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Sir

Consecutive Keratitis and Candida Endophthalmitis in an Immunocompromised Patient with Chronic Lymphocytic Leukaemia

A 75-year-old man with chronic lymphocytic leukaemia (CLL) presented to the eye department in April 1995 with a 1-week history of decreased visual acuity, redness and pain in the right eye. Previous ophthalmic history revealed a right membranous conjunctivitis 6 months earlier on the background of disseminated varicella infection. The membranous conjunctivitis was successfully treated but a right corneal erosion developed that was slow to heal and recurred on two occasions prior to this admission.

CLL was diagnosed in 1989. The patient had initially been treated with chlorambucil. His disease progressed with rising white blood cell counts, and lymphadenopathy was noted in mid-1994. He received fludarabine (Schering Health Care, The Brow, Burgess Hill, West Sussex, UK) 25 mg/m^2 daily for 5 days each month between 10 October 1994 and 18 January 1995. Following that he had maintenance therapy with prednisolone 10 mg. At that time his disease status was stage 4 with diffuse marrow involvement.

Following fludarabine treatment, the disease course was complicated by suppression of neutrophils and platelets. He had recurrent chest infections and received antibiotics and prophylactic intravenous immunoglobulin every 4 weeks with some reduction in severity of recurrent chest infections.

On this occasion, visual acuity in the right eye was 6/36 corrected to 6/18 with pinhole and 6/6 in the left eye. The right eye was intensely injected with a large corneal ulcer associated with inflammatory infiltrate. There was a 1.0 mm hypopyon and intensely injected iris vasculature. Fundal details were obscure because of the corneal ulcer and lens opacities. The left eye was clinically normal.

A diagnosis of right microbial keratitis was made and corneal samples and conjunctival swabs were taken for microscopy and culture. The patient was admitted and an intensive regime of half-hourly gentamicin 1.5% and cefuroxime 5% drops administered day and night. Cephradine 500 mg q.d.s. was given orally. The patient was already on prednisolone 10 mg daily as maintenance therapy for his haematological disorder.

Because of the previous history of disseminated varicella, systemic acyclovir 400 mg and acyclovir ointment were prescribed, both five times daily. After 1 week of treatment there was no significant clinical improvement and culture results were negative. Topical treatment was stopped for 24 hours and another corneal sample was taken for microscopy, culture and sensitivity, looking specifically for viruses, bacteria and fungi. The patient was then started on ofloxacin 0.3% drops and cefuroxime 5% drops hourly, prednisolone 1% drops q.d.s. and atropine 1% b.d. After 1 week the condition deteriorated with extension of the hypopyon to 3 mm and persistence of the stromal abscess and epithelial defect. A repeat corneal sample was taken and a diagnostic vitreous tap with intravitreal amikacin (0.4 mg in 0.1 ml) and amphotericin B (10 μg in 0.1 ml) injection was performed to aid the diagnosis of the corneal problem. The vitreous sample was culture-positive for *Candida albicans*. Therefore, hourly econazole drops and fluconazole 200 mg b.d. were started. Topical treatment with ofloxacin, cefuroxime, prednisolone and acyclovir was stopped. After another week the hypopyon had resolved but the stromal abscess persisted with the formation of a thick endothelial plaque obscuring the visual axis. Visual acuity deteriorated to perception of light only and an ultrasound scan of the eye revealed a dense cataract but no retinal detachment or vitreous haemorrhage.

Because of the very slow progress despite appropriate therapy and the presence of a dense cataract, a combined corneal graft, extracapsular cataract extraction and intraocular lens implant was performed. On histological examination the cornea had a large ulcer crater with a predominantly polymorphonuclear leucocyte infiltrate consistent with an infective inflammatory process. Fungi were not demonstrated. The polymorphs did not exhibit features of a leukaemic infiltrate.

Six months after the operation the graft remains clear with a corrected visual acuity of 6/36.

Discussion

Candida albicans causes the majority of opportunistic fungal infections.[1] Furthermore, 90% of fungal infections occurring in neutropenic patients are due to *Candida* and *Aspergillus* species.[2] Patients who are immunocompromised due to long-term cytotoxic drug therapy are susceptible to infection by such opportunistic organisms.[3]

The incidence of systemic mycotic infections has increased dramatically in recent years.[4] *C. albicans* is the most common pathogen in endogenous fungal endophthalmitis.[5] A review of 76 cases has revealed that 78% of patients with *C. albicans* endophthalmitis have diffuse systemic candidiasis.[5] This highlights the importance of the ophthalmologist in early

diagnosis and therapy, because ocular findings may provide the first clue to an underlying candidaemia.[6]

