LETTERS TO THE EDITOR

Ochroconis gallopava endophthalmitis in fludarabine treated chronic lymphocytic leukaemia

EDITOR,—Disseminated fungal infection is an important cause of morbidity and mortality in immunocompromised patients, often due to candida and aspergillus species. Endogenous endophthalmitis is a recognised complication. In our knowledge, the first reported case of endogenous intraocular infection with the emerging pathogen Ochroconis gallopava, acquired following treatment for chronic lymphocytic leukaemia (CLL).

CASE REPORT
A 69 year old man presented with a 4 day history of painless loss of vision in the left eye after receiving four courses of fludarabine (25 mg/m² over 5 days) for CLL. Standard infection prophylaxis following myelosuppression included oral fluconazole 50 mg once daily. His neutropenia improved (7.96×10⁹/l) but profound lymphopenia persisted (0.11×10⁹/l). Visual acuity was right eye 6/6+4 and left eye hand movements. The right eye was normal throughout. Anterior uveitis, hypopyon, lens opacity, and vitritis compromised funduscopy. A proliforative or infective aetiology was suspected. Anterior chamber paracentesis revealed leucocytes but no intact cells or organisms. Culture was negative. After 2 days of topical steroids vision improved to 1/60. A large preretinal grey/white mass at the posterior pole became evident with keratic precipitates on the posterior cornea. Vitreous biopsy revealed a filamentous fungus. An isolate was reported as the saprophytic mould Ochroconis gallopava. The specimen was included in the National Collection of Pathogenic Fungi (No 7195) (Figs 1 and 2). The minimum inhibitory concentration (MIC) for amphotericin B was 0.5 mg/l and itraconazole <0.125 mg/l. Fluconazole was changed to intravenous amphotericin (0.6 mg/kg) but stopped after 14 days owing to deteriorating renal function. No further intravitreal involvement was suspected clinically, concern over meningitic spread remained. Oral itraconazole 200 mg twice daily commenced. Evisceration was refused. Following informed consent an intravitreal injection of 0.5 ml of amphotericin (0.02 mg in 0.1 ml) was performed. Visual acuity deteriorated to no perception of light. Dense lens opacity precluded further funnel examination. Generalised debilitation ensued. The patient died 2 months later after congestive cardiac failure and sepsis from heel ulcers. A post mortem was not performed.

COMMENT
In our case of endophthalmitis vitreous biopsy was able to confirm the presence of fungal mycelium with isolation of Ochroconis gallopava in pure culture. Dematiaceous (dark pigmented) fungi are increasingly reported as potential pathogens in transplant recipients and patients immunocompromised following chemotherapy. These thermophilic fungi have been isolated from self heated waste piles, thermal soils, and chicken litter. The species O gallopava has caused significant mortality through encephalitis in turkey pouls, turkeys and chickens. A neurotropic potential is well recognised from the literature on avian disease and studied with animal models. Since 1990, eight cases of invasive systemic infection have been described in the world literature with brain abscesses as common sequelae and exceedingly high mortality. Six were transplant recipients, one had T cell CLL, and one large cell lymphoma. Neutropenia has not been a major predisposing factor to infection. More important is a long standing T cell immunosuppression, in this case secondary to the underlying leukaemia and fludarabine. This nucleoside analogue, with good response rates in CLL, is the agent of choice when alkylating agents fail but results in myelosuppression with a more prolonged suppression of cell mediated immunity.

Infection occurred despite prophylaxis with fluconazole, an observation previously documented. Fluconazole has excellent penetration into the cerebrospinal fluid and diffusion into ocular tissue. However, it appears to lack in vitro activity against O gallopava with a MIC of >100 mg/l. Successful treatment of cerebral abscess has been reported using systemic amphotericin B and itraconazole. In our case renal function deteriorated on treatment and repeated intraocular injections were poorly tolerated.

Although rare, infectious invasions with O gallopava are aggressive and it is important that clinicians and laboratory personnel are aware of the significance of this organism in lymphopenic individuals who, even on fungal prophylaxis, may be at increased risk.

