

Endophthalmitis

Subjects: Ophthalmology

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Exogenous fungal endophthalmitis (EXFE) represents a rare complication after penetrating ocular trauma of previously unresolved keratitis or iatrogenic infections, following intraocular surgery such as cataract surgery.

Keywords: endophthalmitis ; fungal endophthalmitis

1. Introduction

The term “endophthalmitis” is referred to one of the most striking eye infections due to infection of the ocular cavity and adjacent structures by fungi and bacteria. Most cases of endophthalmitis are exogenous, in which pathogens from an external source or on the ocular surface, are introduced into the eye. Exogenous endophthalmitis (EE) account for 85% to 98% of all cases of endophthalmitis ^[1]. Despite the burden of fungal aetiology in this field being small, this type of infection is often associated with poor visual outcomes, being influenced by climate conditions and mode of infection ^{[1][2][3][4]}. According to *Rychener* classification ^[5], exogenous fungal endophthalmitis (EXFE) occurs as a result of extension of keratomycosis, eye surgery, or penetrating ocular trauma. Fungal endophthalmitis accounts increased, over the last 20 years, from 8.6% to 18.6% of culture-positive cases. The clinical presentation of *Aspergillus*-EXFE may vary from an indolent, mild external disease to fulminant, necrotizing destruction of the globe ^[1]. Asian studies have reported fungi as the causative organisms in approximately 11.1% to 17.54% of total cases of EE, with the rest being attributed to bacterial causes ^[6]. *Aspergillus* is a saprophyte fungus, and it is present everywhere ^[7]. *Aspergillus* commonly infects the lungs and the paranasal sinuses. Furthermore, it can rarely cause tear duct infections and prolonged local therapy with antibiotics and corticosteroids is a high risk factor ^[8]. Therefore, in early onset endophthalmitis, *Aspergillus* infection should be considered in differential diagnosis with bacterial endophthalmitis, especially in tropical climates ^{[1][2]}. In most cases, the dominant *Aspergillus* subspecies responsible for EFE were *A. fumigatus*, *A. flavus*, *A. niger*, *A. nidulans* and *A. terreus*. Other species detected in ophthalmic disease are *A. glaucus*, *A. ustus*, *A. terreus* and *A. versicolor* ^{[3][4]}. Wykoff et al. (2008) reported the differences between the clinical categories of exogenous fungal endophthalmitis. Culture-positive exogenous fungal endophthalmitis occurred in 41 eyes, including 35 cases (85%) associated with filamentous fungi and 6 cases (15%) regarded *Candida* species. Although *Fusarium* was correlated with most keratitis cases (13 of 18; 72%), while *Aspergillus* was detected in postoperative cases (5 of 13; 38%), 18 cases (44%) associated with fungal keratitis, 10 cases (24%) were correlated with penetrating ocular trauma, and 13 cases (32%) with intraocular surgery ^[9]. A recent study including 91 patients with culture-proven *Aspergillus* endophthalmitis showed that trauma was the most common cause of EXFE and that *A. flavus* (34, 1%) was the predominant infecting species ^[10]. Early diagnosis and aggressive treatment are the key for better visual outcomes, but proven diagnosis is troublesome and therapeutic options are scarce ^{[1][2][3][4][5]}.

2. Endophthalmitis Post-Cataract Surgery

The incidence of post-cataract endophthalmitis is rare, ranging from 0.03% to 0.2% and the majority of them are caused by bacteria ^{[7][8][9][10][11][12][13][14]}. Among fungi, *Aspergillus* spp. is the most common reported after cataract surgery, followed by *Fusarium* spp. with recent reports of isolated outbreaks ^{[11][12][13][14][15][16][17][18]}. During the last years, new approaches in cataract surgery, from intracapsular cataract extraction to laser-assisted surgery, led to less invasive surgical methods (e.g., microincisions, injectable lenses, topical anaesthesia and sutureless surgical wounds), thus reducing the rate of post-operative endophthalmitis ^{[1][2][3][4]}. On the other hand, in place of silicone intraocular lenses, the absence of intracameral antibiotic administration, occurrence of intraoperative complications and old age can increase the risk of ocular infections ^{[3][4][5][6][7][8][9]}. Fungal endophthalmitis after cataract surgery is more prevalent in developing countries such as China and India, where up to 12.7% and 21.8% of the cases, respectively, were attributed to fungi ^{[9][14][18]}. In the US the rate of fungal endophthalmitis after cataract surgery is low, ranging from 0.002% to 0.005% ^{[12][18]}. In a study conducted by Sen et ^[19], 17 patients with culture-proven fungal endophthalmitis after cataract surgery were

evaluated including intravitreal antibiotics and antifungals, pars plana vitrectomy (PPV), intraocular lens explantation (IOL) and scleral fixated IOL implantation (SFIOL). Following the assessment of visual acuity the presence of *A. terreus* and corneal involvement in addition to endophthalmitis have been found to be prognostic markers [19].

