ABSTRACT – Metastatic or endogenous endophthalmitis (EE) is a serious consequence of systemic sepsis. It is defined as intraocular infection resulting from haematogenous spread of organisms in which the initial focus of infection is at a site distal to the eye. A red/sores eye in a patient with a known septic focus needs urgent attention as EE can be a major cause of visual loss. Early diagnosis and treatment are associated with better visual outcome. This article focuses on the two main causes of EE, namely bacterial and fungal infections, and also briefly mentions dissemination of cytomegalovirus to the eye in immunocompromised patients. Although conscious patients may notice an ocular problem, unconscious or very sick patients may not; vigilance by medical staff in looking for early signs of this is extremely important.

KEY WORDS: candida, ciprofloxacin, cytomegalovirus (CMV), endophthalmitis, floaters, hypopyon, red eye, retinal infiltrates, retinitis, septicaemia

Endogenous fungal endophthalmitis

Fungal sepsis is identified most frequently in hospitalised patients who are seriously ill. Endogenous fungal endophthalmitis (EFE) occurs in 28–45% of patients with candidaemia1,2,3 and is the most common form of endogenous endophthalmitis (EE)4. Patients usually present with floaters and decreased vision, unilateral or bilateral. Onset is often insidious; in its early stages EFE can be asymptomatic5, but if left untreated can have devastating consequences for visual function. Therefore, regular screening of high risk cases is undertaken in many centres6,7. High risk characteristics include those listed in Table 1.

Candidiasis

Candida albicans is the most common pathogen causing EFE and in some series is the causative agent in 85–99% of all cases6,9. Non-albicans candida spp are important as aetiological agents10 because fungaemia with these species is associated with a higher incidence of endophthalmitis than with C. albicans11. Other causes of EFE in descending order of importance are Aspergillus fumigatus, coccidioides, cryptococcus, fusarium, histoplasmosis and paecilomyces4.

Diagnosis of ocular candidiasis. The clinical diagnosis of ocular candidiasis is largely made on the ocular appearance8. The organism typically causes inflammation in the choroid and retina, with subsequent spread into the vitreous cavity8. The ophthalmoscopic appearance is of one or more creamy-white, usually round and sometimes elevated retinal lesions, often sited in the posterior pole of the eye (Fig 1). They may vary in size from small pinpoint lesions to two-disc diameter in width8. If the vitreous is involved, multiple clumps may form (‘puff balls’) (Fig 2). Thread-like strands may connect these, producing a so-called ‘string of pearls’ appearance.

Ocular lesions can indicate otherwise occult deep tissue fungal infection and are useful indicators of systemic candidiasis12,13. Although autopsy studies have demonstrated a high incidence (78%) of ocular involvement in patients with candidaemia12, the eye can be the only organ involved8. Conversely, only 11% of patients with endophthalmitis have had documented systemic fungal infection9. In disseminated candidiasis, haematogenous spread occurs early in the disease, most commonly to the eye, kidney, liver, spleen and skin with resultant abscess formation at these sites12. The diagnosis of fungaemia can be difficult as it is usually transient and blood cultures are relatively insensitive9,14,15. Patients in whom multiple blood cultures are positive have a greater incidence of EFE9. Positive fungal cultures from a deep body site also increase the risk (19 times) of fungal endophthalmitis6.
Treatment of endogenous fungal endophthalmitis

Patients have been successfully treated with:
- systemic antifungal therapy alone\textsuperscript{7,16,17}
- intravitreal amphotericin B alone\textsuperscript{15,18,19,20}, or
- vitrectomy with or without intravitreal amphotericin B and with or without systemic antifungal agents\textsuperscript{21–23}.

Most ophthalmologists would agree, however, that involvement of the vitreous in the disease process warrants consideration of vitrectomy to prevent retinal detachment occurring in these eyes\textsuperscript{8,23–25}.

Systemic disease

Treatment of systemic disease includes the following:
- Amphotericin B is often given intravenously (iv). It does not achieve adequate therapeutic levels inside the eye\textsuperscript{26}, although resistance is rare.
- 5-Fluorocytosine can be given orally, causes few adverse reactions and penetrates well into the eye\textsuperscript{27}. It is rarely used in isolation as resistance has been reported in up to 53% of cases\textsuperscript{28}.
- The azoles, in particular fluconazole, also penetrate well into the eye, have good absorption following oral administration and few adverse effects\textsuperscript{29}.

The most common management for EFE involves intravitreal injection of amphotericin B (5–10 \(\mu\)g in 0.1 ml) with systemic fluconazole and vitrectomy if the vitreous cavity is involved. Although resistance to azoles is uncommon, care should be taken when a non-albicans candida spp is isolated as their sensitivities may be different\textsuperscript{11}.