JEREMY D BOWYER
St Paul’s Eye Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP

ELIZABETH M JOHNSON
Public Health Laboratory Service, Mycology Reference Laboratory, Myrtle Road, Bristol BS2 8EL

ELIZABETH H HORN
Department of Haematology and Oncology, Queen’s Medical Centre, University Hospital, Nottingham NG7 2UH

RICHARD M C GREGSON
Department of Ophthalmology, Queen’s Medical Centre, University Hospital, Nottingham NG7 2YH

Correspondence to: Dr Bowyer
Accepted for publication 8 November 1999

References

Vancomycin and ceftazidime incompatibility upon intravitreal injection

EDITOR,—The recommended treatment of endophthalmitis includes intravitreal injection of broad spectrum antibiotics. Vancomycin is the drug of choice for Gram positive bacteria, while Gram negative coverage can be obtained by either amikacin or ceftazidime. Owing to potential retinal toxicity with amikacin, the option of its substitution by ceftazidime seemed very attractive.

Fiscella, and the pharmacological handbooks have already described physical incompatibility of vancomycin and ceftazidime. We encountered this phenomenon in two cases of post-traumatic endophthalmitis, which were treated with intravitreal vancomycin and ceftazidime. Immediately upon injection the antibiotics were seen to form yellow-white precipitates along the needle tract.

CASE REPORTS

Case 1
A 17 year old male was treated for post-traumatic endophthalmitis. Following anterior chamber and vitreous tap and cultures, intravitreal ceftazidime 2.2 mg/0.1 ml and vancomycin 1 mg/0.1 ml were slowly injected, as well as subconjunctival injection ceftazidime 100 mg/0.5 ml and vancomycin 25 mg/0.25 ml. This was done using different needles and syringes for each drug. Immediately upon injection dense yellow-white precipitates were observed along the needle tract in the vitreous cavity.

The subconjunctival vancomycin (25 mg/0.25 ml) and ceftazidime (100 mg/0.5 ml) were injected separately at different sites of the lower conjunctiva. Some of both diffused over the conjunctival surface and immediately whitish precipitates formed, which were washed away from the ocular surface.

Postoperatively indirect opthalmoscopy revealed yellow-white precipitates along the needle tract through which the ceftazidime and the vancomycin were injected.

The vitreous precipitates were observed to dissolve gradually with a complete clearing of the vitreous cavity over a period of 2 months, with a final visual acuity of 1.0 (20/20).

Figure 1 Opacification after injection of vancomycin and ceftazidime into the vitreous cavity of a fresh pig’s eye

that the mixture is opaque compared with the clear liquids on either side.

COMMENT

We encountered two similar cases of endophthalmitis following perforating trauma, which were treated with intravitreal injection of vancomycin and ceftazidime. Vancomycin was chosen for its broad spectrum Gram positive coverage, and ceftazidime for the broad spectrum Gram negative coverage it provides.

Recent reports describe retinal toxicity due to aminoglycosides, including amikacin. This has led some authors to recommend the use of ceftazidime as an alternative to amikacin. However, the Endophthalmitis Vitrectomy Study Group prefers the continued use of amikacin. The reasons are that even though amikacin is potentially more retinotoxic than ceftazidime, it has a concentration dependent bactericidal effect, is not dependent on the inoculum size for its effect, and is synergistic with vancomycin.

The theoretical advantages of ceftazidime lie in its lower potential for retinal toxicity, and better efficacy in acidic and hypoxic environments (such as endophthalmitis) compared with amikacin.

From the pharmacological literature it is clear that vancomycin and ceftazidime are incompatible. Vancomycin and ceftazidime precipitate when mixed. This is thought to be due to the pH of vancomycin (pH 5–7.5) compared with ceftazidime (pH 2.5–4.5) and the presence of bicarbonate in most ceftazidime preparations, even though precipitation also occurred in preparations that did not contain bicarbonate.

Most authors who recommend the combination of intravitreal vancomycin and ceftazidime were unaware of its physical incompatibility. Fiscella stated the possibility of the formation of microprecipitates, and the unknown pharmacological consequences of this combination. From our experience, the precipitates that form after the injection of vancomycin and ceftazidime clear completely without adverse sequelae within 2 months. It is unclear whether the antibiotic properties of these drugs after precipitation in terms of bioavailability, efficacy, and toxicity, have not been compromised.

