance imaging

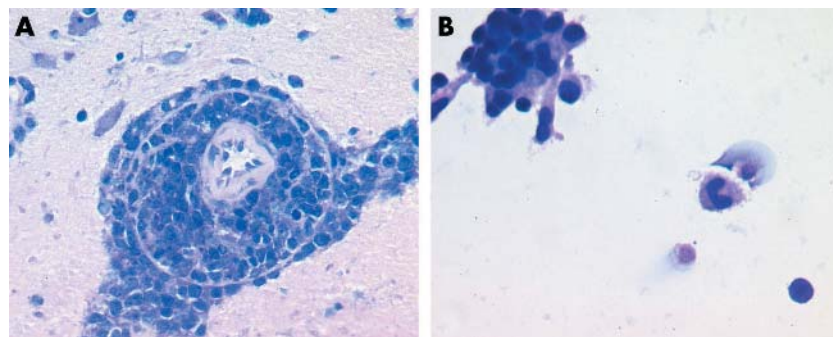


Figure 1 (A) Histological examination of the perivascular orientated neoplastic lymphocytes in the stereotactic brain biopsy (Giemsa, original magnification $\times 40$). (B) Cytology of the vitreous aspirate demonstrating grouped and isolated pleomorphic cells (May-Grunewald-Giemsa, original magnification $\times 40$).

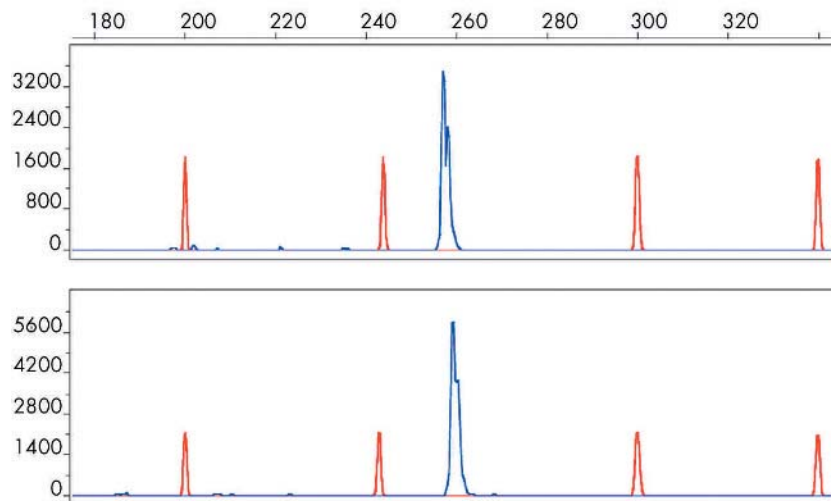


Figure 2 (Top) GeneScan analysis following IgH-PCR (FR2) of the vitreous biopsy demonstrating a monoclonal peak (blue) of 257 base pairs in size. The smaller red peaks represent controls. (Bottom) GeneScan analysis following IgH-PCR of the paraffin embedded cerebral biopsy, with a monoclonal peak of 257 base pairs.

demonstrated a mass with intensive contrast enhancement in the left fronto-parietal area. A stereotactic biopsy was performed, establishing the diagnosis of a high grade malignant B cell NHL (fig 1A). The neoplastic cells consisted of medium to large sized blasts and were orientated perivascularly. They demonstrated immunoreactivity for CD20, a monotypic expression of Ig-kappa, and a large growth fraction (Ki-67 antigen) of 90%. Staging procedures did not reveal any systemic lymphoma. Two cycles of high dose methotrexate chemotherapy (4 g/m^2 intravenously per cycle) were commenced. The patient developed recurrent epileptic attacks, and repeat imaging studies demonstrated tumour size increase. The patient was treated with whole brain irradiation (total dosage, 45 Gy), resulting in complete remission for 14 months. In August 2003, the patient complained of "floaters" and a bilateral decrease in vision. On examination, the

visual acuity (VA) was 20/25 and 20/32 in the right and left eyes, respectively. Funduscopy revealed bilateral dense cellular infiltrates in the vitreous.

Conventional and immunocytological examination of a diagnostic vitrectomy of the left eye disclosed an intraocular manifestation of B cell NHL. The infiltrating atypical lymphocytes (fig 1B) expressed CD20, and displayed a monotypic expression of Ig-kappa. The remaining vitreous aspirate and the paraffin embedded cerebral biopsy material were submitted for clonality analysis using IgH-PCR and GeneScan techniques. For the detection of IgH rearrangements, three single step PCRs were performed employing family specific framework (FR) 1, FR2, and FR3 Bio-Med 2 primers together with a common JH consensus primer (JH22).⁹ The cycling conditions (50 rounds of amplification) for all PCRs are described in detail elsewhere.⁹ Both samples revealed dominant PCR products of the same size (FR1 327 base pairs, FR2 257 base pairs, FR3 125 base pairs), demonstrating the identical neoplastic B cell population in both lymphomatous manifestations (fig 2). Further, DNA sequencing of the amplicates revealed a functional VH3/JH4 rearrangement of the tumour cells.

Thorough imaging studies revealed neither a cerebral recurrence nor evidence of systemic lymphoma. The patient was commenced on high dose ifosfamide (1500 mg/m^2 intravenously daily over 3 days/cycle). In January 2004, follow up examinations demonstrated a complete resolution of lymphomatous infiltrates in both eyes, and the VA was 20/20 bilaterally.

Comment

Cytological studies of vitreous biopsies remain the first step in the histomorphological

diagnosis of PIOL. Previous reports have described the use of PCR examining for monoclonal rearrangements of immunoglobulin heavy (IgH) or light (IgL) chains in B cell lymphoma or T cell receptor genes in T cell lymphoma as an adjunctive diagnostic tool in the evaluation of vitreous specimens for PIOL.³⁻⁸ The success of these analyses is dependent on the quantity of material provided and the extent of DNA degradation. The quality of DNA extracted from paraffin embedded biopsy material can be compromised by fixation solutions, and the duration of fixation. Improved primers for IgH-PCR and TCR-PCR have recently been developed, thereby increasing the chances of detection of clonal B and T cell populations in tissues and fluids.⁹ In oculocerebral lymphoma, it is assumed on the basis of clinical, morphological, as well as immunohistochemical findings that the cerebral and ocular infiltrations represent the same tumour. To our knowledge, this association between PIOL and PCNSL has not yet been proved genetically. This case, therefore, represents the first in the literature, whereby molecular biological evidence is provided showing that the lymphomatous manifestations in oculocerebral lymphoma consist of the identical neoplastic B cell population and that they derive from the same tumour precursor cell. Furthermore, DNA sequencing of both specimens demonstrated a similar VH gene usage to that previously reported by PCNSL.¹⁰

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The prevalence of pseudoexfoliation syndrome in Chinese people: the Tanjong Pagar Survey

Young and colleagues report that pseudoexfoliation syndrome (PXS) was uncommon in 500 Chinese people aged 60 years and older attending general ophthalmic clinics in Hong Kong with a presumed diagnosis of cataract.¹ We have previously carried out a population based assessment of the prevalence of prevalence and risk factors for glaucoma in a district of Singapore, which allowed us to assess the prevalence of PXS in a representative Chinese adult population.²

Case report

This study was approved by the ethics review board of Singapore National Eye Centre. All subjects gave written, informed consent. A total of 2000 Chinese Singaporeans aged 40 years and older were identified from the electoral register of Tanjong Pagar district. A total of 283 were considered ineligible (they had died, moved, or were medically unfit to be examined), leaving 1717 potential subjects. From this number 1232 underwent a slit lamp examination before and after pharmacological dilatation of the pupil with phenylephrine (2.5%) and tropicamide (1%). Gonioscopy was carried out before dilatation on all subjects. Pseudoexfoliation material (PXM) on the anterior lens surface and/or pupil margin was specifically sought. Glaucoma was diagnosed on the basis of structural abnormalities of the optic nerve

(dimensions of the cup:disc ratio lying outside the 97.5th percentile) combined with a reproducible visual field defect, or advanced structural damage consistent with glaucoma (dimensions of the cup:disc ratio lying outside the 99.5th percentile) if the subject could not complete formal field testing.³

We identified PXM in six eyes of four people (table 1). Two people had definite glaucomatous optic neuropathy, and three had undergone glaucoma surgery. None was using topical or oral medication for glaucoma when seen. The age and sex standardised rate of PXS in Chinese Singaporean adults aged 40 years and older is 0.2% (95% confidence interval; 0.0 to 0.4). In the over 60s, this rose to 0.7% (95% CI: 0.5 to 0.9).

Comment

In contrast with the report from Hong Kong, we identified two people in Singapore with PXS and angle closure sufficient to require incisional surgery. Only one person had PXS with glaucoma and open drainage angles.

In previous studies in east Asia, PXM was identified in three of 22 (13.6%) people with glaucomatous optic neuropathy in a Mongolian population. Two of these were classified as open angle glaucoma. The third was blind in both eyes from primary angle closure glaucoma.⁴ The relative scarcity of PXS in east Asian people contrasts with rates of 6-7.7% in adult black South Africans.⁵ Similarly, PXS appears relatively common (3.8-6.0%) in south India.^{6,7} The slightly lower rate among European settlers in Australia aged 49 years and older (2.3%, 95% CI:1.8 to 2.8) is probably genuinely higher than that seen among east Asians.⁸

In summary, we agree with Young and colleagues that PXS is uncommon in the Chinese cohorts studied to date. However, the tendency for the condition to cluster geographically and in racial subgroups suggests that it may occur with greater frequency in areas not yet studied.