Visual prognosis

Visual prognosis is determined by the location of the retinal abscess and time from onset to treatment. Brod et al\textsuperscript{15} reported that 80% of cases with less than two months from onset to treatment had 20/50 or better vision at six months, whereas those whose treatment was delayed by more than two months were all worse than 20/80.

Infection with \textit{A. fumigatus} carries a poorer visual prognosis than with \textit{C. albicans}\textsuperscript{9}. One study\textsuperscript{10} showed that the longer the period of time before resolution of the fungal infection, the greater the likelihood of surface membrane (epiretinal membrane) and scar formation involving the macula, and thus a poor visual outcome. In another study, 65% of 15 eyes infected with candida achieved final visual acuities of 20/400 or better, whereas all three eyes infected with aspergillus had final visual acuities worse than 20/400\textsuperscript{9}.

Another important factor in determining the final visual outcome is retinal detachment: 50% of patients in whom retinal detachment occurred had a final visual acuity of 20/400 or worse\textsuperscript{15}. Other complications that can reduce vision include epiretinal membrane formation, choroidal neovascularisation, and cataract formation\textsuperscript{15}.

Endogenous bacterial endophthalmitis

Endogenous bacterial endophthalmitis (EBE) accounts for 2–8% of all cases of endophthalmitis\textsuperscript{31}. It is usually associated with debilitating medical disease (eg uncontrolled diabetes mellitus\textsuperscript{32}) and chronic renal failure, or occurs after invasive medical procedures (eg endoscopy) or major surgery. It may also occur following iv drug abuse and recent trauma to a body site other than the eye\textsuperscript{33,34}. The disease is usually unilateral, but has been reported as bilateral in 10–25% of cases\textsuperscript{35}.

Fig 1. Macular abscess in the posterior pole in a patient with endogenous fungal endophthalmitis. \textit{Candida albicans} was cultured from the blood of this patient.

Fig 2. Puff ball/string of pearls appearance in a patient with candida endogenous fungal endophthalmitis involving the vitreous.
Unlike EFE, the onset is usually rapid, with the majority of patients developing ocular symptoms within one week. Patients complain of decreased vision, floaters, a red sore eye and headache. Some patients have associated systemic symptoms such as fever, weight loss or malaise at the time of onset of ocular symptoms. Ocular examination may reveal eyelid oedema, chemosis, conjunctival injection, corneal oedema, anterior chamber cells and flare, or a hypopyon (Fig 3), iris microabscess, absent red reflex, vitreous cell and debris, retinal infiltrates (Fig 4) and flame-shaped retinal haemorrhages with or without white centres (Roth’s spot). Orbital involvement is suggested by proptosis and restricted ocular motility (known as panophthalmitis). Subretinal abscesses have been reported secondary to haematogenous spread of klebsiella spp, nocardia spp, Pseudomonas aeruginosa, Streptococcus viridans and Staphylococcus aureus.

Once the diagnosis is suspected, the source of the infection needs to be identified if unknown. Chest X-ray, echocardiogram, blood and urine cultures are useful, together with aqueous and vitreous samples for microbiological analysis.

**Key Points**

A red/sore eye, especially if the vision is reduced, in a patient with a known septic focus needs urgent ophthalmological assessment NOT antibiotic drops

Endogenous fungal endophthalmitis occurs in 28–45% of patients with candidaemia and can destroy vision

A wide variety of bacteria can cause endophthalmitis in a patient with bacteraemia and result in severe visual loss

Cytomegalovirus (CMV) viraemia in an immunosuppressed patient can result in CMV retinitis

Loss of vision occurs more frequently in all types of metastatic infection involving the eye if treatment is delayed

**Treatment of endogenous bacterial endophthalmitis**

Collection of intraocular fluids is followed by injection of broad spectrum antibiotics into the vitreous (such as vancomycin 2.0 mg in 0.1 ml and amikacin 0.4 mg in 0.1 ml). Topical antibiotics and often steroid drops are commenced immediately, together with systemic antibiotics. Few antibiotics given systemically other than ciprofloxacin achieve therapeutic levels inside the eye, so this compound is commonly used. The role of systemic steroids in metastatic endophthalmitis is controversial and may not be appropriate in a debilitated patient, but they are often useful in reducing the associated inflammatory response inside the eye.