3. Endophthalmitis Post-Vitrectomy

Several pieces of evidence in literature support the use of pars plana vitrectomy to manage fungal endophthalmitis. Vitrectomy can increase the likelihood of establishing a proper diagnosis, of improving treatment of infection by removing fungal elements in the vitreous. Moreover, vitrectomy can be a useful aid in the removal of other structures intraocularly inoculated and is an important tool in the management of infectious complications that can lead to detachment of the retina and epiretinal membrane [20]. Mould infections after vitrectomy remain a rare event with high variability between temperate to tropical zones, and high heterogeneity of epidemiological data between hospitals [21]. In a single, tertiary eye care in India [22], of 111,876 pars plana vitrectomy (PPV) performed, 45 cases developed acute onset postoperative endophthalmitis. Among the microorganisms isolated in the 24 culture-positive cases, *Aspergillus* was the only fungus isolated (5/24; 20.8%). Conversely, the article compared the incidence rates of endophthalmitis in both 20 G PPV and mini-invasive approach PPV, demonstrating a higher incidence of endophthalmitis in 20 G PPV (0.057% vs. 0.012%) [22]. The same study suggests a protective role of intraocular tamponade [21]. Dave et al. [23] collected data from four tertiary eye cares in India, with 38,591 patients undergoing PPV between 1990 and 2014: the clinical incidence of post-vitrectomy endophthalmitis was 0.052%, and culture-positive incidence was 0.031% with no *Aspergillus* spp. cases [23]. Similarly, in a 20-year study (1984–2003) in US [24] the incidence of endophthalmitis after PPV was about 0.039% and no *Aspergillus* spp. infections occurred.

4. Endophthalmitis Post-Intravitreal Injection

The incidence of endophthalmitis as a consequence of intravitreal injection has been recognized to be in the range from 0.016% to 0.053%, according to several published studies [25]. The rates are higher after intravitreal corticosteroids than after intravitreal anti-VEGF agents [26]. While prophylaxis with topical antibiotics has been shown to increase, rather than reduce, the risk of post-injection endophthalmitis [27], preoperative disinfection with topical 5% povidone iodine represents the most commonly used and safest method against endophthalmitis [28][29]. Incidence of endophthalmitis does not seem to be affected by the type of intravitreal anti-VEGF drugs [25][26]. No case of *Aspergillus* spp. after anti-VEGF or corticosteroids intravitreal administration was reported at the time of writing; nevertheless, the rate of culture-negative suspected infections remains high.

5. Endophthalmitis Post-Keratoplasty

Fungal infection following both lamellar and penetrating keratoplasty are most commonly caused by *Candida* spp. and only rarely by *Aspergillus* spp. [30][31]. As a matter of fact, a recent retrospective cohort study including 3069 patients who underwent penetrating and lamellar keratoplasty reported only 3 cases of EXFE, none of which caused by *Aspergillus* spp. [30]. A study conducted by Alharbi et al. [32] to identify the causative organisms of post-keratoplastic endophthalmitis evidenced that the review of charts of all patients with endophthalmitis diagnosis after keratoplasty in a tertiary hospital between January 1990 and January 2007, endophthalmitis developed in 55 cases in the penetrating keratoplasty group and the majority of isolated microbes were Gram positive bacteria (86.3%) [32]. Microbiology, as above mentioned, tends to vary worldwide [30][31]. Of 124 cases of fungal endophthalmitis post-keratoplasty reported in Saudi Arabia, the most common isolated organisms were *Aspergillus* spp. (29.8%) [31]. Isolated clinical cases on infection supported by *A. flavus* and *A. niger* were also reported in Italy and in Asian and Middle East countries [33][34].

