

Candida endophthalmitis: A critical diagnosis in the critically ill

L Au
K Guduru
G Lipscomb
SP Kelly

Bolton Hospitals, NHS Trust, Bolton,
UK

Abstract: Three cases of *Candida* endophthalmitis complicating critical illness in young adult surgical patients with implications for safer practice are presented. We highlight how early ophthalmological examination can aid in the management of such critically ill patients. Clinicians need to be vigilant for the early diagnosis and aggressive treatment of hospital acquired opportunistic *Candida* infection in at risk patients. Time may be of the essence as sight and life are at risk.

Keywords: *Candida*, endophthalmitis, critical care, septicemia, ocular infection

Introduction

Endogenous *Candida* endophthalmitis is a serious sight threatening condition. We present three cases seen over a 2 year period; all were young adult surgical patients treated in intensive care units. We highlight how early ophthalmological examination can aid in the management of such critically ill patients.

Patient 1

A 33-year-old female was referred to the eye clinic complaining of floaters and visual loss. Emergency cesarean section for fetal distress had been required 3 weeks previously, complicated by the HELLP syndrome (Hemolysis, Elevated Liver enzyme, and Low Platelets), hypertension and renal failure. She had required admission to the intensive care unit. *Candida albicans* septicemia had developed, confirmed by blood cultures. *Candida* was also isolated from patient's central line. Fluconazole 400 mg daily by intravenous injection for one week, followed by 200 mg daily orally had been administered. The patient's visual symptoms were only reported to nursing staff when her general condition had improved. The visual acuity was 6/24 Snellen right eye and 6/9 left eye. Ocular examination revealed bilateral vitritis and multiple creamy-white, well circumscribed retinal lesions (Figure 1). White, forward extending vitreous opacities – reminiscent of a 'string of pearls' in their appearance – were observed in the left eye (Figure 2). The working clinical diagnosis was that endogenous *Candida* endophthalmitis was present. An intravitreal injection of 10 µg of amphotericin B was administered to the left eye. Oral fluconazole 100 mg daily was administered for 5 weeks. The retinal lesions disappeared within 3 months. Vision in the left eye recovered fully while the right eye required further surgery due to macular hole formation. Patient's final Snellen visual acuity was 6/12 right, 6/6 left.

Patient 2

A 24-year-old female underwent open cholecystectomy which was complicated by the post-operative development of a subphrenic abscess. An acute confusional state and respiratory distress requiring endotracheal intubation and ventilation in the intensive care unit developed. Broad spectrum intravenous antibiotics were administered for suspected

Correspondence: Leon Au
Ophthalmology Dept, Bolton Hospitals
NHS Trust, Bolton, BL4 0JR, UK
Tel +44 01204 390694
Fax +44 01204 390554



Figure 1 Colour photograph image of right fundus showing creamy white lesions involving the fovea and mild disc swelling.

septicemia. Lung abscesses were detected on chest X-ray and computerized tomography (CT) scan. Systemic fungal infection was suspected and an ophthalmological opinion for funduscopy was requested. Recording of visual acuity was not possible as the patient was critically ill. Multiple creamy-white intra-retinal lesions with Roth spots were observed in both eyes. The clinical picture was considered suggestive of *Candida* chorioretinitis. This prompted reconsideration of her clinical condition and intravenous fluconazole 400 mg daily was initiated. *C. albicans* was isolated from specimens from a drain in the abdomen and from blood and sputum specimens. The patient's condition improved gradually with full recovery in 6 weeks. The visual outcome was 6/6 Snellen acuity in both eyes.

Patient 3

A 34-year-old female was admitted with a 4 week history of vomiting, diarrhea, abdominal pain, and pyrexia. Flexible sigmoidoscopy showed ulceration suggestive of inflammatory bowel disease. Intravenous hydrocortisone followed by oral steroids was administered to good effect and she was discharged home after one week. However she re-presented with further diarrhea eight days later. After failing to respond

to further systemic steroid treatment, oral administration of azathioprine 100 mg and infliximab 300 mg by intravenous infusion was prescribed. After some initial improvement, her condition deteriorated further and a subtotal colectomy, with formation of an ileostomy and a recto-sigmoid mucous fistula was undertaken. The bowel specimen had histo-pathological evidence of severe ulcerative colitis with cytomegalovirus infection. Her post-operative course was complicated by intra-abdominal sepsis with small bowel obstruction requiring further laparotomy. Nineteen days following the subtotal colectomy, her condition worsened with intermittent pyrexia, tachycardia, and tachypnea. A total of 160 mg of gentamicin, 2 g of cefotaxime, and 1.5 g metronidazole were administered intravenously daily. When *Candida* species was isolated from a previously sited central line sent for microbiological examination fluconazole 100 mg daily orally was prescribed. An ophthalmological opinion for funduscopy was requested. The distance visual acuity recording on a Snellen chart was not possible. Bedside testing of near vision was normal. Three small white yellow vitreous opacities were observed in the right eye. Several Roth spots were observed in the left fundus. The ophthalmological findings were considered consistent with *Candida* endophthalmitis complicating systemic



Figure 2 Color photograph image of the left fundus showing 'string of pearls', appearance of vitreous opacities inferiorly, and mild disc swelling.