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Table 1 Characteristics of patients with pseudoexfoliation syndrome

	Age/sex	Intraocular pressure		Cup:disc ratio		Surgery		Glaucoma
		Right	Left	Right	Left	Right	Left	
1	66/M	16*	13*	0.6*	0.7*	Nil	Nil	Nil
2	74/F	13*	10	1.0*	0.9	Trab	Trab	PACG
3	77/F	14*	16*	0.3*	0.7*	Nil	Trab	OAG
4	79/F	13*	12	0.5*	0.6	SPI	Trab	PAC

*Eye with pseudoexfoliation material.
Trab, trabeculectomy; SPI, surgical iridectomy; PAC, primary angle closure; PACG, primary angle closure with glaucomatous optic neuropathy; OAG, open angle glaucoma.

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Hoarse voice and visual loss

Giant cell arteritis (GCA) often presents atypically. An under-recognised presentation is with speech or respiratory involvement. We report a case of GCA with dysphonia and visual loss, a previously unreported combination.

Case report

A 67 year old woman presented with sudden, non-progressive, painless blurring of the vision in her right eye for 4 days. Her left eye, which had been poor since childhood, was unchanged. She had no other ophthalmic symptoms or history. She smoked and was on treatment for hypertension. On questioning, she reported pain in her throat for 3 weeks, worse on swallowing, which had not responded to oral antibiotics. Her voice had been markedly hoarse for the same period. She denied other respiratory symptoms. She did not have anorexia, weight loss, myalgia, muscle stiffness, scalp tenderness, or jaw claudication, but had been experiencing a dull ache all over her head for 6 weeks.

On examination, she had deep tissue tenderness on the anterolateral aspect of her neck, bilaterally. She had no scalp tenderness, and her temporal arteries were pulsatile. Her corrected visual acuity was 6/24 in

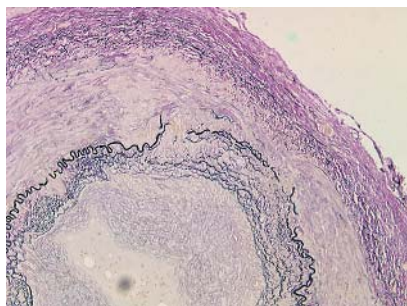


Figure 1 Section of temporal artery biopsy stained for elastin.

both eyes. Her right optic disc was swollen, consistent with an anterior, ischaemic, optic neuropathy. The left optic disc was normal. The remaining ophthalmic and systemic examinations were unremarkable. Blood tests revealed an erythrocyte sedimentation rate of 130 mm in the first hour, a C reactive protein of 125 mg/l, and a mild, normochromic, normocytic anaemia. A diagnosis of right anterior, ischaemic optic neuropathy secondary to giant cell arteritis (GCA) was made, and she was admitted for pulse, intravenous methylprednisolone and high dose oral prednisolone. Temporal artery biopsy confirmed the diagnosis of GCA (fig 1).

The following day, her headache and throat pain were much better, her right optic disc was less swollen, and her inflammatory markers began to fall. She was referred to an otorhinolaryngologist regarding her prolonged hoarse voice. Examination and flexible laryngoscopy showed no abnormalities. Chest radiograph was normal. On day 2, her voice began to improve, and by day 3 it was back to normal. She was discharged on oral prednisolone.

Comment

Giant cell (temporal) arteritis is the most common of the vasculitides, and presents with varied and often non-specific symptoms. Diagnosis may be further hindered by the possibility of non-elevated inflammatory markers¹ and negative temporal artery biopsy.² Ophthalmic artery involvement may cause irreversible, bilateral blindness, and may occur even in the absence of systemic symptoms and signs, a scenario termed occult GCA.³

Speech and respiratory features in giant cell arteritis have been described only infrequently.^{4,5} They include cough, sore throat, pain on swallowing, anterior neck tenderness, and dysphonia (hoarse voice). Nevertheless, it has been estimated that 4% of patients have respiratory symptoms as the initial presentation of GCA, and that as many as 9% will display them at some time during the course of the disease.⁴

Voice changes have been reported in eight patients with GCA, seven with hoarseness,^{4,7} and one with a broken, falsetto voice.⁸ None of these were reported to have had visual involvement. It had been suggested that the vasculitis in cases of GCA with speech or respiratory features might show a preference for branches of the external carotid artery (which supplies the larynx) over the internal carotid (which supplies the eye).⁵ Our case, however, demonstrates the possibility of dual involvement.

In considering the diagnosis of GCA, non-classic features, such as speech and respiratory symptoms, can be easily overlooked. In the absence of classic symptoms they should be specifically asked about. The label of occult GCA, therefore, should not be applied without first excluding the whole spectrum of recognised GCA features. In addition, GCA should be considered in cases of prolonged dysphonia with concomitant visual symptoms.

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Subconjunctival migration of silicone oil through a Baerveldt pars plana glaucoma implant

Extravasation of intraocular silicone oil through a sclerotomy into the subconjunctival space has been described.¹ Oil migration through Molteno and Ahmed implants has also been reported in the literature.^{2,3} However, literature search revealed no cases of oil migration through a Baerveldt pars plana implant after a vitrectomy. We report such a case.

Case report

In May 2001, a 58 year old white man presented with dense vitreous haemorrhage, hyphaema, and neovascular glaucoma (intraocular pressure (IOP) was 55 mm Hg by applanation tonometry) associated with proliferative diabetic retinopathy in his phakic right eye (RE), and background diabetic retinopathy in his left eye (LE). Visual acuity (VA) was RE: counting fingers, LE: 20/20. There were mild cortical and nuclear sclerotic cataracts in both eyes. The high IOP along with severe headache and nausea was refractory to maximal medical therapy. A pars plana vitrectomy, endophotocoagulation, and placement of a Baerveldt pars plana glaucoma implant (Model BG-102–350, surface area: 350 mm² Pfizer Inc, New York, NY, USA) in the superior temporal quadrant allowed an immediate relief of severe ocular and systemic discomfort, and normalisation of the IOP to 14 mm Hg (applanation), RE, after surgery. Owing to the increased cataract, his general ophthalmologist performed cataract extraction by phacoemulsification and inserted a posterior chamber implant, RE, in October 2001. Subsequently, intraocular silicone oil tamponade for multiple retinal breaks including a large inferior relaxing retinotomy was required during a repeat vitrectomy for proliferative vitreoretinopathy, RE, in January 2002. Examination in May 2002 revealed disappearance of 50% of intravitreal

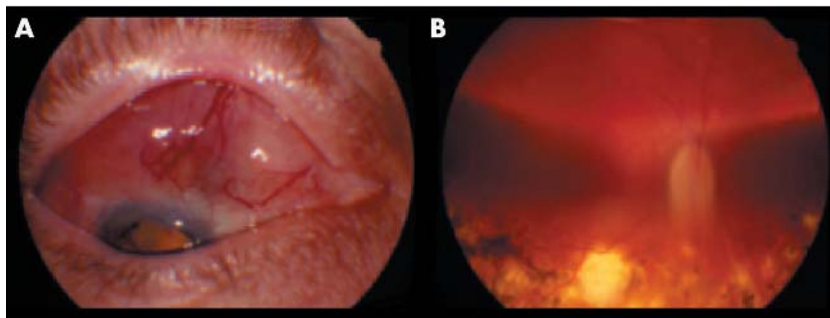


Figure 1 (A) External photograph of inflamed and elevated superior conjunctival bleb infiltrated with extravasated silicone oil from the vitreous cavity of RE. (B) Fundus photograph shows a high intraocular oil-fluid level as a result of extravasation of more than 50% of oil. Note retina is still completely attached despite loss of a large volume of oil.

oil because of its migration into the superior subconjunctival space via the Baerveldt shunt (fig 1). Patient complained of increasing ocular discomfort as a result of conjunctival inflammation and IOP rise to 30 mm Hg by applanation tonometry, associated with an enlarging superior conjunctival bleb with underlying infiltration of emulsified oil in the subsequent weeks. Application of dorzolamide hydrochloride-timolol maleate and brimonidine tartrate 0.2% ophthalmic solutions lowered the IOP to 18 mm Hg, RE. Removal of intraocular and subconjunctival silicone oil was performed on 28 May 2002. Surgical exploration showed widespread oil infiltration involving the posterior plate of the implant and the subconjunctival soft tissues. Extensive resection of swollen subconjunctival tissues infiltrated with oil droplets was performed (fig 2). The surgical dissection involved primarily the anterior subconjunctival tissues associated with most of the oil infiltration, and stayed away from the posterior orbital space where fibrous encapsulation around the implant plate was noted. The Baerveldt implant was not removed. The ocular inflammation subsided and the IOP was brought down to 16 mm Hg (applanation) without ocular hypotensive medications, RE, within 1 week after surgery. Ocular hypotensive medical therapy was no longer required afterwards. The VA was 20/200 and the IOP was 15 mm Hg (applanation) with complete retinal attachment, RE, 6 months later.

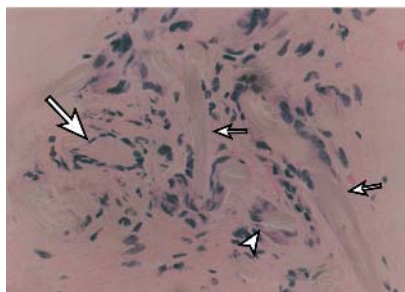


Figure 2 High power photomicrograph of excised conjunctival tissue infiltrated with silicone oil shows a ring of epithelioid cells (large arrow), foreign body material (small arrows), and giant cell (arrowhead).

