Chapter 36
Management of Endogenous Endophthalmitis

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Abstract Endogenous endophthalmitis is a potentially blinding ocular infection resulting from hematogenous spread from a remote primary source. Endogenous endophthalmitis accounts for only 2–8% of cases of endophthalmitis and usually occurs in the setting of at least a relatively immunocompromised state. Causes include both gram-positive and gram-negative bacteria and fungi. Streptococcal species are the most commonly implicated bacterial organisms; *Candida* species are the most commonly implicated fungal organisms. Endogenous mold endophthalmitis is rare and typically occurs in the setting of relative immunocompromise or intravenous drug use. Early diagnosis of endogenous endophthalmitis requires a high degree of suspicion and is critical if vision is to be preserved. Therapeutic management includes hospitalization and delivery of broad-spectrum systemic and intravitreal antibiotics. Vitrectomy may be appropriate in some cases. The prognosis of patients with endogenous endophthalmitis is disappointing; even with aggressive treatment, useful vision (i.e., ability to count fingers or better) is preserved in only about 40% of patients.

36.1 Introduction

Endogenous endophthalmitis is a potentially blinding ocular infection resulting from hematogenous spread from a remote primary source. Endogenous endophthalmitis is relatively uncommon compared to exogenous endophthalmitis (endophthalmitis associated with an extrinsic portal of entry), accounting for only 2–8% of cases of endophthalmitis [1]. It usually occurs in the setting of at least a relatively immunocompromised state, such as that seen in patients with diabetes

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mellitus (30.7% of cases of endogenous endophthalmitis), chronic obstructive airway disease (23.1%), end-stage renal disease (15.4%), or cancer (7.7%) [2]. Cancer patients are intrinsically immunocompromised because of the malignancy and are also iatrogenically immunocompromised because of cancer treatment, which can involve intensive chemotherapy, radiation therapy, and bone marrow transplantation with lifelong immunosuppressive therapy. Although each of these factors presumably leads to further immunocompromise and predisposition to endophthalmitis, the literature lacks a comprehensive study examining the cumulative insult delivered by these factors to cancer patients.

Endogenous endophthalmitis is relatively rare but may become more common in clinical practice because of the rapid advance of medical technology, a longer life span of patients with chronic diseases, and a rising prevalence of long-term intravenous access. It is important that oncologists be aware of endogenous endophthalmitis because early diagnosis and prompt aggressive treatment are imperative if significant vision loss is to be avoided. Many organisms (gram-positive bacteria, gram-negative bacteria, and fungi) have been reported to cause endogenous endophthalmitis. Risk factors include most causes of immune suppression [2, 3].

36.2 Epidemiology

Endogenous endophthalmitis can occur at any age and has no gender predilection. The right eye is involved twice as often as the left eye, because of the more proximal and direct blood flow to the right carotid artery. Bilateral involvement occurs in approximately 25% of cases. The population at greatest risk includes immunocompromised patients with leukemia, lymphoma, asplenia, or hypogammaglobulinemia and patients taking immunosuppressive therapy, including corticosteroids. Chronic diseases such as diabetes mellitus, renal insufficiency, and malignancies also increase the risk because of compromised immunity and increased likelihood of undergoing invasive procedures. Persons with AIDS may develop endogenous bacterial retinitis, but surprisingly few cases of endophthalmitis have been reported in AIDS patients. Alcoholics have an increased incidence of endogenous endophthalmitis. Intravenous drug use is specifically associated with *Bacillus cereus* infection and fungal endophthalmitis. Patients undergoing intravenous hyperalimentation are particularly predisposed to fungal endophthalmitis [4, 5]. One study demonstrated a mean interval between the start of intravenous hyperalimentation and the onset of disease of 11 days [5].

36.3 Microbiology

Etiologic agents of endogenous endophthalmitis are restricted to bacterial or fungal, as viruses and parasites infect the retina or uvea, leading to retinitis or uveitis, respectively. Bacterial endophthalmitis is the most common, followed by yeast and mold endophthalmitis [2].

36.4 Clinical Manifestations and Diagnosis

A high degree of suspicion is necessary to make an early diagnosis of endogenous endophthalmitis. Information about the risk factors mentioned above should be elicited, in addition to information about symptoms that suggest the presence of the primary infection.