C. albicans is part of the normal flora of the oral cavity, vagina, gastrointestinal tract and rectal area. It is rarely isolated from normal human skin. When a mucosal barrier is breached (e.g. inflammation of mucous membranes secondary to chemotherapy) haematogenous access is gained. The organs most often involved are the lungs, kidney, liver, heart and brain.[3] Exogenous fungal endophthalmitis has been described after many intraocular surgical procedures but remains an uncommonly encountered complication. A recent case has been published of *Candida parapsilosis* endophthalmitis with a consecutive keratitis after phacoemulsification surgery.[7] Our patient had *C. albicans* endophthalmitis with a keratitis without previous surgery. He was neutropenic and had sustained an epithelial defect of his cornea that was very slow to heal. This, together with previous chemotherapy and a maintenance dose of systemic prednisolone, would certainly have predisposed him to systemic candidiasis.

Our case is unique because *C. albicans* endophthalmitis occurred in an individual who had become immunocompromised after treatment with a potent cytotoxic agent, fludarabine, and this has never been reported before. The two main recognised groups at risk are intravenous drug abusers and patients with intravenous lines.[8] We must now be aware of immunocompromised patients who have had long-term treatment with cytotoxic drugs as another important group at risk.

In patients with lymphocytic leukaemia significant risk factors for candidaemia include previous bacteraemia, prolonged neutropenia, prolonged fever, prolonged administration of antibiotics, treatment with multiple antibiotics and a relatively high concentration of *Candida* organisms in the stool.[2] Such immunocompromised patients are prone to intermittent episodes of fungaemia that may be difficult to diagnose accurately by laboratory studies.[10]

This case illustrates certain important points. Vitreous biopsy was required to isolate the pathogen. Even after successful culture and appropriate antibiotic therapy significant corneal damage had occurred necessitating penetrating keratoplasty. Despite appropriate antibiotic therapy the corneal plaque can continue to seed the eye causing a persistence of infection.[7] There is insufficient evidence to support this for our case since *Candida* was not grown from the cornea. Although the study by Edwards *et al.*[5] showed that 78% of cases of endogenous *Candida* endophthalmitis have an associated diffuse systemic candidiasis, our case may fall into the group which does not have the systemic association – in other words, the other 22%. Or it may be that our patient did indeed have intermittent episodes of fungaemia that were not detected by laboratory studies. Blood cultures performed during the patient's febrile episodes did not isolate *Candida.* To salvage some useful vision penetrating keratoplasty was required in our case. After 6 months of follow-up the graft remains clear with no evidence of disease recurrence, but long-term follow-up is required to establish success of transplantation for our patient.

Fluconazole is a safe and effective antifungal agent that can be taken orally and is useful in treating intraocular infections.[11] It does not have the serious side-effects of amphotericin B and has far superior vitreous penetration.[8] The usual dose is 100–200 mg daily, but doses of up to 1600 mg daily are being evaluated.[11]

Fludarabine, a purine analogue, is used in the treatment of low-grade non-Hodgkin's lymphoma and B-cell CLL patients who have not responded to, or whose disease has progressed during or after treatment with, at least one standard alkylating-agent-containing regimen.[12] It is a potent antineoplastic agent with very toxic side-effects. The commonest adverse event is myelosuppression, and opportunistic infections have occurred in CLL patients.[12] Of particular concern is the decrease in $CD4^+$ T-cells, which appears to be long-lasting and possibly associated with an increased risk of opportunistic infections.[9] Our patient is a classic example of these potentially serious side-effects.

Our main message is that the immunocompromised patient on prolonged cytotoxic drug therapy should now be recognised as being at risk of developing endogenous fungal endophthalmitis. Leukaemic patients undergoing chemotherapy are at particular risk of disseminated fungaemia that is potentially fatal.[6] Furthermore, the eye is an important clinical indicator of systemic candidiasis, stressing the important role of the ophthalmologist in early diagnosis and therapy of such a fatal condition. When such patients develop ocular symptoms then opportunistic ocular infection must be strongly suspected and appropriate efforts made to isolate the responsible organism so that therapy can be started early.

Use of such potent antineoplastic agents as fludarabine is associated with serious side-effects. This is the first case where use of such a drug has been associated with endogenous fungal endophthalmitis and reminds the clinician that such immunocompromised patients can have devastating problems in a variety of organ systems including the eye. The resultant visual morbidity may have far-reaching consequences, especially for the working age group. Immunocompromised patients with ocular symptoms must therefore be managed aggressively to avoid a

prolonged and downhill course of events leading to significant visual morbidity. Even if there are no ocular symptoms, periodic detailed ophthalmic examination has been recommended in patients with candidaemia.[6]

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