Comment

In recent years, Baerveldt pars plana glaucoma implants have become increasingly popular for control of refractory glaucoma in eyes with vitreoretinal complications that also require a pars plana vitrectomy.⁴ Frequently, silicone oil tamponade may also be indicated for such eyes. Emulsification of intraocular silicone oil usually takes many months after surgery to develop, the exact timing of which varies and depends on multiple factors, including the purity and viscosity of the oil.⁵ It is interesting that extraocular migration of silicone oil did not occur until 4 months after its placement, coincidental with the start of oil emulsification in this case. Despite the loss of intraocular oil, previous long term retinal tamponade with oil proved sufficient for maintaining retinal attachment after oil removal. The drainage tube was not removed or ligated during the second vitrectomy when silicone oil was inserted to avoid recurrent excessive rise of IOP after surgery in the absence of a patent drainage channel, potentially aggravated by reduced volume of the vitreous cavity for posterior aqueous flow due to the intravitreal silicone oil. Measures that may delay or prevent extraocular oil migration through a drainage tube include placement of the pars plana drainage tube in an inferior quadrant, replacement of the pars plana shunt with another tube shunt inserted into an inferior quadrant of the anterior chamber, and use of highly purified and super-viscous oil with lower tendency for emulsification. In addition, the patient is encouraged to sleep on the side of the drainage tube, since oil may rise from the dependent side and away from the tube. Eventually, emulsified oil droplets may find their way into the drainage tube for extraocular migration. However, this case shows that Baerveldt pars plana implant and silicone oil may coexist for a prolonged period for select cases. Silicone oil extravasation through a glaucoma shunt is not unique for a Baerveldt pars plana implant, but a phenomenon associated with other types of shunt implants as well, as shown by previous case reports.²⁻³ To our knowledge, however, this is the first written report of silicone oil migration through the drainage tube of a Baerveldt pars plana implant.

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Rosai-Dorfman disease: isolated epibulbar masses in two adult patients

Rosai and Dorfman first characterised sinus histiocytosis with massive lymphadenopathy in 1969.¹ This condition most commonly presents as a massive painless cervical adenopathy in children or young adults of African ancestry. The lymphadenopathy typically has a protracted course, lasting for several years before spontaneously resolving. Complications can include compression of vital organs or associated anaemia or leucopenia. The results of chemotherapy or radiation treatments have generally been disappointing; however, surgical debulking, when necessary, has been effective.

Microscopic examination of the lymph nodes reveals a polymorphous infiltrate composed of plasma cells, other lymphocytes, and histiocytes. The histiocytes often contain phagocytised lymphocytes, a histological finding termed emperipolesis. Since these histiocytes fill and expand lymph node sinuses, the disease was first named morphologically as sinus histiocytosis with massive lymphadenopathy. Extranodal involvement, most commonly in the upper respiratory tract and stomach, displays a histology similar to lymph node infiltrates. Because extranodal infiltrates are often found in the absence of lymphadenopathy, the eponym Rosai-Dorfman disease is now preferred.²

The orbit is a common extranodal site of RDD.³ Four cases of RDD manifesting as an epibulbar conjunctival mass have also been reported.⁴⁻⁷ In two of these cases, both in children, the epibulbar mass was an isolated finding.^{5,7} We present RDD occurring as an isolated epibulbar mass in two adult patients.

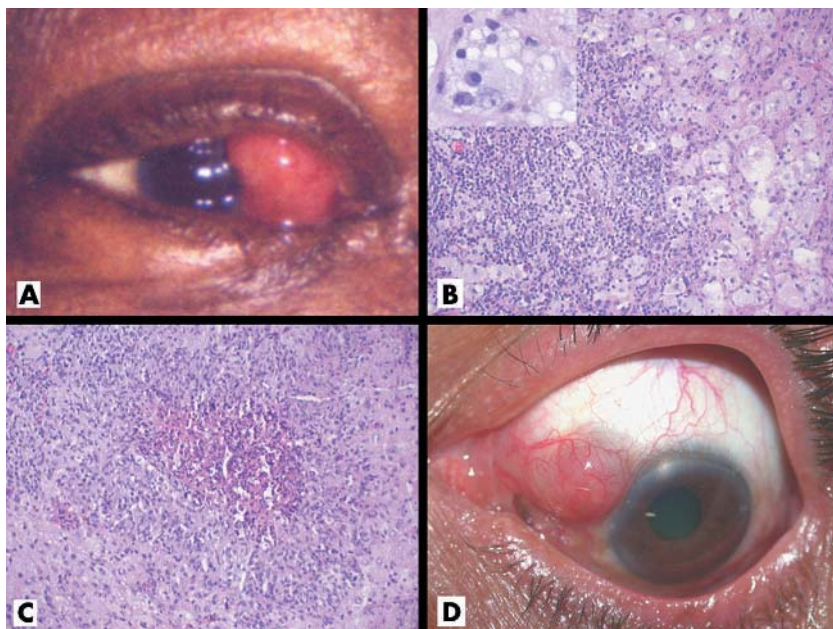


Figure 1 Clinical photograph of patient 1 (A), demonstrating the vascularised epibulbar mass. Haematoxylin and eosin stained section through the excised mass patient 1 (B). Chronic inflammatory infiltrate with lymphocytes, plasma cells, and histiocytes is present. Inset shows higher magnification of histiocyte containing lymphocytes and plasma cells within its cytoplasm, demonstrating the characteristic histological finding termed emperipolesis. Haematoxylin and eosin stained section for patient 1 (C), demonstrating small focus of necrosis. Clinical photograph of patient 2 (D), demonstrating the vascularised epibulbar mass.

Case reports

A 71 year old African-American man with a history of hypertension, benign prostatic hyperplasia, asthma, gout, and degenerative joint disease was evaluated for a painless 1.5 cm episcleral mass on the medial aspect of the right eye, adjacent to the limbus (fig 1A). The mass had been growing for

4 months. The patient was examined by an internist, who found no lymphadenopathy, anaemia, or leucopenia. The mass was excised for histopathological diagnosis. Haematoxylin and eosin stained sections of the episcleral nodule revealed a mixed cellular infiltrate, predominantly composed of histiocytes mixed with lymphocytes,

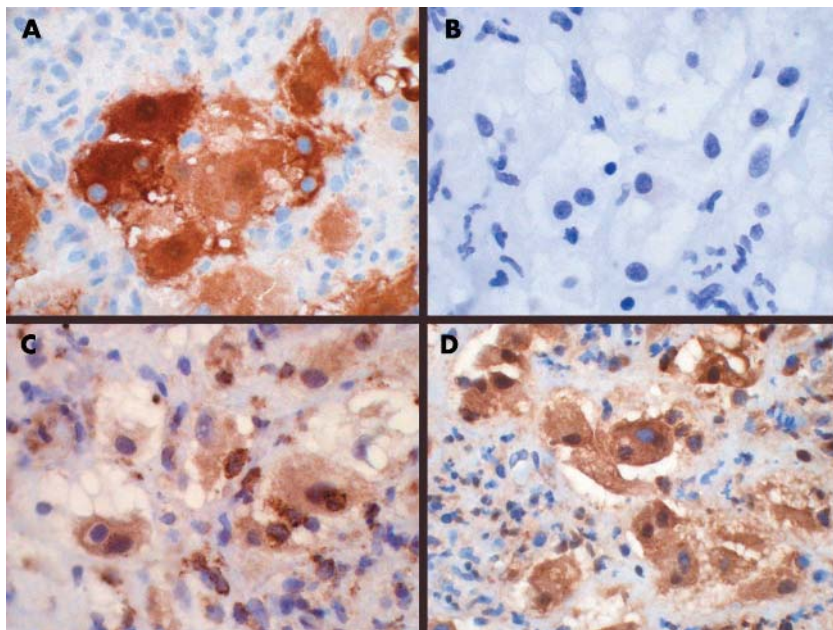


Figure 2 Immunohistochemistry of histiocytes in patient 1 (A), consistent with RDD (400 \times). Stain for S-100 was positive. Stain for α -1-antitrypsin (B) was positive. Stain for lysozyme (C) was positive. Stain for CD-1a (D) was negative.

including plasma cells and polymorphonuclear leucocytes (fig 1B). The histiocytes exhibited a large, round, vesicular nucleus with abundant pale staining and finely vacuolated cytoplasm. Several of these cells displayed the presence of polymorphonucleocytes, lymphocytes, and plasma cells within the cytoplasm (fig 1B, inset). Several foci of necrosis were noted, without the formation of granulomas (fig 1C). Stains for bacteria, acid fast bacilli, and fungi were negative. On immunohistochemistry, histiocytes stained positive for S-100, CD-68, lysozyme, and α -1-antitrypsin and negative for CD-1a (fig 2). The lymphoid infiltration showed the presence of kappa and lambda immunoglobulin chains.

A 51 year old African-Brazilian man with no medical problems presented with a 5 mm erythematous, subconjunctival mass. The mass was adjacent to the limbus and appeared to be adherent to the underlying tissues (fig 1D). Systemic evaluation was negative and there was no lymphadenopathy. The patient underwent a superficial sclerectomy with excision of the mass, and the lesion was submitted for histopathology. Follow up examination at 4 months showed no signs of recurrence. Haematoxylin and eosin stained sections of the nodule revealed a mixed cellular infiltrate, predominantly composed of histiocytes mixed with lymphocytes, including plasma cells and polymorphonuclear leucocytes. Several of these histiocytes showed emperipolesis, displaying phagocytosed polymorphonucleocytes, lymphocytes, and plasma cells. Stains for bacteria, acid fast bacilli, and fungi were negative.