Further studies to evaluate those properties should be conducted. Meanwhile we have stopped using the combination of vancomycin and ceftazidime for intravitreal injection, until conclusions can be drawn.

Acute zonal occult outer retinopathy

EDITOR,—Acute zonal occult outer retinopathy (AZOOR) is a clinical syndrome described as acute zonal loss of outer retinal function associated with photopsia, minimal or no fundal findings initially, full field ERG abnormalities, and visual field loss. Most patients previously reported with AZOOR show normal full field flash electroretinogram (ERG). The diagnosis of the patient reported here is consistent with AZOOR. However, she showed a normal full field flash ERG and, interestingly, an abnormal multifocal ERG.

CASE REPORT

A 73 year old white myopic female presented in Italy in September 1996 with the sudden appearance of a dark spot in the visual field of the right eye associated with photopsia. She was first seen at Princess Alexandra Eye Pavilion, Edinburgh, in November 1996 with the same complaint. She had no systemic problems and was taking no medications. Vision was 6/5 N5 in each eye with correction. She

Table 1 Electrophysiological finding from full field ERG recording (µV) along with confidence intervals. Although some disparity is evident between eyes, both responses fall within normal limits

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TOVA LIFSHTZ
RUTH LAPID-GORTZAK
YARON FINKELMAN
ITAMAR KLEMPERER

RUTH LAPIGORTZAK
YARON FINKELMAN
ITAMAR KLEMPERER

Department of Ophthalmology, Soroka University Medical Center, Ben Gurion University of the Negev, Beer Sheba, Israel

Correspondence to: Tova Lifshitz, Department of Ophthalmology, Soroka University Medical Center, Ben Gurion University of the Negev, POB 151, Beer Sheba 84101, Israel

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ERG in the investigation of localised retinal pathologies is of limited value. The recent advances in the application of pseudo random binary sequences (PRBS) to signal averaging has addressed the limitation of local ERG measurements and made them a routine clinical practicality.

It should be mentioned however that the multifocal technique, in its present form, is not a replacement for either full field electrophysiology or its subjective partner perimetry. It merely complements the arsenal of investigative techniques available to clinicians.

NADA AL-YOUSUF
Princess Alexandra Eye Pavilion, Edinburgh and the
Tennent Institute of Ophthalmology, Glasgow

STUART PARKS
Electrodiagnostic Imaging Unit, Tennent Institute of
Ophthalmology, Gartnaval General Hospital, Great
Western Road, Glasgow, G12 0YN

B DHILLON
Princess Alexandra Eye Pavilion, Chalmers Street,
Edinburgh, EH3 9HA

DAVID KEATING
Electrodiagnostic Imaging Unit, Tennent Institute of
Ophthalmology, Gartnaval General Hospital, Great
Western Road, Glasgow, G12 0YN

Correspondence to: Dr Nada Al-Yousuf, Corneos
Plastic Unit, Queen Victoria Hospital NHS Trust,
East Grinstead, West Sussex RH19 3DZ
Accepted for publication 15 September 1999

93–5.
291–300.

**Figure 1** Multifocal ERG maps showing records of initial and subsequent measurements performed after 5 month interval. (A(i), A(ii)) multifocal waveforms indicate reduction in inferior nasal response. (B(i), B(ii)) Topographical maps of retinal function (scalar product plot, see Sutter et al) and (C(i), C(ii)) plan views topographical maps.

1–3 8–10 4–6

**Linear naevus sebaceous syndrome, optic disc staphyloma, and non-rhegmatogenous retinal detachment**

EDITOR,—Linear naevus sebaceous syndrome, with its synonyms Schimmelpenning-Feuerstein-Mims syndrome, epidermal naevus syndrome, and Solomon syndrome, is a rare congenital and sporadic disorder without known familial aetiology. It includes deformities and dysplasias of the skin, eyes, brain, skeleton, and heart, such as a linear naevus sebaceous Jadassohn, mental retardation, convulsions, asymmetry of the cranial structures and dilated cerebral ventricles ipsilateral to the naevoid. Ocular abnormalities described in patients with Schimmelpenning-Feuerstein-Mims syndrome are microphthalmia, colobomas of the eyelids, large optic nerve heads, and congenital teratomas or dermoids of the conjunctiva and cornea.