Patients with endogenous endophthalmitis commonly complain of eye pain, blurring of vision, ocular discharge, and photophobia [6, 7]. Patients who present at a later stage in the disease may have obvious signs such as chemosis, proptosis, and hypopyon [7]. Earlier signs, such as retinal hemorrhages, Roth's spots (round, white retinal spots surrounded by hemorrhage), and retinal periphlebitis, can be seen using fundoscopy [8]. Slit-lamp examination and ocular ultrasonography should be performed to look for vitreous inflammatory cells and retinochoroidal thickening. A thorough systemic examination is required to identify the primary source of infection. Although these clinical markers are important, they occasionally have limited reliability in cancer patients, further emphasizing the need for a high degree of suspicion to make an early diagnosis of endogenous endophthalmitis. In cancer patients with endogenous endophthalmitis, the inflammatory markers and other clinical signs may be less evident given patients' immunosuppression and inability to mount an inflammatory response. Heightened awareness and careful examination are thus critical, particularly in cancer patients who are significantly immunocompromised or extremely ill and sedated, such as posttransplant patients and those in intensive care units.

In addition to initial diagnostic laboratory tests, testing for human immunodeficiency virus infection should be considered in otherwise healthy persons with endogenous endophthalmitis [9, 10]. Routine radiographs are warranted and may reveal a primary pulmonary infection. Echocardiography is also warranted to assess the possibility of endocarditis.

Other tests may be necessary, depending on the clinical presentation. Blood cultures and intraocular cultures obtained from both anterior and posterior chambers of the eye before institution of antimicrobial therapy have the highest yield for isolating the pathogen [11]. The direct inoculation of ocular specimens in blood culture bottles may increase the yield [12]. Cultures of specimens from other sites, including intravenous line catheter tips should be obtained when appropriate. Giemsa, Gomori methenamine silver, and periodic acid-Schiff staining should be done for direct examination of fungi. Polymerase chain reaction may be used for rapid diagnostic results and may aid in early differentiation between bacterial and fungal etiologies [13]. Gram stains of intraocular fluid may not be reliable. Immunologic tests for specific bacterial antigens can be performed in patients who have already received antibiotics; however, the utility of these tests has been challenged [14].

36.5 Treatment

Therapeutic management of endogenous endophthalmitis includes hospitalization and delivery of broad-spectrum systemic and intravitreal antibiotics in consultation

with an infectious disease specialist and based on the proven or presumed infectious agent [15]. Small trials have suggested improved outcomes with intravitreal antibiotic administration and with vitrectomy, which provides the dual benefit of reducing infective load and supplying adequate diagnostic material, although both of these approaches are still controversial [16]. Topical cycloplegics and topical steroids, depending on the degree of anterior segment inflammation, may be used to supplement primary therapeutic options [17].

36.5.1 Bacterial Endophthalmitis

Endogenous bacterial endophthalmitis occurs in the setting of bacteremia secondary to endocarditis (40% of cases of endogenous bacterial endophthalmitis), urinary tract infections, abdominal abscesses, meningitis, indwelling catheters, organ transplantation, malignancy, and chemotherapy [1, 6].

The patient's risk factors may help the physician predict the etiologic agent or narrow the list of potential organisms. The most common bacterial pathogens are gram-positive organisms, especially the streptococcal species, including *Streptococcus pneumoniae*. *Staphylococcus aureus* is found more often in patients with diabetes mellitus, renal failure, cutaneous infections, or intravenous catheters [2]. Infected arteriovenous fistulae have also been reported as a source of staphylococcal infection [1, 18, 19]. In the past 10 years, *B. cereus* has become a common bacterial agent in intravenous drug users. It is an aggressive agent, leading to blindness if antibiotic therapy is not instituted very early [19].

Gram-negative organisms are also sometimes encountered. *Neisseria meningitidis* was the most common pathogen in the preantibiotic era [3]. The number of cases of endophthalmitis related to *Haemophilus influenzae* is expected to decrease with the advent of vaccination, paralleling the documented decrease in meningitis. Cases of endophthalmitis related to *Escherichia coli* and *Klebsiella* species have been associated with diabetes, liver disease, and urinary tract infections [2, 20].

One report on the bacteriology of endogenous bacterial endophthalmitis reported that streptococci caused 32% of cases, *S. aureus* caused 25%, and *E. coli* caused 18% [1]. *Klebsiella pneumoniae* invasive primary liver abscess syndrome can lead to systemic spread of infection in approximately 5–15% of cases [20].