Comment

The cases show that RDD can present as an isolated epibulbar mass in the elderly, as late as the eighth decade. Two previous cases of RDD manifesting as an isolated epibulbar mass in children have been described.^{5,7} One case of epibulbar and cutaneous RDD in a 40 year old has also been described.⁶ Although most cases of RDD occur in children or young adults, the disease is known to manifest in the elderly as well. A review of 423 cases of RDD showed a median age at presentation of 20 years (SD 20 years).⁸ The oldest patient in that series was 74 at the time of presentation. The mean age in cases with ocular involvement was 6 years. Patients with soft tissue lesions are known to be older than patients with nodal or solid organ involvement, with a mean age of 46 years in one series.⁹

Although clinical features of RDD may vary from benign soft tissue masses or lymphadenopathy to life threatening compression of vital organs, anaemia, or leucopenia, the characteristic histological features are histiocytic infiltration admixed with lymphocytes and other inflammatory cells. One typical feature of this entity has been emperipolesis, with histiocytes displaying phagocytosed lymphocytes and plasma cells. Histiocytes in RDD, Langerhans cell histiocytosis, and other histiocytoses express S-100, a neural tissue specific protein; however, the pathophysiology of this S-100 expression remains obscure. Although positive staining for S-100 strongly suggests RDD, it is not absolutely required to make the diagnosis in the presence of typical histology for RDD.⁹ CD68 is a monocyte/macrophage marker frequently expressed by histiocytes in all histiocytic disorders and believed to be associated with lysosomal

granules. In all histiocytoses other than Langerhans cell histiocytosis, the histiocytes frequently stain positive for lysozyme, indicating that these cells are activated and have strong phagocytic potential. α -1-Antitrypsin is a proteinase inhibitor expressed by monocytes, inhibiting overexpressed proteinases during inflammation. It has been variably expressed in histiocytes in RDD.⁹ CD-1a is a marker for the Langerhans histiocyte and may be involved in antigen presentation. Staining for CD-1a is negative in RDD. Early reviews of RDD stress the lack of necrosis on histopathology. Despite the lack of documentation in the early literature, small foci of necrosis are sometimes present in RDD. Consistent with our case 1, small foci of necrosis resembling microabscesses were observed in a series of soft tissue RDD.⁹

Rosai-Dorfman disease should be considered by the clinician and pathologist when evaluating epibulbar masses in children, adults, and the elderly. The diagnosis is made by the pathologist based on the typical histology, including emperipolesis and confirmatory immunohistochemistry. Surgical excision is the treatment of choice. Patients should be managed in conjunction with the internist to evaluate for lymphadenopathy, multiple extranodal lesions, anaemia, and leucopenia.

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Systemic FK506 improved tear secretion in dry eye associated with chronic graft versus host disease

Dry eye is one of the major symptoms of chronic graft versus host disease (CGVHD).^{1,2} Although effective therapy for dry eye associated with CGVHD has not been well established, successful treatment with systemic FK506,^{3,4} topical retinoic acid,⁵ topical cyclosporin A,⁶ and topical autologous serum have been reported.^{7,8} However, improved tear secretion was reported only in one patient with systemic FK506 by Masaoka *et al.*,³ with limited description of ocular findings. We present a patient with dry eye associated with CGVHD, where systemic administration of FK506 resulted in improved ocular surface findings along with the Schirmer test value.

Case report

A 33 year old man had HLA matched sibling allogeneic peripheral blood stem cell transplantation in December 2000 for acute myeloid leukaemia in remission. He received cyclosporine A as GVHD prophylaxis, but it was discontinued on day 85. On day 98, he was referred to an ophthalmologist for screening of CGVHD. On examination, slight tarsal and bulbar conjunctival injection, and slight superficial punctate keratitis (SPK) were noted bilaterally. The Schirmer test value was 10 mm in the right eye and 9 mm in the left eye.

On day 105, he developed bilateral pseudo-membranous conjunctivitis, lichenoid oral lesions, skin eruptions in the upper half of the body, and liver dysfunction. The diagnosis of CGVHD was made. On day 123, oral cyclosporin A (5 mg/kg /day) and oral prednisolone (60 mg/day) were started, and then skin eruptions and liver dysfunction gradually subsided. On day 140, although pseudo-membranous conjunctivitis was settled down, SPK worsened (fig 1) in both eyes. Prednisolone was discontinued on day 186. On day 196, the Schirmer test values decreased to 1 mm in the right and 3 mm in the left eye, and tear break up time (BUT) was 1 second bilaterally. Because lichenoid oral lesions and SPK were unchanged and skin eruptions gradually worsened, oral cyclosporine A was discontinued and oral FK506 was started on day 221.

On day 287, the trough level of FK506 was 8.5 ng/ml and the Schirmer test values improved to 4 mm in the right and 5 mm in the left eye. SPK had gradually improved in both eyes. On day 322, the Schirmer test

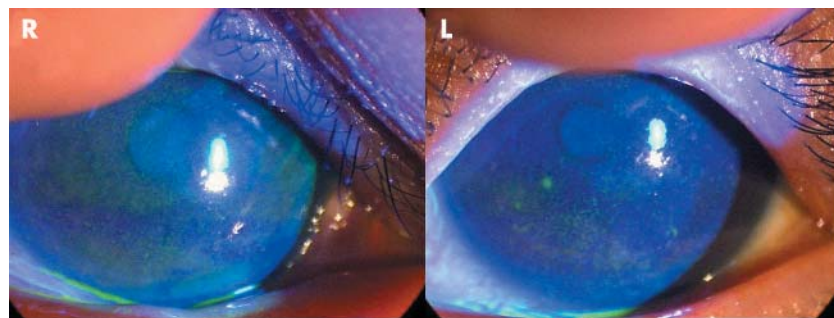


Figure 1 Fluorescein staining of the corneal epithelium on day 140, showing diffuse superficial punctate keratitis.

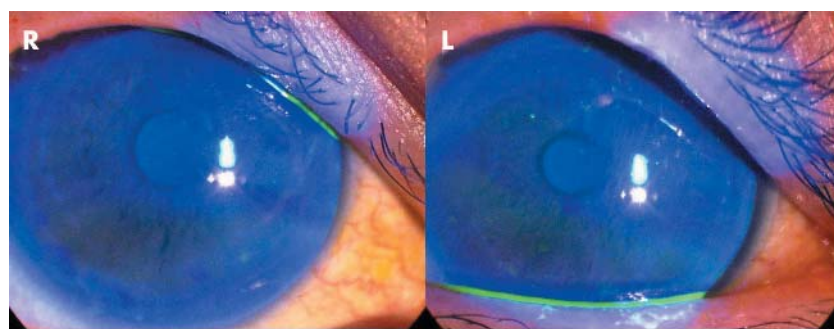


Figure 2 Fluorescein staining of the corneal epithelium on day 553. There was no recurrence of superficial punctate keratitis.

value improved to 16 mm and SPK disappeared in both eyes. On day 421, the trough level of FK506 was 7.9 ng/ml. The Schirmer test value was maintained over 10 mm up to day 553 without recurrence of SPK (fig 2) in both eyes, although BUT remained 1 second bilaterally.

Comment

Ogawa *et al*⁴ reported that in two patients with CGVHD, the symptoms of dry eye and the findings of the ocular surface markedly improved after the administration of systemic FK506 with corticosteroids. However, in their cases the results of Schirmer tests were not normalised in contrast with the result of Masaoka *et al*.³ Ogawa *et al*⁴ speculated that this difference is probably the result of the degree of lacrimal gland destruction. They demonstrated the result of biopsy of the lacrimal gland with prominent interstitial fibrosis and T cell infiltration in one of their patients.

The degree of lacrimal gland destruction may vary with the duration and/or severity of CGVHD. In two patients reported by Ogawa *et al*,⁴ FK506 had been administered 246 days after the onset of CGVHD in one patient, and the other had mild dry eye before haematopoietic stem cell transplantation. The lacrimal gland in these patients might have been irreversibly damaged before the administration of FK506. We speculate that in our patient, because FK506 substituted for cyclosporin A 101 days after the onset of CGVHD before irreversible damage of the lacrimal gland occurred, thereby may effective in improving tear secretion. The lack in the improvement of BUT in our case may be the result of severe damage to goblet cells with preceding pseudomembranous conjunctivitis.

This case indicates that systemic administration of FK506 is effective for dry eye associated with CGVHD, although the degree of improvement in tear secretion may vary between cases with the duration and/or severity of CGVHD.

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3D ultrasound coronal C-scan imaging for optic nerve sheath meningioma

The use of three dimensional (3D) ultrasonography (3DUS) for optic nerve measurements has been described in normal eyes utilising coronal 'C-scans'.^{1,2} This study demonstrates the use of 3DUS generated C-scans for optic nerve measurements in orbits with optic nerve sheath meningioma and compares those with measurements obtained from computed tomography (CT) scans.

Case reports

A 69 year old woman with a left optic nerve sheath meningioma was treated with external beam radiation therapy 6 years earlier.

On 3DUS coronal C-scans, an optic nerve sheath diameter (ONSD) 3 mm behind the globe was measured to be 7.4 mm in the left eye (fig 1, top left) and 6.4 mm in the right (fig 1, top right).

CT of the orbits was obtained. The centre of each optic nerve could clearly be identified on the axial imaging. At a distance of 3 mm posterior to the junction of the optic nerve with the sclera, the diameter of the optic nerve was measured. The ONSD was found to be 7.6 mm in the left eye (fig 1, bottom left) and 6.4 mm in the right (fig 1, bottom right).

A 74 year old woman with left optic nerve sheath meningioma was treated by external beam radiation 12 years before our evaluation. On 3DUS coronal C-scan imaging, the ONSD 3 mm behind the globe was measured to be 7.2 mm in the left eye (fig 2, top left) and 5.4 mm in the right (fig 2, top right).

CT of the orbits was obtained. The ONSD 3 mm behind the junction of the optic nerve with the sclera was measured to be 7.2 mm in the left eye (fig 2, bottom left) and 5.4 mm in right (fig 2, bottom right).

Comment

C-scan ultrasound imaging provided ONSDs similar to those obtained by CT of the orbits. Each was consistent with tumour related thickening of the left optic nerve. At 3 mm posterior to the globe, an ONSD discrepancy of at least 1 mm between the left and the right eyes was independently observed by both 3DUS C-scans and by CT axial scans.

