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Sir,

**Bilateral Endogenous *Candida* Endophthalmitis and Chorioretinitis following Toxic Megacolon**

Endogenous *Candida* endophthalmitis has been reported with increasing frequency in hospitalised patients with recognised risk factors. Confirmation of the diagnosis is often difficult and delayed. Treatment must proceed on the basis of the clinical appearance, behaviour and history. Intravitreal antifungals should be given at the time of vitreous biopsy. Vitrectomy is not always necessary but may considerably accelerate recovery and should be considered early. High-dose oral fluconazole, if tolerated, brings about a slow but steady resolution. Final prognosis is good if no significant chorioretinal scarring occurs at the macula and the patient recovers from any concurrent systemic illness.

*Case Report*

A 61-year-old woman developed *Salmonella* gastroenteritis with persistent diarrhoea while on holiday in Mallorca. She was admitted to the medical ward but within 2 weeks required a total colectomy and ileostomy for toxic megacolon. She also underwent bilateral radical oophorectomy for ovarian tumours, later confirmed histologically as moderately well differentiated serous cystadenocarcinoma. She received vancomycin, clarithromycin, metronidazole and ciprofloxacin intravenously or orally over a period of 4 weeks.

Visual symptoms were of a steady deterioration of left vision over 1 week with accompanying floaters. Corrected visual acuity on presentation was 6/12 in the right eye and counting fingers in the left. There was mild anterior segment activity in the right eye and moderate activity in the left with flare, 3+ cells and posterior synechiae. Vitritis was marked (3+) in the left eye and a focal fluffy area of active chorioretinitis was noted at the left macula (Fig. 1).

The possibility of fungal aetiology was considered at presentation because of the history and appearance. She was admitted and investigations showed negative serology for *Toxoplasma*, *Toxocara* and syphilis, as well as negative blood cultures. However, the wound swab from her ileostomy site was positive for *Candida albicans*. She underwent left vitreous biopsy and intravitreal injection of antibiotics and antifungal (amikacin 0.4 mg and vancomycin 1 mg, both in 0.1 ml of normal saline and amphotericin B 5 μg in 0.1 ml of 5% dextrose solution) to cover the likely causes of endogenous endophthalmitis including the suspected fungal cause. She was also started on oral fluconazole (100 mg b.d.), topical steroids and a mydriatic. Prompt microscopy was unable to detect any fungal mycelia and cytology failed to detect any fungal elements. Over the next 5 days

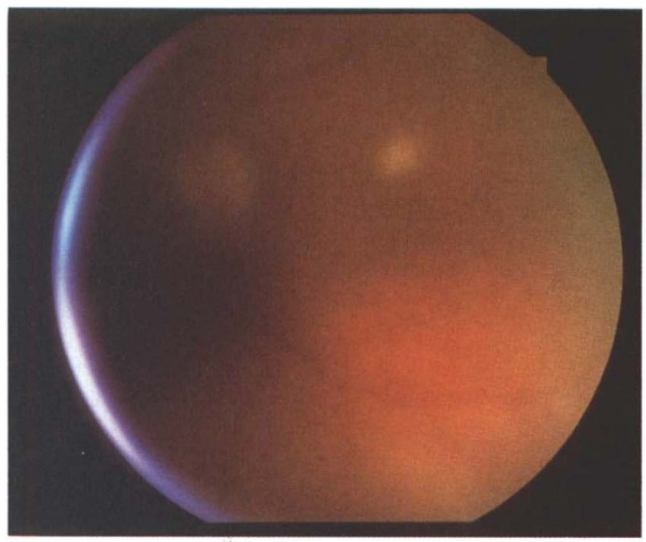

**Fig. 1.** *Left fundus at presentation. A dense focus of active chorioretinitis is visible in the central macula through considerable overlying vitritis.*