**Identification of microorganisms**

Okada et al have demonstrated a 96% identification rate of organisms obtained from at least one body fluid, and positive cultures from 74%, 72%, 60% and 30% vitreous, blood, aqueous and urine samples, respectively. Most organisms causing EBE are Gram-positive (66% in one case series). Organisms include S. aureus, S. viridans, bacillus spp (common in iv drug abusers), Neisseria meningitidis, Haemophilus influenzae, salmonella spp (in immunocompromised patients), Clostridium septicum and, rarely, capnocytophaga spp. The most common presumptive source of EBE has been reported as infectious endocarditis, followed by gastrointestinal and genitourinary tract infection. One series from Taiwan of 180 consecutive patients with a pyogenic liver abscess (whatever the organism) found a 1.7% incidence of metastatic endophthalmitis, rising to 5.2% in patients with a liver abscess due to klebsiella and 8% when there was added evidence of klebsiella...
bacteraemia\textsuperscript{36}. In four patients with EBE from either pneumo-
coccal or meningococcal infection, both endocarditis and meningitis were found\textsuperscript{35}. Multi-organ involvement should therefore be considered, and management altered as required.

Management of endogenous bacterial endophthalmitis

Management of patients with EBE requires an early aggressive approach to achieve the best visual outcome. Factors influencing the outcome of treatment include:

- diagnostic delay
- type of organism involved
- timely treatment\textsuperscript{35},
- initial presenting visual acuity
- the presence of retinal detachment.

In one study of 28 patients, 22 had a final visual acuity of 20/400 or worse and eight patients had the infected eye enucleated due to poor response to treatment, corneal perforation or intractable pain\textsuperscript{35}.

Cytomegalovirus retinitis in the immunocompromised host

Patients who are immunosuppressed either by disease or medication can lose the normal immune control of cytomegalovirus (CMV) replication and develop CMV viraemia and disease\textsuperscript{40}. They may present with systemic symptoms such as fever, anorexia and malaise, but can also develop pneumonia, hepatitis, gastrointestinal ulceration, encephalo-

pathy and chorioretinitis, all of which have a high morbidity or mortality\textsuperscript{41}. Untreated CMV retinitis is slowly and relentlessly progressive, resulting in blindness from posterior pole involvement or retinal detachment. The patients may present with blurred vision and floaters but may also be asymptomatic.

Ocular examination usually reveals a white uninflamed eye with areas of whitening and haemorrhage in the retina either unilateral or bilateral (Fig 5). The diagnosis is usually made on the history and clinical appearance, although polymerase chain reaction for CMV/DNA of vitreous fluid is valuable in confirming the diagnosis especially when the clinical features are not classic.

Management of cytomegalovirus retinitis

Management is aimed at reducing both the systemic immuno-
suppression, where possible, and the circulating CMV load with iv antiviral agents such as ganciclovir. The retinitis can be managed with systemic ganciclovir, but additional therapy may be given into the vitreous\textsuperscript{42–44}.

Conclusion

Sick patients who are known to have an infective focus or are at risk of sepsis, who complain of eye problems or have a red eye must undergo ophthalmological assessment. Collaboration between different specialties is crucial in managing patients with intraocular infection. Not only can the visual outcome of endogenous endophthalmitis be poor but the associated septicaemia may be life-threatening, with up to 15% of patients dying during the course of the disease\textsuperscript{9,35}. These patients need to be managed aggressively with local and systemic therapy, and surgical intervention when necessary, as early diagnosis and treatment are associated with a better visual outcome.

References

\begin{enumerate}
  \item Brooks RG. Prospective study of Candida endophthalmitis in hospital-
  \item Parke DW 2nd, Jones DB, Gentry LO. Endogenous endophthalmitis
  \item Bross I, Talbot GH, Maislin G, Hurwitz S, Strom BL. Risk factors for
nosocomial candidemia: a case-control study in adults without
  \item Samiy N, D’Amico DJ. Endogenous fungal endophthalmitis. Review.
  \item Pizzo PA. Infectious complications in the child with cancer. I. Pathophysiology of the compromised host and the initial evaluation and management of the febrile cancer patient. Review. \textit{J Pediatr}
  \item Enzenauer RW, Calderwood S, Levin AV, Elder JE, Morin JD. Screening
  \item Johnson DE, Thompson TR, Green TP, Ferrieri P. Systemic candidiasis
in very low-birth-weight infants (less than 1,500 grams). \textit{Pediatrics}
  \item Chignell AH. Endogenous candida endophthalmitis. \textit{J R Soc Med}
  \item Essman TF, Flynn HW Jr, Smiddy WE, Brod RD \textit{et al}. Treatment out-
comes in a 10-year study of endogenous fungal endophthalmitis.
\end{enumerate}