Values obtained by C-scan correlated well with CT scan measurements. The diameters of the left optic nerves were thicker than the normative CT scan range of 4-6 mm.³

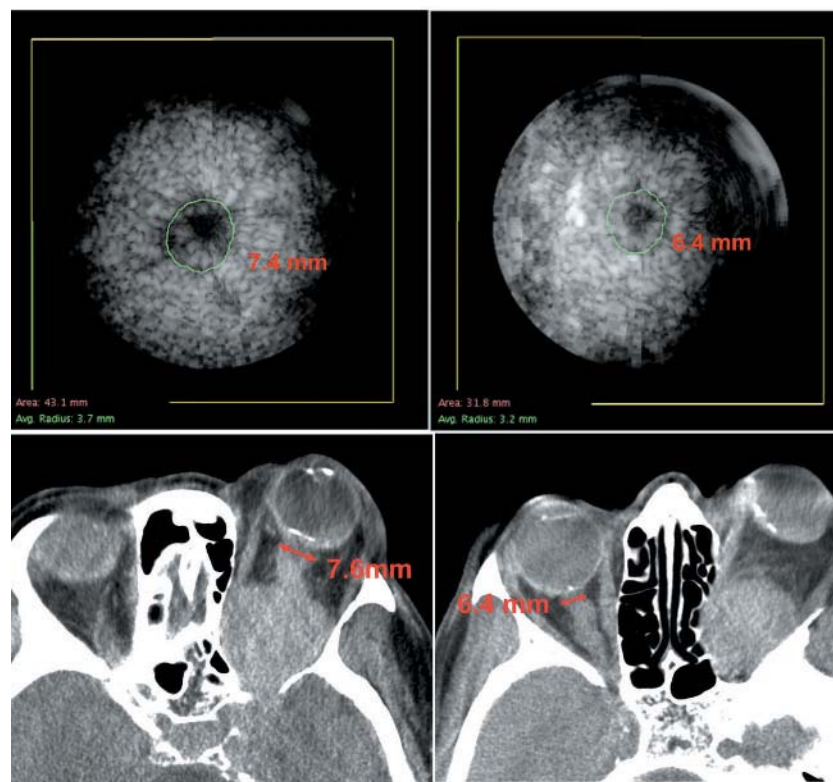


Figure 1 Case 1. The patient's left (top left) and right (top right) optic nerve sheath diameters are shown by 3DUS coronal C-scans. The patient's left (bottom left) and right (bottom right) optic nerve sheath diameters are shown by axial CT scans.

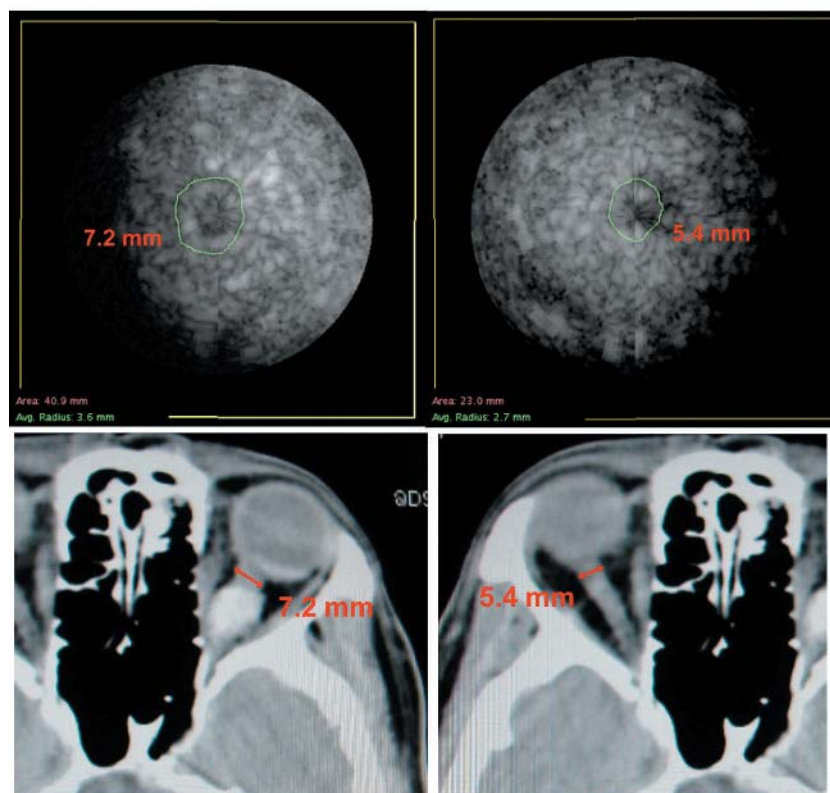


Figure 2 Case 2. The patient's left (top left) and right (top right) optic nerve sheath diameters are shown by 3DUS coronal C-scans. The patient's left (bottom left) and right (bottom right) optic nerve sheath diameters are shown by axial CT scans.

Although the right optic nerve of case 1 was slightly beyond the normative range by 3DUS and by CT, the right optic nerve of case 2 was within normal limits by both tests.

We have found that 3DUS could image the optic nerve up to 15 mm behind the globe. However, the full coronal outline of the optic nerve was no longer apparent starting 7 mm posterior to the globe. Proceeding from this point towards the posterior orbit, parts of the optic nerve sheath outline became indistinct, blending with the blackness of the optic nerve shadow. This is complicated by the twisting manner by which the optic nerve traverses the orbit and sound attenuation that occurs at these distances from the transducer. In contrast, CT allows for a better overall view of the optic nerve (and tumour) as they traverse the orbit.^{4,5}

Three dimensional ultrasound C-scan imaging is a non-invasive, quantitative, and inexpensive method to screen for optic nerve asymmetry and optic nerve tumours.

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An infected hydrogel buckle with *Corynebacterium pseudotuberculosis*

Scleral buckling is still the most common procedure to repair a rheumatogenous retinal

detachment. Acute or chronic infection of scleral explant is rare but well recognised serious postoperative complication threatening the eye and jeopardising the retinal attachment and visual outcome. They may present acutely as painful red eye with purulent discharge or chronically with extrusion of the explants. The reported incidence varies between 0.5% and 5.6%.¹ Surgical technique, different synthetic materials of scleral explants, duration of surgery, size, and position of buckle affect the rate of infection.

In the largest retrospective review of 757 patients with episcleral buckle for rhegmatogenous retinal detachment, Roldan-Pallares and associates had reported 1.3% patients requiring removal of the implant with the commonest seen in silicone sponge (9%) and the least common encountered in hydrogel implant (1.3%).²

Smiddy *et al* have studied 45 cases of scleral buckling infection and identified coagulase negative staphylococci being the most common isolates (17 of 33 positive cultures), and the others include *Staphylococcus aureus*, *Bacillus*, and *Mycobacterium*.¹ *Corynebacterium pseudotuberculosis* is a rare zoonosis and, apart from its rare description in human lymphadenitis, it has not been reported in the ophthalmology literature. The isolates from the scleral buckle infection of our case was susceptible to penicillin and vancomycin. The treatment regimen and possible sources of the infection have been explored.

Case report

A 63 year old white man presented with 8 week history of dull ache over his left eye coupled with mucopurulent discharge. He had received an uneventful scleral buckling surgery with encircling silicone rubber band, 5 mm radial hydrogel episcleral sponge, and cryopexy for his left eye retinal detachment 8 years earlier. On examination, the visual acuity was 20/20 in his right eye and 20/50 in his left. Examination revealed exposed hydrogel scleral buckle with surrounding conjunctival oedema and hyperaemia (fig 1). Fundus examination showed a clear view and an attached retina with good buckle support. There was no feature of erosion and the chorioretinal adhesion from previous retinal cryopexy looked adequate. An infected buckle was diagnosed and the removal of buckle was arranged. Intraoperatively, the hydrogel buckle was noticed to be decomposed into a mess and it had to be removed in pieces. The scleral bed was irrigated with copious gentamicin solution. Gram smear of the specimen showed Gram positive bacilli and culture

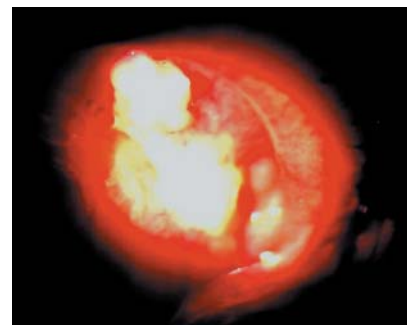


Figure 1 Exposed hydrogel scleral buckle with conjunctival chemosis, hyperaemia, and purulent discharge.

grew *Corynebacterium pseudotuberculosis*, which was sensitive to penicillin and vancomycin but resistant to erythromycin. One week of systemic ampicillin and cloxacillin together with 4 weeks of topical penicillin and vancomycin were prescribed. The conjunctival wound healed without sequelae and the retina remained attached. Upon inquiry, he did not have any history of trauma or gross contamination over the ocular surface. There was no recent travel history within 6 months from buckle exposure. He had constant contact with animals, as a dog was kept as a pet at home.

Comment

A hydrogel episcleral implant is the most resistant material to be infected in buckling surgery.² This peculiar clinical and bacteriological pattern may be related to the intricate physiochemical and biocompatibility characteristics of hydrogel. The low infective incidence of hydrogel implant was believed to be because of the lack of dead spaces and probable antibiotic absorption and depot effect.³ However, observations related to the fragility, swelling, and fragmentation of the hydrogel material with time were made since the first report in 1997 and the dead spaces created could possibly contribute to delayed episcleral implant infection years after surgery.^{2-4,6}

Corynebacterium pseudotuberculosis is a veteran infection and throughout the literature only 25 cases have been reported in humans and 22 of them have been reviewed.⁷ Exposure is usually occupational especially with a history of contact with sheep. The sheep farming industries within New Zealand and Australia are particularly involved. Infected humans generally presented with lymphadenitis, abscess, and constitutional symptoms.