Management of endogenous bacterial endophthalmitis includes broad-spectrum systemic antibiotics and intravitreal antibiotics covering gram-positive and gram-negative organisms. A standard regimen is vancomycin (systemic dose: 1.0 g intravenously every 12 h; intravitreal dose: 1.0 mg in 0.1 mL may repeat at 48–72 h) plus either ceftazidime (systemic dose: 2 g intravenously every 12 h; intravitreal dose: 2.2 mg in 0.1 mL may repeat at 48–72 h) or ciprofloxacin (500–750 mg by mouth twice daily). If the patient has severe or persistent inflammation, a second intravitreal injection (depending on culture results) may be considered at 48–72 hours.

Early intravenous antibiotic therapy remains the cornerstone of treatment. Although systemic antibiotics are not necessary in the treatment of exogenous endophthalmitis, endogenous endophthalmitis is particularly responsive to intravenous antibiotics. Systemic antibiotics also treat distant foci of infection and prevent continued bacteremia, thereby reducing the chances of invasion of the unaffected eye. Empiric broad-spectrum antibiotic therapy with vancomycin and an aminoglycoside (e.g., amikacin) or a third-generation cephalosporin (e.g., ceftazidime) is warranted.

The nature of the clinical presentation, as well as the presumed (or confirmed) source of infection, can be used to guide the decision about which antibiotic to use. Third-generation cephalosporins penetrate ocular tissues and are effective against gram-negative organisms. In cases of documented gastrointestinal or genitourinary infection, second- or third-generation cephalosporins and aminoglycosides are considered the drugs of choice. Vancomycin should be given to patients with a known history of drug abuse, covering the possibility of *Bacillus* infection. In the presence of wounds, oxacillin or a first-generation cephalosporin should be used.

Intravitreal antibiotic injections have revolutionized the treatment of exogenous endophthalmitis, but their utility in treating endogenous endophthalmitis is controversial. Similarly, surgical intervention (i.e., vitrectomy) is widely accepted in postsurgical and posttraumatic endophthalmitis, but its benefits in endogenous endophthalmitis have been debated [15, 21].

The roles of intravitreal antibiotics and vitrectomy are evolving, and these therapeutic modalities will likely become more widely accepted in the future.

Surgical intervention is generally recommended for patients infected with especially virulent organisms, visual acuity of 20/400 or less, or severe vitreous involvement. The outcome of posterior diffuse endophthalmitis or panophthalmitis is frequently blindness, regardless of treatment measures. Vitrectomy and intravitreal antibiotics may, however, prevent ocular atrophy or the need for enucleation. (For further details on the role of vitrectomy in cancer patients, see Chapter 38.)

Inflammatory mediators may also impart some damage. Steroids such as dexamethasone have been administered intravitreally, although their role is not clear. Topical steroids have been used empirically in patients with anterior focal or diffuse disease to prevent complications such as glaucoma and formation of posterior synechiae.

36.5.2 Fungal Endophthalmitis

Fungal endogenous endophthalmitis (Fig. 36.1) secondary to yeast is often treated successfully, whereas endogenous endophthalmitis secondary to mold often results in considerable visual loss. If the patient's history, stains, or culture results suggest a fungal infection, amphotericin B, fluconazole, or itraconazole should be included in the regimen.

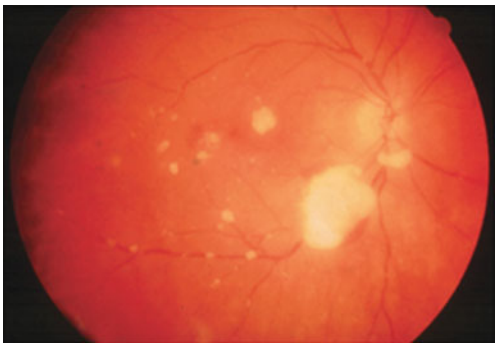

Fig. 36.1 Multifocal fungal chorioretinitis with snowball vitreous involvement

36.5.2.1 Yeast Endophthalmitis

In patients with endogenous endophthalmitis secondary to yeast, *Candida* species are the most common offending agent. Risk factors for candida endophthalmitis include central venous catheters, total parenteral nutrition, neutropenia, prior abdominal surgery, broad-spectrum antibiotic therapy, corticosteroid therapy, and intravenous drug use [22, 23]. Of the *Candida* species, *Candida albicans* is the most frequent offending agent, consistent with its higher virulence and higher incidence of candidemia.

One study examined fungal endophthalmitis in cancer patients specifically and confirmed *C. albicans* as the most frequent offending organism of the *Candida* species. A propensity of *Candida* to affect patients with solid tumors was also suggested, as 50% of those with *Candida* endophthalmitis had solid tumors [24].