Candida septicemia. Intravenous fluconazole 400 mg daily was therefore administered. *C. albicans* was subsequently isolated from blood culture. Intravitreal amphotericin B injection was not possible due to the patient's ill-health and the inability to be transferred to operating theatre. Acute respiratory distress syndrome with severe acidosis followed. Three days later, fatal cardio-respiratory collapse occurred. Multi-organ failure, disseminated candidiasis (with involvement of the kidneys, heart, and thyroid), and inflammatory bowel disease were reported at autopsy. Post mortem ocular tissue examination was not undertaken.

Discussion

Endogenous, or metastatic, endophthalmitis is rare. Fungal organisms account for the majority of such cases, of which *C. albicans* is the pathogen most often responsible (Sallam et al 2006). Systemic *Candida* infection in critically ill patients in hospital high dependency and intensive care units is problematic and increasing (Schelenz and Gransden 2003).

Risk factors for the occurrence of disseminated *Candida* infection in critically ill adults include; the use of broad-spectrum intravenous antibiotics, the placement of central venous

devices, parenteral nutrition following major surgery (eg, abdominal surgery with intestinal wall disruption), and immunosuppression (Munoz et al 2000; Tanaka et al 2001; Schelenz and Gransden 2003). Intravenous heroin abuse-utilizing proprietary lemon juice as a solvent – is a further risk factor in nonsurgical adults (Bibes et al 1992).

Symptoms of endogenous endophthalmitis complicating disseminated *Candida* infection include the recent onset of floaters and reduced vision (Sallam et al 2006). Importantly, affected patients in critical care settings may be too unwell to communicate such visual symptoms to staff. Vitreous opacities with single, or multiple, creamy-white, well circumscribed chorio-retinal lesions may be observed by ophthalmoscopy. These lesions contain the organisms with surrounding granulomatous and suppurative host reaction (Sallam et al 2006). The clinical diagnosis of *Candida* endophthalmitis is reserved for eyes that have ophthalmoscopic signs of vitreous involvement. The vitreous opacities often form in chain like patterns, extending forward into the vitreous cavity giving an appearance reminiscent of a 'string of pearls' or 'balls of fluff'.

Ocular involvement in systemic candidiasis varies in published studies, because of various case ascertainment

methodologies, with ranges from 2% to over 45% of patients being affected (Edwards et al 1974; Donahue et al 1994; Feman et al 2002; Peyman et al 2004). By the time *Candida* endophthalmitis becomes symptomatic, two thirds of patients may have developed disease in both eyes, and more than half have multiple lesions and vitreous involvement (Edwards et al 1974).

The early stages of ocular *Candida* infection may respond to high doses of systemic antifungal agents (Smiddy 1998; Sallam et al 2006). As fluconazole has excellent ocular penetration it is considered the treatment agent of first choice. Resistance to fluconazole is estimated to be as low as 5% at present (Charlier et al 2006). Intra-vitreous injection of amphotericin B may be required for more advanced cases of *Candida* endophthalmitis ocular involvement (ie, with vitreous involvement) and those who responded slowly to systemic treatment alone (like Patient 1 in this report). Voriconazole and caspofungin are recently available new drugs that can be given systemically and intravitreally with promising results (Breit et al 2005). Vitrectomy to reduce the ocular inflammatory and fungal load and improve vision may also be required. The outcome for vision when ocular involvement occurs is favorable when treatment is administered early, before the onset of retinal complications such as epiretinal membrane formation or development of macular hole (Smiddy 1998). Importantly it is vital to recognize that patients with *Candida* endophthalmitis in hospital care are often critically ill and at risk of multi-organ fungal infection and death (Menezes et al 1994; Schiedler et al 2004; Leibovitch et al 2005). Mortality rates of 50% or more have been reported (Menezes et al 1994). Clinicians should have a high degree of suspicion of *Candida* super-infection and a low threshold for aggressive treatment in such at risk patients.