Animal acquired infection was deemed as the most probable source of infection in our patient since he had a contact history with domestic animals, but otherwise no gross ocular soiling or contaminations was noted. Just like other human infection, the presentation of scleral buckling infection is closely related to the virulence and infective dose of the offending organisms. Our case may represent the first human ocular *Corynebacterium pseudotuberculosis* infection involving a scleral buckle after retinal reattachment operation.

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A deficit in visits to the optometrist by preschool age children: implications for vision screening

Vision screening in children is aimed primarily at detecting non-strabismic amblyopia (other forms of vision defect are generally evident to parents). Such non-strabismic amblyopia occurs mostly as a result of uncorrected refractive errors.^{1,2} In the December 2003 report by the Child Health Sub-group³ it was recommended that all 4-5 year olds should receive vision screening. The Health For All Children 4 (HFAC4, 2003) 'Hall Report'⁴ and the Children's Eye Health Working Party guidelines⁵ similarly suggest vision screening should be undertaken in all 4-5 year olds. This advice is in accord with the results of the first randomised controlled trial of treatment for amblyopia,² which found that treatment of moderate amblyopia (acuity 6/36-6/18) in

preschool aged children was effective. However, currently the coverage of vision screening is patchy, and numbers of specialist screening personnel may be insufficient to meet demand if the recommendation to screen all 4-5 year olds were to be implemented.⁶ In districts where vision screening is not carried out, optometrists might act as an important safety net by providing an additional route for referral of non-strabismic amblyopes.

Methods

As part of an investigation into the genetics of myopia,⁷ we investigated the age distribution of individuals attending for a sight test at 19 optometry practices in northern England during the period January 2000-December 2001. For subjects attending more than once, only the most recent visit was recorded. Of the 90 884 attendees, age was known for 90 750. None of the optometry practices operated in a manner that would be expected to discourage the attendance of children. The age distribution of this optometric cohort was compared with data from the census of England and Wales, conducted in 2000.

Results

Figure 1 shows the age distribution of the optometric cohort compared with that of the year 2000 census. Although the optometry practices were not selected according to defined epidemiological sampling criteria, the high similarity in the age distribution of the two datasets after the age of 10 suggests the optometry attendees are generally representative of the UK population. However, there was a clear deficit in visits to optometrists in the preschool age group, which was highly significant ($\chi^2 = 4186.4$, $df = 1$;

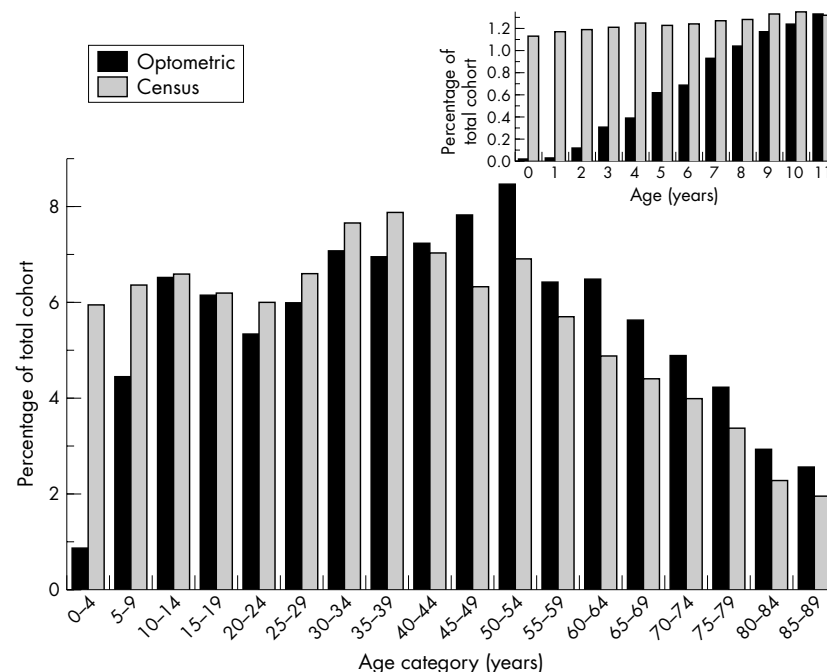


Figure 1 Age distribution of subjects visiting optometric practices ($n = 90\,750$) and in the 2000 population census for England and Wales ($n = 52\,041\,916$). Note the deficit in numbers of children under the age of 10 years (see inset figure for detail), and the increased attendance of patients >45 years old coinciding with the onset of presbyopia.

$p < 0.0001$). Attendance to optometrists appeared to increase linearly until about age 11 when it reached adult levels (fig 1, inset). Our analysis suggests that only ~7% of children aged 0–5 years visit an optometrist (1.48% of visits in the optometric cohort were for infants aged 0–5 years, and there were 16.6 million sight tests carried out in Great Britain in total,⁸ in the year 2000, suggesting 246 000 tests on the 3.7 million infants in this age group). Because infants in whom a refractive error has been detected are likely to visit their optometrist each subsequent year, this figure must be an overestimate of the proportion attending for the first time—that is, in a screening context.

Comment

The fact that a visit to the optometrist is such an exception to the rule at this age underlines the importance of vision screening programmes, and suggests that every effort should be made to implement a comprehensive system of screening at age 4–5 in order to detect children likely to benefit from early treatment for amblyopia. However, where such programmes are not in place, we suggest that encouraging children to visit an optometrist should help in the early referral of non-strabismic amblyopes.

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"Only rarely seen in dreams"—visual experiences during cataract surgery

Cataract surgery is the most commonly performed elective surgery in many countries including the United Kingdom.¹ With the majority of procedures performed under local anaesthesia, it is important for surgeons to recognise if patients are indeed visually aware of their environment. Understanding their experience would be a step forward in providing the safest and the most effective ophthalmic care to cataract patients.

Clinical significance of patients' visual experience lies in the fact that a large number of patients are frightened by their experience, which potentially leads to a number of problems.^{2,3} This could range from poor cooperation during surgery to a sympathetic surge with undesirable adverse effects of hypertension, tachycardia, hyperventilation, and acute panic attack.

Since the visual disturbances during cataract surgery can cause fear and anxiety and adversely affect patient satisfaction, any measure that could reduce its negative impact would contribute to making the operation safer and more bearable.

Visual experiences during cataract surgery have not been discussed in any major ophthalmic textbooks and have not been well studied until recently.^{2–6}

It is commonly expected by the majority of ophthalmologists that patients are not able to perceive much with the eye being operated on during surgery. Even the patient information leaflet published by the Royal College of Ophthalmologists, London, states, "you will not be able to see what is happening, but will be aware of a bright light."¹ This advice, unfortunately, may not be accurate in a sizeable proportion of patients undergoing cataract surgery.⁷

A number of artists have expressed their experience during cataract surgery previously.^{5,8} Two of our patients also wrote back describing their visual experiences. Both underwent uneventful cataract surgery by phacoemulsification and intraocular lens implantation in our unit. One was a professional artist and the other a local poet. The artist sent us an elaborate drawing resembling a "colourful monkey" which portrayed his visual experience (fig 1). The poet sent us a poem, inspired by his visual perception (fig 2). His words clearly reflect the drawing. Taken together the drawing and the poem can in fact provide a tangible insight into how patients may visually experience cataract surgery under local aesthetic.

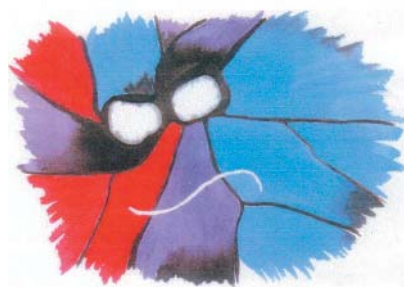


Figure 1 Artist's impression of his visual experiences during cataract surgery.

Wondrous light from laser beams
To show such strong dramatic scenes
Only rarely seen dreams
This helps the eye to see

Bright and beautiful coils of light
Crystal clear to heal the sight
Soft and warm and glowing bright
Fascinating mystery

Subtle shades of pink and blue
Smoky white and yellow too
Will these show the same for you
As they did for me?

Our thanks to those who show the light
Their skills and loving care delight
And much improve our failing sight
A wondrous place to be

Figure 2 Poem inspired by visual experiences during cataract surgery.

This documentation of visual experiences during cataract surgery could prove helpful to counsel patients on what to expect during the procedure. An explanation of possible visual experiences during local anaesthesia may relieve patient anxiety and should be included in patient information leaflets regarding cataract surgery. This could provide a useful tool to offer some reassurance to the anxious patients about to undergo the procedure. Patient counselling in this way may increase patient comfort and cooperation during the entire procedure.

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Spontaneous closure of microaneurysms in diabetic retinopathy with treatment of co-existing anaemia

Pathogenesis of diabetic retinopathy is multifactorial. Various potential risk factors include hypertension, proteinuria, and duration of diabetes, use of insulin, chronic renal disease, and anaemia. Management of diabetic macular oedema has mainly focused on laser photocoagulation of leaking microaneurysms. While anaemia has been found as an independent risk factor for the development of high risk proliferative diabetic retinopathy,¹ its correction has not received due attention in the management of diabetic retinopathy. We report a patient with insulin dependent diabetes mellitus (IDDM) with coexisting nutritional anaemia, who showed spontaneous closure of the microaneurysms on correction of anaemia and metabolic control.