Studies have shown that among patients with candidemia, 2.2% develop chorioretinitis and 6.3% develop endophthalmitis [21, 25]. Ocular candidiasis with only chorioretinitis can be managed with systemic antifungals (fluconazole 400–800 mg by mouth daily or amphotericin B 0.7–1 mg/kg daily plus flucytosine 100 mg/kg by mouth daily in four divided doses), since these achieve therapeutic concentrations in the choroid and retina. When overt endophthalmitis is present, management recommendations include the combination of systemic therapy with fluconazole (400–800 mg by mouth daily), vitrectomy, and intravitreal injection of amphotericin (10 μg). In amphotericin-resistant cases, fluconazole can be used intravitreally; however, fluconazole is usually not preferred because of its retinal toxicity. For fluconazole-resistant *Candida* species (*C. krusei* or *C. glabrata*), voriconazole (6 mg/kg intravenously every 12 h for two loading doses, then 4 mg/kg by mouth twice daily) has shown some success.

36.5.2.2 Mold Endophthalmitis

Endogenous mold endophthalmitis is rare and typically occurs in the setting of relative immunocompromise or intravenous drug use. One review of 86 cases of endogenous *Aspergillus* endophthalmitis from 1949 to 2001 identified associations

with intravenous drug use (27% of cases), solid organ transplantation (23%), chronic lung disease (17%), corticosteroid treatment (43%), hematologic malignancy (8%), and other malignancy (1%) [26]. *Aspergillus fumigatus* was the predominant species noted in this study [26].

A study of 23 cancer patients with fungal endophthalmitis confirmed the propensity of mold endophthalmitis in patients with hematologic malignancies—100% of the patients with mold endophthalmitis ($n = 15$) had hematologic malignancies. However, this study revealed *Fusarium* species and *Scedosporium apiospermum* as the most frequent offending organisms, followed by *A. fumigatus* [24].

Studies suggest that endogenous mold endophthalmitis is an often-missed diagnosis. An autopsy study of orthotopic liver transplant recipients revealed that 7% of patients had unrecognized endogenous endophthalmitis [26]. Even patients who are diagnosed have a poor prognosis: studies show that only one-third of patients retain useful vision in an eye affected with endogenous mold endophthalmitis [12].

The treatment of choice for endogenous mold endophthalmitis is oral voriconazole (loading dose of 6 mg/kg intravenously every 12 h for two doses, then 4 mg/kg by mouth twice daily), intravitreal injection of amphotericin (10 μg), and vitrectomy. Studies have indicated that fluconazole is a poor choice for systemic treatment as it has poor activity against molds. Posaconazole has been used for systemic therapy but does not achieve adequate intravitreal levels [14]. Isolated case reports have shown success with caspofungin treatment, but caspofungin is not the mainstay of treatment (Table 36.1) [27].

Table 36.1 Treatment options for endogenous endophthalmitis

Bacterial	Yeast	Mold
Broad-spectrum intravenous antibiotics (vancomycin 1 g IV every 12 h + either ceftazidime 2.2 mg in 0.1 mL IV every 8 h or ciprofloxacin 500–750 mg by mouth twice a day); possibly intravitreal antibiotics and/or vitrectomy	Oral fluconazole (400–800 mg daily), vitrectomy, and intravitreal injection of amphotericin	Oral voriconazole (loading dose of 6 mg/kg IV every 12 h for two doses, then 4 mg/kg by mouth twice daily), intravitreal injection of amphotericin, and vitrectomy

IV, intravenously

36.6 Prognosis

Compared with the outcome of exogenous endophthalmitis, the outcome of endogenous endophthalmitis is disappointing. The three main factors that contribute to a poor prognosis are more virulent organisms, immunocompromised host conditions, and delay in diagnosis. Even with aggressive treatment, useful vision (i.e., ability to count fingers or better) is preserved in only about 40% of patients.

36.7 Summary

Endogenous endophthalmitis is potentially sight-threatening in cancer patients and necessitates emergent diagnosis and management. Etiology includes hematogenous bacterial, yeast, or mold seeding. Recognition of the risk factors is critical to making an early diagnosis. Management includes broad-spectrum intravenous antibiotics and possibly intravitreal antibiotics and vitrectomy.

Although management has improved considerably over the last several decades, limitations persist, and the devastating consequence of visual loss is not always preventable. Thus, our most important management strategy as clinicians should remain vigilance, through close monitoring of immunocompromised cancer patients with systemic infections, which will allow earlier diagnosis and improved prognosis [2].

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