COMMENT

The system used for the multifocal ERG recording was similar to the commercially available VERIS system. However, it was custom built to run on Microsoft/PC platform. Care was taken to assure maximum filter bandwidth as differentiation of the response is known to lead to signal distortion. Ground electrodes were placed on the forehead, reference electrodes were placed on the outer canthus, and active electrodes were placed in the lower lid.

Conventional Ganzfield ERGs were recorded using our custom build system triggering a Ganzfield stimulator. Multifocal and conventional ERGs were repeated after 5 months.

Electrophysiological findings from full field ERG recordings along with confidence ratings are summarised in Table 1. These results indicate that although some disparity is evident between the two eyes, both responses fall within normal limits. The multifocal ERG results are reported as topographical maps of retinal function. The evoked response maps in Figure 1 are a good record of the initial and subsequent recording performed after a 5 month interval. These responses indicate localised dysfunction in the inferonasal field of the right eye. Repeat measurements indicated no significant improvement or deterioration over this short period.

Given the suggested outer retinal dysfunction associated with AZOOR, the electroretinogram, it would appear, is an ideal test for assessing and diagnosing such pathologies as its record is a direct measure of photoreceptor and bipolar cell function. However, if suggestions are correct that AZOOR represents a localised dysfunction in the outer retinal system and since the full field flash ERG represents a global response to a diffuse stimulus, and information derived from the full field flash...
Four months later, silicone oil was removed. Intentionally performing a small peripheral subretinal fluid became possible first after the vitreous cavity. Endodrainage of the carbon liquid, the subretinal fluid was pressed to the fundus periphery without leaking into the subretinal surface, temporary instillation of perfluorocarbon liquid, and ocular endotamponade by a retinotomy, and ocular endotamponade by silicone oil endotamponade. Again, a peripheral, central, or paracentral retinal defect was not detected. After additional 12 months, silicone oil was removed leaving a new retinal detachment, again starting in the intrapapillary nasal inferior region of the optic nerve head. In the following retinectomy, no retinal defect was found, neither in the periphery nor in the vicinity of the optic disc where the retinal detachment started. During the first operation, a subconjunctival tumour located at the 12 o’clock position close at the limbus in the right eye was removed. Its histological examination showed ectopic lacrimal gland tissue. This report suggests that an optic nerve head staphyloma with a macrodisc, pit-like appearance of the nasal region of the optic disc (Fig 1), a para-papillary chorioretinal atrophy at the temporal border of the optic disc, and alterations of the retinal pigment epithelium in the fovea in addition to the retinal detachment. A retinal defect was not found. In the left eye, ophthalmoscopy was not possible owing to the corneal opacification. Sonography of the left eye was unremarkable. General findings included a linear sebaceous naevus and patchy alopecia on the anterior and posterior part of the scalp. There was no family history of consanguinity or birth defects.

After retinal detachment surgery including encircling band, trans scleral exodrainage of the subretinal fluid, and exodocoagulation of the retinal pigment epithelium in the fovea to the centre of the cornea. Ophthalmoscopy and patchy alopecia on the anterior and posterior part of the scalp. There was no family history of consanguinity or birth defects.

After a follow up period of an additional 3 months, in which visual acuity increased to 20/33, the retina redetached again necessitating a second pars plana vitrectomy with silicone oil endotamponade. Again, a peripheral, central, or paracentral retinal defect was not detected. After additional 12 months, silicone oil was removed leaving a new retinal detachment, again starting in the intrapapillary nasal inferior region of the optic nerve head. In the following retinectomy, no retinal defect was found, neither in the periphery nor in the vicinity of the optic disc where the retinal detachment started. During the first operation, a subconjunctival tumour located at the 12 o’clock position close at the limbus in the right eye was removed. Its histological examination showed ectopic lacrimal gland tissue. This report suggests that an optic nerve head staphyloma with a macrodisc, pit-like appearance of the nasal region of the optic disc, and associated non-rhegmatogenous retinal detachment.