6. Epidemiology of Endophthalmitis after Keratomycosis

Fungal keratitis is a widely distributed infection of the cornea caused by a broad-spectrum of filamentous fungi and yeasts with annually increasing incidence. Incidence of endophthalmitis after keratomycosis was estimated to range from 0.5% to 6.3%, with an evisceration rate of 31% to 62.2% [35][36]. The main causative microorganisms, among moulds, were *Fusarium* and *Aspergillus* [2][3][4]. Shen et al. analyzed 10 cases of post keratitis endophthalmitis and isolated *Aspergillus* spp. in two out of ten cases [37]. Similarly, Wykoff et al., evaluated the microbiological pattern of 41 eyes affected by culture-positive fungal endophthalmitis [1]. Eighteen out of 41 EXFE were complications of a fungal keratitis [1]. Among them, only 6% were caused by *Aspergillus* spp. [9].

7. Epidemiology of Post-traumatic Endophthalmitis

Post-traumatic endophthalmitis is a rare but devastating complication that includes risk factors such as the presence of an intraocular foreign body (IOFB), rupture of the lens, delayed repair of the primary globe, trauma with contaminated objects. The visual prognosis in post-traumatic endophthalmitis depends on the virulence of the microbe, the presence of detachment of the retina, the time of treatment, the presence or absence of an IOFB and the extent of the initial injury [38]. Post-traumatic endophthalmitis represents 25% to 30% of all endophthalmitis cases and its incidence was reported 10 times higher than post-surgical endophthalmitis [36][37][38][39]. Due to the lack of recent reports, we cannot estimate the prevalence of *Aspergillus* spp. etiology secondary to trauma. However, several authors reported that the incidence of fungal agents in post-traumatic endophthalmitis range from 0% to 15.4% [9][38][39]. Eye injuries with complications that degenerate into endophthalmitis are frequent in the workplace or in more rural areas where the main safety devices to protect the eyes are not properly used or not used at all [6][36][37][38][39]. In general, the risk of endophthalmitis is much greater with injuries produced by non-metallic foreign bodies, generally with contamination of microorganisms found in the soil, and especially when accompanied by crystalline lens lesions [38]. In addition, an increased risk of endophthalmitis has been reported following injuries from dental procedures, scratches from domestic and/or wild animals and from some food products [38][40]. In practice, mainly bacteria but also fungi are the major microorganisms responsible for the occurrence of post-traumatic endophthalmitis [2][3][4]. Therapeutic treatment and fundamentally prognosis are greatly influenced by the type of pathogenic microorganism involved, the nature of the lesion, the presence of IOFB and the geographic region in which ocular trauma occurs [3][34]. It should be considered that the presence of a positive intraocular culture does not always lead to the development of endophthalmitis, in fact, in at least one third of the eyes subject to trauma and in the absence of endophthalmitis, bacterial growth has been demonstrated in intraocular fluids [38][39][40]. Therefore, it is crucial that all cases of samples positive to culture techniques must be suitably supported by clinical results [3][34]. While considering that the frequency of post-traumatic fungal endophthalmitis is much lower than that of bacterial origin, in the case of endophthalmitis due to injuries caused by accidents with trees and other vegetation, particular attention must be paid to exclude the involvement of fungal agents [3][34].

8. Clinical Features

EXFE clinical presentation is very variable, ranging from the classic endophthalmitis triad of decreased vision, red eye and ocular pain, to an insidious presentation with aspecific ocular findings and progressive vision loss [3][41][42]. Unlike bacterial endophthalmitis which usually has a hyperacute presentation, EXFE often presents with a latency period of weeks-months [3][34]. The intraocular inflammation in fungal endophthalmitis shows up in “clumps” within the aqueous and/or vitreous area, whereas intraocular inflammation is typically diffuse in bacterial endophthalmitis [2][3][41][42]. An intraocular infection has devastating consequences, leading to reduced vision and possibly irreversible blindness. Similarly, symptoms can be very different: vision loss can be mild for cases with peripheral vitreous lesions (snowballs and snowbanks) or severe for cases with great vitreous and/or anterior chamber inflammation [2][3][34]. Perikeratic reaction is a possible ocular finding as well as keratic precipitates, hypopyon and fibrinous anterior chamber (AC) exudation [3]. Scleritis has been reported as a presentation finding of EXFE following PPV [21][22][23].

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