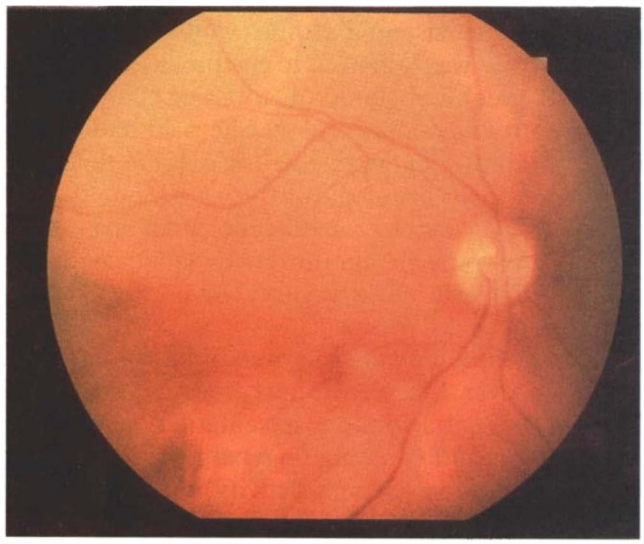

**Fig. 2.** *Right fundus 3 months later. Persistent intravitreal opacities overlie the inferior arcade vessels, which remained inactive in this non-vitrectomised eye.*

there was no demonstrable improvement in the left eye but the vitritis in her better (right) eye became more marked with an accompanying reduction in visual acuity to 6/24. She underwent left vitrectomy at a tertiary referral centre. The left foveal retinitis was confirmed and multiple small foci noted along the retinal vessels. She received a further intravitreal injection of amphotericin B (10 μg in 0.1 ml). No vitrectomy was carried out on the right eye though an area of focal retinitis in the inferior peripheral retina was noted along with moderate vitritis. The vitrectomy specimen did finally yield a positive identification for *Candida albicans* and showed no evidence of neoplastic cells. After expert microbiological advice she was commenced on oral fluconazole 400 mg b.d. This was reduced to 200 mg b.d. after 1 week as she

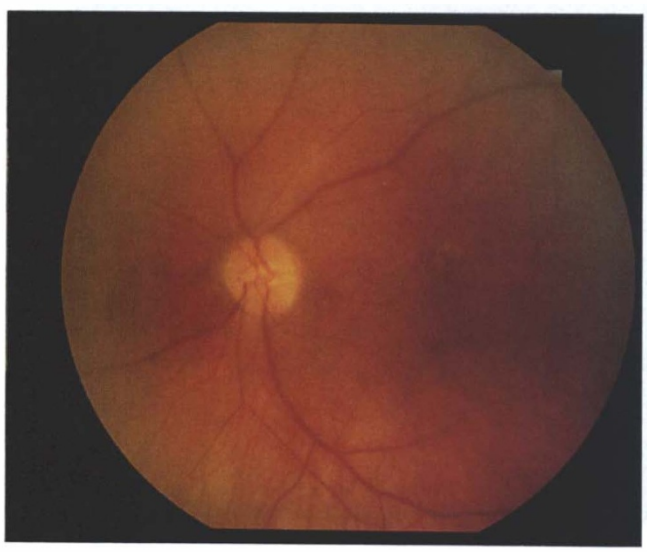

**Fig. 3.** *Left fundus 3 months later. Quiescent chorioretinal scarring is present, unfortunately involving the fovea.*

experienced a degree of nausea. Four weeks later the dose was reduced to 100 mg b.d. and both eyes became quiet over the next 6 weeks, when oral fluconazole and topical steroids were stopped. Visual acuity recovered steadily to 6/5 right eye and 6/36 left eye by 3 months, the left eye having quiescent foveal scarring (Figs. 2 and 3). Review at 8 months from onset showed no reactivation.

*Discussion*

*Candida albicans* is a commensal on the skin, in the gastrointestinal tract and the vagina. It is a yeast with mycelial and spore-forming phases. Candidaemia can occur in debilitated patients, of whom one third go on to develop endogenous fungal endophthalmitis, one third of cases being bilateral. This woman had recognised risk factors for fungal endophthalmitis, namely prolonged intravenous access and recent bowel and pelvic surgery. Typically she had a positive culture result for *Candida* from another site, the ileostomy, representing the most likely source of her infection. Her presentation with gradual loss of vision with little discomfort is characteristic. This case shows the contrasting fortunes of the two eyes, with excellent recovery of vision in the right eye without vitrectomy and only moderate recovery in the vitrectomised left eye because of foveal scarring. No recurrence developed on cessation of treatment.

