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Endophthalmitis and COVID-19: A Narrative Literature Review

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ABSTRACT

Endophthalmitis is a severe form of intraocular inflammation which is caused by bacteria or fungi. It is a medical emergency with an imminent threat to vision and permanent structural and functional complications. The condition affects the anterior and posterior segments of the eye. It may be either exogenous – following penetrating trauma or intraocular surgery, or endogenous, in which the pathogens enter the eye hematogenous. The diagnosis is based on the clinical picture and on specialized testing – aqueous and/or vitreous cultures, with or without additional PCR for panbacterial and panfungal primers. If endogenous endophthalmitis is suspected, blood and urine cultures may also be performed. The most common bacterial pathogens in acute postoperative endophthalmitis belong to the Staphylococcus and Streptococcus groups. Endogenous endophthalmitis is most frequently fungal and caused by *Candida*. The incidence of post-traumatic endophthalmitis ranges from 0.9 to 17% and of postoperative - from 0.016 to 5.7%, depending on the surgical procedure and the geographic location. Endogenous endophthalmitis has been observed in up to 8% of all cases. Therapy is urgent and may include intravitreal medications or pars plana vitrectomy (PPV), according to the Endophthalmitis Vitrectomy Study criteria. The combination of COVID-19-associated severe pneumonia, systemic corticosteroid therapy, and diabetes appear to be risk factors for endogenous endophthalmitis. The ethology has mostly been linked to fungal infections, especially *Candida*, as in the pre-COVID-19 era. There has been a tendency to perform PPV with intravitreal medications as the primary procedure, but the results have been mixed.

1. Introduction

Endophthalmitis is a severe form of intraocular inflammation which is caused by bacteria or fungi.^{1,2} It is a medical emergency with an imminent threat to vision and permanent structural and functional complications¹. The condition affects the anterior and posterior segments of the eye with prominent vitritis and inflammatory infiltration of the retina and choroid.¹ It may be either exogenous, following penetrating trauma or intraocular surgery, or, much more rarely, endogenous, in which the pathogens enter the eye hematogenous.^{3,4} The diagnosis is based on the clinical picture and on additional specialized testing – aqueous and/or vitreous cultures, with or

without additional PCR for panbacterial and panfungal primers. If endogenous endophthalmitis is suspected, blood and urine cultures may also be performed¹.

The most common bacterial pathogens in acute postoperative endophthalmitis belong to the Staphylococcus and Streptococcus groups.^{1,5} In post-traumatic cases, *Bacillus cereus* also plays a significant role.^{1,6} The mycotic infections have been predominantly associated with *Aspergillus* and *Candida* species.¹ Endogenous endophthalmitis is most frequently mycotic and caused by *Candida*, and more rarely due to Staphylococci, *Klebsiella*, or *Pseudomonas*^{1,7}, as shown in Figure 1.



Figure 1. Fundus photograph of the right eye in a patient with endogenous endophthalmitis secondary to *Candida albicans*; vitritis, papillitis, multifocal yellowish areas of retinochoroiditis, vasculitis, and diabetic retinopathy (courtesy of Gueorgui Markov).

The incidence of post-traumatic endophthalmitis has been described as ranging from 0.9 to 17%¹, and of postoperative - from 0.016 to 5.7%, depending on the surgical procedure and the geographic location.¹ Endogenous endophthalmitis has been observed in up to 8% of all cases.^{8,9} Therapy is urgent and may include intravitreal antibiotics or antifungals or pars plana vitrectomy (PPV) combined with intravitreal medications, according to the Endophthalmitis Vitrectomy Study (EVS) criteria.¹⁰ The role of systemic antibiotics and of systemic and intraocular corticosteroids (CS) in the management of endophthalmitis is controversial and requires further investigation.^{11,12}

The COVID-19 pandemic presents several new problems concerning endophthalmitis. First of all, the management of such cases in hospital settings requires extensive anti-infectious measures for the protection of medical personnel and other hospitalized patients.¹³ Furthermore, the immune dysregulation secondary to COVID-19 predisposes to serious secondary infections, which may theoretically increase the risk of endogenous endophthalmitis.¹⁴ The risk is additionally increased by the necessity of prolonged therapy with CS, antibiotics, and immunomodulators. In keeping with the definition, the panuveitis caused

by the SARS-CoV-2 virus shouldn't be classified as endophthalmitis.