Ocular examination in patients with *Candida* septicemia has been recommended (Donahue et al 1994; Nightingale et al 1995; Piek et al 1998; Feman et al 2002; Rodriguez-Adrian et al 2003). We suggest that ophthalmological consultation should be requested when systemic or disseminated *Candida* infection is suspected, as the ophthalmoscopy features of *Candida* endophthalmitis are characteristic. This clinical diagnosis should lead to early high dose systemic anti-fungal treatment without delay. Microbiological confirmation may take some time, may only become positive late in the disease and has a reported sensitivity as low as 50% (Ellepola et al 2005). Detection of *Candida* DNA using PCR assay offers a more rapid and sensitive test, but it is not widely available yet (Sallam et al 2006). As fluconazole resistance is infrequent in systemic *C. albicans* infections initial aggressive treatment with this agent should be started promptly and this agent

achieves good results in ocular involvement (Akler et al 1995). Early advice from a clinical microbiologist is critical. Identification of *Candida* species with anti-fungal sensitivities should be undertaken and will guide continuing treatment.

Acknowledgement

We are grateful to Prof David Denning and Dr Leela Joseph for comments on an early draft of this paper. There are no competing interests. This paper was unfunded.

References

- Akler ME, Vellend H, McNeely DM, et al. 1995. Use of fluconazole in the treatment of candidal endophthalmitis. *Clin Infect Dis*, 20:657–64.
- Bisbe J, Miro JM, Latorre X, et al. 1992. Disseminated candidiasis in addicts who use brown heroin: report of 83 cases and review. *Clin Infect Dis*, 15:910–23.
- Breit SM, Hariprasad SM, Mieler WF, et al. 2005. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. *Am J Ophthalmol*, 139(1):135–40.
- Charlier C, Hart E, Lefort A, et al. 2006. Fluconazole for the management of candidiasis: Where do we stand after 15 years? *J Antimicrob Chemother*, 57(3):384–410.
- Donahue SP, Greven CM, Zuravleff JJ, et al. 1994. Intraocular candidiasis in patients with Candidemia. Clinical implications derived from a prospective multicenter study. *Ophthalmology*, 101(7):1302–9.
- Edwards JE, Foos RY, Montgomerie JZ, et al. 1974. Ocular manifestations of *Candida* septicemia: Review of seventy-six cases of haematogenous *Candida* endophthalmitis. *Medicine*, 53:47–75.
- Ellepola AN, Morrison CJ. 2005. Laboratory diagnosis of invasive candidiasis. *J Microbiol*, 43:65–84.
- Feman SS, Nichols JC, Chung SM, et al. 2002. Endophthalmitis in patients with disseminated fungal disease. *Trans Am Ophthalmol Soc*, 100:67–70.
- Leibovitch I, Lai T, Raymond G, et al. 2005. Endogenous endophthalmitis: a 13-year review at a tertiary hospital in South Australia. *Scand J Infect Dis*, 37(3):184–9.
- Menezes AV, Sigismund DA, Demanjo WA, et al. 1994. Mortality of hospitalized patients with *Candida* endophthalmitis. *Arch Intern Med*, 154(18):2093–7.
- Munoz P, Burillo A, Bouza E. 2000. Criteria used when initiating antifungal therapy against *Candida* spp. In the intensive care unit. *Int J Antimicrob Agents*, 15(2):83–90.
- Nightingale JM, Simpson AJ, Towler HM, et al. 1995. Fungal feeding-line infections: beware the eyes and teeth. *J R Soc Med*, 88(5):258–63.
- Piek JJ, Knot EA, Schooneveld MJ, et al. 1998. Candidemia, look at the eyes. *Intens Care Med*, 14(2):173–5.
- Rodriguez-Adrian LJ, King RT, Tamayo-Derat LG, et al. 2003. Retinal lesions as clues to disseminated bacterial and *Candida* infections: frequency, natural history, and aetiology. *Medicine*, 82(3):187–202.
- Sallam A, Lynn W, McCluskey P, et al. 2006. Endogenous *Candida* endophthalmitis. *Expert Rev Anti Infect Ther*, 4(4):675–85.
- Schelens S, Gransden WR. 2003. Candidemia in a London teaching hospital: analysis of 128 cases over a 7-year period. *Mycoses*, 46(9–10):390–6.
- Schiedler V, Scott IU, Flynn HW, et al. 2004. Culture-proven endogenous endophthalmitis: clinical features and visual acuity outcomes. *Am J Ophthalmol*, 137(4):725–31.
- Smiddy WE. 1998. Treatment outcomes of endogenous fungal endophthalmitis. *Curr Opin Ophthalmol*, 9(3):66–70.
- Tanaka M, Kobayashi Y, Takebayashi H, et al. 2001. Analysis of predisposing clinical and laboratory findings for the development of endogenous fungal endophthalmitis. A retrospective 12-year study of 79 eyes of 46 patients. *Retina*, 21(3):203–9.