Without evidence of systemic candidiasis intravenous amphotericin B is rarely necessary, so avoiding attendant local irritation, renal toxicity and frequent side effects.[1] Oral fluconazole is then the systemic treatment of choice.[2] Orally well absorbed it is better tolerated than other azoles, achieving adequate intraocular levels provided the oral dose is high enough. Intraocular levels are 50-90% of plasma concentrations.[3] Fluconazole may be given parenterally, but this is seldom necessary unless a patient cannot take oral preparations or is too ill to do so.

Fluconazole may be the only treatment necessary if the diagnosis is suspected early enough.[4] Specifically, if there are few and small areas of chorioretinitis only, with minimal overlying vitreous involvement, then oral fluconazole may suffice. Dosage may be increased to as high as 800 mg b.d. but a starting dose of 200-400 mg b.d. is advised. The dose should be reduced if the patient is unable to tolerate it or if their liver function tests, particularly the alkaline phosphatase, become markedly elevated. The latter is then a useful marker for gradually reducing teratment over the next 6-8 weeks. Fluconazole is metabolised in the liver like ketoconazole but is less hepatotoxic. Side effects are of nausea, vomiting and pruritus, which are dose dependent and resolve as the dosage is reduced.

Additional therapy is indicated in all but very early

cases for two reasons. First, fluconazole is fungistatic and not fungicidal, which may account for reported unfavourable outcomes in patients on monotherapy.[2] Second, the emergence of some fluconazole-resistant strains of *Candida*, particularly *Candida krusei*,[5] supports the use of combination therapy.

The agent of choice for combination therapy is amphotericin B. It is fungicidal, causing leakage of fungal cellular constituents. It is not absorbed orally and produces severe local toxicity if given subcutaneously. It may be administered intravenously or intravitreally or by both routes in patients with disseminated candidiasis with ocular involvement. For ocular involvement alone, intravitreal amphotericin B (dose 5-10 μg in 0.1 ml) is combined with oral fluconazole. Diagnostic vitreous biopsy or pars plana vitrectomy represents an opportunity for intravitreal administration. Amikacin or vancomycin may also be given at the same time to cover other suspected pathogens if the clinical picture is not typical.

The timing and place of vitrectomy is contentious, but if the degree of vitritis is such that monitoring progression or response to treatment is hampered then vitrectomy should be considered and carried out promptly.[6] Other benefits include reducing infection load, providing an adequate sample for positive identification, and intravitreal injection with better penetration of antifungal to foci of activity. The timing of repeat intravitreal antifungal depends on whether a vitrectomy has been carried out. Without vitrectomy the levels of amphotericin B are maintained at greater than the mean inhibitory concentration (MIC) for 10-11 days compared with 2-3 days following vitrectomy, because of a much accelerated rate of clearance from the vitrectomised eye.[7] This should be set against the greater access afforded and more rapid control of intravitreal involvement. Intravitreal use of amphotericin B is not without problems; retinal toxicity can occur even with small doses.[8]

In systemic candidiasis it is usual to use parenteral amphotericin B under close supervision. A formulation of amphotericin B encapsulated in liposomes is available which allows the use of higher dosages by reducing the number of side effects and limiting the degree of nephrotoxicity.[9] High cost means its use should be reserved for patients with compromised renal function and those specifically unable to tolerate the normal formulation. Animal models back up the use of amphotericin in disseminated candidiasis, showing its superiority over fluconazole and suggesting that lesion sterilisation occurs before ophthalmoscopic resolution of endophthalmitis.[10]

The use of steroids is usually limited to topical administration for the resolving panuveitis. Interestingly in an animal model, intravitreal dexamethasone with amphotericin B did not impair antifungal activity or enhance fungal proliferation and resulted in significantly clearer vitreous at an earlier stage.[11] However, systemic and intravitreal steroids should not be used without concomitant antifungal treatment because of the risk of severe exacerbation.

Outcome depends on the extent and site of involvement of chorioretinal lesions as well as prompt diagnosis and correct management.[12]

The above represents a suggested systematic approach to a difficult management problem. Although other antifungals have been used, such as ketoconazole, itraconazole and flucytosine, none has any significant advantages compared with fluconazole and amphotericin when used as described.

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