Figure 1 Fundus photograph showing the large optic nerve head (area 13.75 mm²) with optic disc staphyloma, a pit-like appearance of the nasal region of the optic disc, and associated non-rhegmatogenous retinal detachment (white arrows).

Can leukocoria be the first manifestation of protein C deficiency?

EDITOR—Protein C is a plasma inhibitor protein that, once activated, inhibits clot formation and enhances fibrinolysis. Protein C deficiency has two forms. The homogeneous form presents in the neonatal period with ecchymotic-necrotic skin lesions and widespread thrombosis in major blood vessels with very low or undetectable protein C activity. Heterozygote individuals have protein C levels of approximately 50% and usually remain asymptomatic until adolescence.1

We present a neonate with homozgyous protein C deficiency whose initial finding was leukocoria.

CASE REPORT

A 2 day old female infant was referred to Gazi University Hospital Division of Newborn Medicine with bullous haemorrhagic lesions on both heels and left leg and leukocoria of the left eye. At the time of birth, no intrauterine infections were noted to be completely normal other than the ocular finding. On the second day of life blue-black necrotic lesions appeared on the left leg at the injection site of vitamin K and both heels at the circumcision sites. Family history was remarkable for a first degree consanguinity between the parents. Physical examination revealed purpuric necrotic lesions on her left thigh, and both heels, and leukocoria was present on the left eye.

Laboratory findings were as follows: haemoglobin: 16.7 g/dl, platelets: 46,000/mm³, pro-thrombin time: 24.4 seconds, partial thromboplastin time: 66 seconds, fibrinogen: 41 mg/dl, vWF: 8 ng/ml, fibrinogen degradation product <5 ng/ml. Coagulation tests were abnormal and consistent with disseminated intravascular coagulation. Protein C activity: 1.65%, paternal protein C activity: 18.6%, maternal protein C activity: 50.5%, TORCH screen: negative. Abdominal and cranial ultrasound were both within normal limits. Ophthalmological examination and eye ultrasound revealed leukocoria, and 10×7 mm hypochogenic structure under the retina of the left eye consistent with subretinal haemorrhage.

With these findings the patient was diagnosed to have homozygous protein C deficiency and disseminated intravascular coagulation and was treated with fresh frozen plasma, sodium warfarin, and low molecular weight heparin. No other intrauterine infections or reasons were found to explain ocular findings.

COMMENT

Primary causes of leukocoria in children are catarract, persistent hyperplastic primary vitreous, cysticiridal retinopathy of prematurity, retinal detachments, and retinoblastoma. Retinal vascular or vitreal haemorrhages have been infrequently reported to result in leukocoria in infants with protein C deficiency. Ophthalmological manifestations of protein C deficiency result from retinal arterial or venous occlusions, retinal, preretinal, or vitreous haemorrhages. The lesions may be intrauterine events or occur postnatally. At birth neonates can present with non-reactive pupils, periocral oedema, and chemosis. To our knowledge earliest leukocoria in protein C deficiency was reported in a 2 months old infant.2 However, in our patient leukocoria was present at birth and the skin lesions appeared on the second day of life showing that the infant actually suffered from protein


C deficiency in utero. Therefore, we conclude that leucocoria by itself can be the first manifestation of homozygous protein C deficiency; this should alert the physician to the problem since these infants can also have severe cerebral complications which are preventable if treated on time.

EBRU ERGENEKON
Gazi University, Department of Pediatrics, Division of Newborn Medicine, Ankara, Turkey

BIRSIN SOLAK
Gazi University, Department of Pediatrics, Ankara, Turkey

GÜLYÜZ ÖZTÜRK
Gazi University, Department of Pediatrics, Division of Pediatric Hematology, Ankara, Turkey

YILDIZ ATALAY
Gazi University, Department of Pediatrics, Division of Newborn Medicine, Ankara, Turkey

ESIN KOÇ
Gazi University, Department of Pediatrics, Division of Pediatric Hematology, Ankara, Turkey

Correspondence to: Ebru Ergenekon, Yesilyurt Sokak No 19/9, Cankaya 06690, Ankara, Turkey
Accepted for publication 15 September 1999

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JEREMY D BOWYER, ELIZABETH M JOHNSON, ELIZABETH H HORN and RICHARD M C GREGSON

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