Case report

A 39 year man with IDDM for 12 years, presented with bilateral decrease in vision for 3 months. Examination revealed a visual acuity of 20/40 in both eyes and normal anterior segment. Fundus examination showed multiple microaneurysms, cotton wool spots, and superficial retinal haemorrhages scattered throughout the posterior pole in both eyes. Fundus fluorescein angiography showed multiple microaneurysms with focal leakage in both eyes (fig 1). Review of his systems was essentially normal. Laboratory results showed low haemoglobin (4.7 g%), raised erythrocyte sedimentation

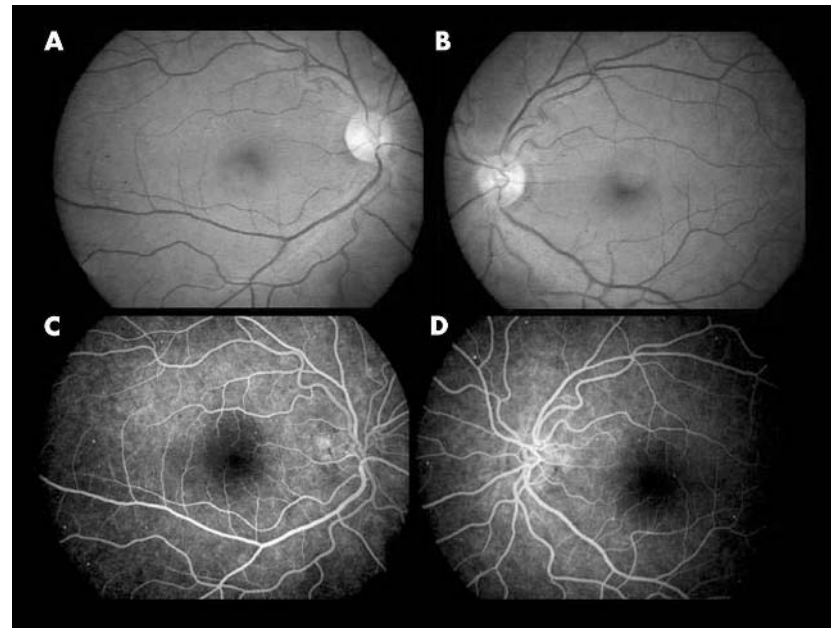


Figure 2 Same patient 3 months later shows resolution of retinopathy (A and B). Multiple microaneurysms in posterior pole of both eyes show spontaneous closure (C and D).

rate (ESR) (65 mm in the first hour) and hyperglycaemia (fasting blood sugars -242 mg/dl). Peripheral blood film showed moderate anisocytosis and microcytosis of red cells. Total leucocyte count, differential leucocyte count, platelet count, serum electrolytes, urea, creatinine, 24 hours urinary proteins, and bilirubin were within normal limits. Chest x ray, ultrasound abdomen, stool for occult blood, duodenal biopsy, and serum electrophoresis for Waldenstrom's microglobulinaemia were normal. He was labelled as a case of nutritional (iron deficiency) anaemia. He received blood transfusion (two units) and started on iron, folic acid, vitamin B1, B6, and B12 supplements.

His insulin regimen was modified. After 3 months of therapy, his haemoglobin improved to 14 g/dl and blood sugars were normal (fasting blood sugars 110 mg/dl). His visual acuity improved to 20/20 in both eyes. Fundus examination showed spontaneous closure of majority of microaneurysms and resolution of superficial haemorrhages and cotton wool spots in both eyes (fig 2).

Comment

In our patient the retinopathy was characterised by multiple microaneurysms, cotton wool spots, and haemorrhages, which were highly suggestive of moderately severe non-proliferative diabetic retinopathy. Anaemia is known to produce a retinopathy that is characterised by haemorrhages and cotton wool spots, and occasionally hard exudates. To our knowledge development of microaneurysms has not been reported in nutritional anaemia. The Diabetes Control and Complications Trial (DCCT)² has shown that intensive management of diabetes reduces the development and progression of retinopathy in the long run but spontaneous closure of microaneurysms was not noted in this study. A large cross sectional study³ found a twofold increase in risk of retinopathy in patients with haemoglobin less than 12 gm/dl, when controlled for other known risk factors. Shorb *et al*⁴ reported three diabetic patients with severe iron deficiency anaemia, who rapidly progressed to severe proliferative retinopathy. Friedman and associates⁵ reported resolution of macular hard exudates in five patients who were treated with erythropoietin for coexisting anaemia. The authors did not speculate on the mechanism of resolution of hard exudates. It is unlikely that a better metabolic control alone led to spontaneous closure of microaneurysms in our patient. It is more likely that anaemia induced retinal hypoxia played a major part in the development of microaneurysms and other retinopathy changes. We postulate that correction of

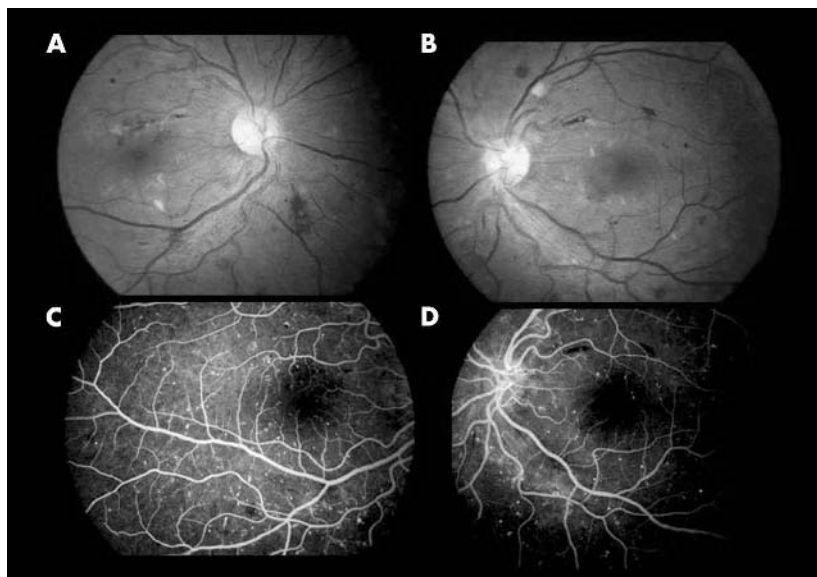


Figure 1 Fundus photographs of right eye (A) and left eye (B) showing superficial haemorrhages and cotton wool spots. Corresponding fluorescein angiograms (C and D) show multiple microaneurysms in posterior pole of both eyes.

hypoxia may be the possible mechanism in improvement of the retinopathy.

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MAILBOX

In answer to "Who is Ivan Schwab?"

Generally, a man must commit a heinous crime, donate prodigious sums of money, or have mortality intervene to have an editorial directly questioning who he is. With this letter, I certify that, at least, as of this writing, none of the above has occurred.

None the less, some concern has been expressed regarding my credentials to write the essays that accompany the cover photographs for the *BJO* of the past few years.¹

As was hinted in the editorial "Eyeshine" early in this series, my education in this regard is not appreciably different from that of most of the readers, but that education has been a powerful tool. Presumably, Papalkar and Francis² are both ophthalmologists and have been trained with a science background, medical school, and the appropriate residency requirements to qualify for their chosen profession. This education allows us to understand optics, neurology, and biology at both a clinical and a basic level. I am also certain that these authors have a highly curious intellect. For proof of that proposition, I offer the fact that they read their journals, ask critical questions of the authors, and question credentials. This is key to the question at hand.

As ophthalmologists our training, curiosity, and the pursuit of truth and honesty will provide the dividends of self education. We are, after all, entirely self educated. As a teacher, I can only hope to recruit, stimulate

and, with luck, inspire my students to become better ophthalmologists than I—a teacher's ultimate goal. I can help to open the door to knowledge; the student must walk through it.

With these essays, I hope to teach a bit of comparative ophthalmology and optics and to stimulate your interest and thinking. All essays are written with the assistance of scientific evidence previously published on the topic and often vetted directly by those who did the original work or by others in the field. In the interest of space, I reference only a few of these publications. If the reader discerns mistakes, notifying me will enable me to correct them.

The editorial asking the question "Who is Ivan Schwab?"³ can be answered simply by "one of you." I am flattered by the interest in my qualifications, because that tells me that you are reading your journals; in particular, you are reading my essays, and above all, you are asking questions. Stay tuned.

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Ciprofloxacin in endophthalmitis: an alternative to ceftazidime and amikacin!

I read with great interest the letter by Doft *et al*¹ suggesting amikacin to be a better alternative to ceftazidime, in response to the article by Galloway *et al*,² that suggested the converse. I would like to suggest that ciprofloxacin is a better alternative to both these drugs. There are certain points that I would like to mention to support my statement.

(1) It has been shown that vancomycin and ceftazidime are incompatible upon mixing, with precipitate formation.³ In addition, Kwok *et al* have suggested ceftazidime to be relatively ineffective owing to its higher rate of precipitation in the vitreous at body temperature resulting in a free antibiotic concentration much less than the MIC₉₀ of the organisms.⁴ Interestingly, in the study, ceftazidime was precipitated to a significant extent, especially when prepared in balanced salt solution plus (BSS Plus) rather than in normal saline (NS), with up to 88% loss in concentrations of the measurable free antibiotics. Such a low antibiotic concentration would be inadequate for the treatment of a potentially blinding disease like infective endophthalmitis. Hui *et al*, in an elegant study, measured the concentrations of vancomycin and ciprofloxacin in an equilibrium dialysis chamber by high performance liquid chromatography and fluorescence polarisation immunoassay.⁵ They did note that ciprofloxacin precipitates in vitreous, but to a much lesser extent than ceftazidime and, significantly, the remaining ciprofloxacin concentration was many times above the MIC₉₀ of the drug against the common Gram

negative bacteria encountered. This suggests that the problem of precipitation might not be so important in the use of intravitreal ciprofloxacin. The precipitation of ciprofloxacin was also found to be independent of the medium, which means that there is no need to avoid the use of BSS Plus during preparation of the ciprofloxacin for intravitreal injection or during intraocular surgery.

(2) Various studies have shown the efficacy of ciprofloxacin. Benz *et al* have shown that 92% of Gram negative organisms in culture proved endophthalmitis were susceptible to ciprofloxacin.⁶ In the Indian scenario too ciprofloxacin is considered to be a very dependable drug. In fact, 88.4% of even the Gram positive organisms in the series of Anand *et al*,⁷ were sensitive to ciprofloxacin. This is a significantly lower rate of resistance of Gram positive organisms to ciprofloxacin than that found in the *ex vivo* study. The series of post-traumatic endophthalmitis over a period of 2 years from our institute also shows 26 of the 39 isolates to be sensitive to ciprofloxacin and a hitherto unreported poor rate of susceptibility to ceftazidime (four out of the 39 isolates) (unpublished data).

(3) The intravitreal combination of choice for the initial empirical treatment of endophthalmitis could be vancomycin and ciprofloxacin. A certain amount of synergy could be expected with this combination, with vancomycin inhibiting the cell wall synthesis of the bacteria allowing ciprofloxacin to penetrate into the cell and inhibiting the DNA supercoiling. This synergy and the resultant greater bactericidal activity would be all the more important considering that there is no assistance from the body's immune system in combating the intraocular infection. Although it has been proved to be non-toxic in animal models,⁸ this substitution of ceftazidime with ciprofloxacin of course, would necessitate further studies on the safety profile of intravitreal ciprofloxacin.

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No evidence for severe retinopathy of prematurity following sildenafil

Marsh and colleagues¹ raise the spectre of a possible association between the use of sildenafil and the development of retinopathy of prematurity (ROP) in a baby of 26 weeks gestation with pulmonary hypertension. We are concerned that this report offers no real evidence for its claims and that a potentially lifesaving agent is being unfairly maligned.

The report describes the use of intravenous sildenafil of unspecified dose for 16 days in a 525 g preterm infant with a very difficult intensive care course. The management included a litany of recognised causes of ROP, including extreme prematurity, >6 weeks of mechanical ventilation with 80-100% oxygen, and bacterial and fungal infections.

Despite this, Marsh *et al* chose to incriminate sildenafil as the causal agent. The suggestion is even more perplexing as the baby had already received inhaled nitric oxide at high levels (40 ppm for 2-3 weeks) before the sildenafil; both are vasodilators and have the same mechanism of action.

The authors make the further statement that they observed a recent increase in treatable ROP in their unit, coinciding with the use of sildenafil. Where is their evidence?

As far as we are aware there is no evidence in the literature that sildenafil has any significant effect on either retinal or choroidal blood vessels. Pache *et al* reported² that in adults, sildenafil induced a 5.8% dilatation of retinal vessels but this was not confirmed by Grunwald *et al* on either retinal or choroidal circulations.^{3,4} To date there are no data on the effect of sildenafil on the developing ocular circulations.

We entirely agree that vigilant monitoring and responsible reporting of side effects are mandatory for any new drug application. To our knowledge the only available intravenous sildenafil is being released on a named patient basis in a prospective study in neonates. How did the authors obtain and administer the drug in neonates? Sildenafil and inhaled nitric oxide are experimental therapies within the preterm population and as clinicians we have a responsibility to ensure that they are used as part of prospective randomised controlled trials with the appropriate short and long term follow up. Although being well intentioned, such unconvincing reports may impede the use of agents that might have an important future role in the management of primary pulmonary hypertension of the newborn.

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Conflict of interest: The authors have acted in an independent consultant capacity (CMP, AJP, ARF) and are in receipt of financial support in the form of a research grant (CMP, AJP) from the manufacturers of sildenafil, Pfizer Ltd.

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Identification of silicone oil in ocular tissues

I read with interest the article by Miyamoto *et al*.¹ Numerous studies have examined the inter-relation between silicone oil and various ocular structures, such as the retina, iris, or anterior chamber. However, the silicone oil itself was never evident in these studies, but rather small vacuoles suspected to be ghosts of the incorporated silicone oil were apparent. Nevertheless, the vacuoles also could have been artefacts² because silicone, which is solubilised in the organic solvents during the preparation,³ is never detected. We previously demonstrated silicone oil emulsion in the rabbit retina using phthalocyanine blue as a marker.⁴ This compound contains a copper molecule that imparts a blue colour and remains in the tissue after the silicone oil is washed out and enables visualisation of the silicone emulsion in the trabecular meshwork at the light and electron microscopic levels. When we injected a suspension of the dye into the anterior chamber, the dye filled the small vacuoles within the cells. In contrast, when silicone droplets containing the dye were injected into the chamber, the blue dye formed clusters in small cellular vacuoles (light microscopy) and touched the limiting membranes of the vacuoles (electron microscopy). The silicone droplets were washed out by the organic solvents used to prepare the specimens, and since the dye was insoluble in the organic solvent, it probably precipitated around the vacuoles.⁵ However, figure 5 of this article did not show any limiting membranes or the low magnification of this figure precluded their identification. In addition, energy dispersive x ray analysis is also a useful method to detect silicone oil in tissues.⁶

The authors injected silicone oil that was not emulsified into the vitreous cavity after vitrectomy. However, silicone oil that is not emulsified has a large surface area and high interfacial surface tension and is not incorporated into the tissues. The authors did not show by gross examination whether silicone oil became emulsified during the experiment. They should discuss why they could see residual silicone oil in the rest of the anterior capsule. The readers were not able to obtain information about silicone oil structure.

Although the authors described emulsification of silicone oil related to protein, many factors are involved in this process. Contamination of low molecular weight siloxanes may enhance silicone oil emulsification.

In the discussion, the authors state: "It is likely that lens epithelial cells attaching to oil droplets might be stimulated to express many wound healing related molecules including extracellular matrix components." This is speculation. The central area of the posterior surface of the rest of the anterior capsule is covered with accumulated fibrous extracellular matrix in figures 2B and 4B. However, there were no differences in the expression of collagen types I, III, V, and cellular fibronectin by immunohistochemistry. The authors did not provide these data in the text. If this information is related to their hypothesis, they should demonstrate differences by providing immunohistochemical data.

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Severe ocular trauma caused by an ostrich

We read with great interest the case report of severe vision loss caused by ostrich pecking trauma and would like to bring readers' attention to a case we recently reported about an adult farm worker who lost his vision as a result of an ostrich attack.¹

In our case, a 34 year old man was attacked by the giant bird with consequent severe pain and immediate loss of vision to no light perception. On examination, patient's right eye had significant proptosis with severe limitations of the globe in all directions and irregular full thickness lacerations of the skin. Exploration of the wound revealed two fragments of bony-like tissue but no fractures. Ultrasound examination and computed tomography scan of the orbits revealed a disorganised right globe with multiple scleral ruptures without any bony fractures. Microscopic examination of bony fragments was consistent with avian rostrum.

Human eye injuries caused by pecking of birds are uncommon and are usually labelled as humorous or incidental, and,

consequently, most go unreported. Serious injuries to humans caused by birds have been sparsely reported in the English literature. In the non-English literature, Kuhl reviewed a series of 14 patients with severe eye injuries from 1875 through 1970 caused by birds.² All were penetrating ocular injuries, and some caused permanent visual injuries and/or blindness.

In general, birds are viewed as presenting less of a danger because of the assumption that the bird will take flight if frightened. On the contrary, some birds show aggressive behaviours related to territoriality or breeding. The male ostrich (a flightless bird) is known to establish territory, display aggressive territorial behaviour, and may attack potential predators.³ These two reports of an ostrich attack causing permanent visual loss in adult humans are the first in the ophthalmic literature and emphasise the potential for serious ocular injuries from birds. People living in rural areas and those who work or plan to visit farms should be aware that territorial behaviour of many domestic animals and birds may be a potential risk factor.

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Cost accounting in cost utility analysis of screening and treatment

I would like to make some comments regarding the cost utility analysis in the paper by Hopley *et al*¹ because it is important to understand that the costs should be accounted at the same time and with the same degree of accuracy as outcome data. The economic definition of costs should be used in cost valuation, not the financial definition.^{2–5} The concept implies that all resources consumed by an intervention should be valued, not just those constituting a budget-line item.

All methods (that is, cost effectiveness, cost minimisation, cost utility, and cost benefit) of economic evaluation in health care have one principle in common: they examine one or more possible interventions and compare the inputs or resources necessary to carry out such interventions with their consequences or effects.⁶ Cost utility analysis aimed to compare different interventions in terms of both quantity and quality of life; we express them as utilities. In this case, competing interventions are compared in terms of cost per utility (for example, cost per QALY).^{6,7} Values of resources in the cost utility analysis are assigned by defining costs. In accounting costs both tangible items (for example, equipment, drugs, materials, money etc) and intangible items (for example, time and treatment mode) must be taken into account, regardless of whether they are used by and accrue to health services, society, or the single individual.⁶ Costs for some resources may vary because of market forces—for example, rent, exploitation, so it is important to present results not only in monetary terms but also in quantity of resources used.

To allow comparability across different interventions, a 3% discount rate must be used as recommended by most guidelines if economic evaluations are made at different times.⁷

While this is increasingly becoming the practice, most studies have either attempted to estimate costs for alternative therapies retrospectively or, using literature reviews, budgetary line items and healthcare insurance costs sheets. This should be avoided from economic evaluations because it mainly reflects on budgetary formulations and has very little in common with the real cost of intervention.

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NOTICES

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British Oculoplastic Surgery Society

Call for papers for the 5th annual meeting of the BOPSS to be held on 15 and 16 May 2005 at The Belfry, Birmingham. The abstract submission deadline is 4 February 2005, and abstracts can be submitted online at www.bopss.org.

CORRECTION

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In the letter titled Bilateral ischaemic optic neuropathy and stroke after multiple bee stings (*Br J Ophthalmol* 2004;**88**:1596–8) the authors were listed incorrectly. The correct listing is as follows; J S Schiffman, R A Tang, E U Dorotheo, S S Singh, H M Bahrani. The journal apologises for this error.