Endophthalmitis and COVID-19

As mentioned above, in the setting of COVID-19 disease, the risk of secondary bacterial and fungal infections is increased. This would theoretically lead to a heightened probability of the development of endogenous endophthalmitis. Das et al.,¹⁴ indeed reported an increased frequency of endogenous cases in their institution, along with a decreased rate of post-traumatic. Additional risk factors for the development of endophthalmitis could be advanced age, concomitant health problems, such as diabetes mellitus, congenital immunodeficiencies, sepsis, tuberculosis, HIV, hepatitis, urinary infections, skin infections, keratitis, indwelling catheters, intravenous drug abuse, and the prolonged use of antibiotics, CS and immunomodulators.^{1,2,4,7-9}

The rate of postoperative endophthalmitis during the COVID-19 pandemic does not appear to have increased with regard to the frequency after intravitreal injections in most studies.^{13,15,16} Only Blom et al.¹⁷ reported a slightly higher frequency, which, according to their study, was associated with patient mask use. The risk has not been increased in cataract surgery as well, even in cases with

simultaneous bilateral surgery.^{18,19} On the contrary, regarding PPV, Sakamoto et al. observed a higher rate of endophthalmitis relative to face mask wearing during the pandemic.²⁰ Some of their cases were associated with oral commensals, an unusual cause of post vitrectomy endophthalmitis.²⁰

Endogenous cases, on the other hand, have been on the rise¹⁴, especially those caused by fungal pathogens. Schroff et al.,²¹ reported on 5 eyes with endophthalmitis in 7 patients with severe COVID-19 pneumonia and long-term CS therapy (80-180 days). *Candida* was isolated in 4 cases and *Aspergillus* in one case.²¹ All patients reportedly did well following PPV with intravitreal antifungals.²¹ Khatwani et al.²² had 7 patients who were COVID-19 positive and had been treated with systemic CS, oxygen therapy, anticoagulants, and antivirals. Three of their cases were mucormycosis-related, and one was polymicrobial.²² All patients had undergone PPV with intravitreal antifungals.²² Agarwal et al.,²³ treated 6 diabetic patients, 5 of whom had received intravenous CS therapy. Endophthalmitis had developed on average 40 days after the COVID-19 infection, and it was associated with a fungal infection in two (*Candida* and *Balaria*), and with *Staphylococci* in another 2 of them, with 2 being culture negative.²³ Abdelkader et al.²⁴ reported on 9 patients with simultaneous orbital cellulitis and endophthalmitis. Vitreous cultures had been negative, and the visual outcome was poor in those who survived.²⁴ Bilgic et al.,²⁵ described 3 patients with pneumonia, treated with CS, remdesivir and tocilizumab (in 2). Vitreous cultures were positive for *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Stenotrophomonas maltofila*.²⁵ All the patients had improved following PPV with intravitreal antibiotics²⁵. In a study by Bayram et al.²⁶, 54.5% of their patients had mucormycosis-associated endophthalmitis, 63.6%-associated with orbital apex syndrome, and 36.4%-orbital cellulitis. All patients had COVID-19-related acute respiratory distress syndrome and had received CS therapy.²⁶ Most were diabetic with poor control.²⁶ Therapy included intravenous, intravitreal, and retrobulbar Amphotericin B, along with

debridement of affected sinuses.²⁶ Nayak et al.,²⁷ reported on 33 patients with endogenous endophthalmitis with varying severity of COVID-19 infection. They could perform vitreous cultures on 19 patients, which were positive in 14 patients. 11 patients had fungal infections, mostly with *Candida*, in 2 cases with *Aspergillus*, and in 1 – with *Mucor*.²⁷ Bacteria were isolated in 3 cases – *Streptococcus pneumoniae* in 2 and *Escherichia coli* in 1 patient.²⁷ Therapy included PPV with intraocular medications, and improvement was noted in 40.9% of eyes. Sahu et al.,²⁸ found *Aspergillus* from vitreous samples in 4 out of 5 patients with endophthalmitis following severe COVID-19 infection with CS treatment. They performed PPV with silicone oil tamponade in 4 patients with anatomical but no functional improvement.²⁸ Deepa et al.,²⁹ described a case of *Cryptococcus laurentii* endophthalmitis following COVID-19 pneumonia treated with CS and remdesivir, and they had improvement after PPV and intravitreal voriconazole.⁴

The experience with post-traumatic endophthalmitis has been more controversial – some authors, like Das et al.¹⁴, report decreasing rates, while others – Parchand et al.,³⁰ have observed an increase in the number of cases secondary to the higher frequency of domestic violence-related ocular trauma and late presentation.

2. Conclusion

In conclusion, the combination of COVID-19-associated severe pneumonia, systemic corticosteroid therapy, and diabetes appear to be risk factors for endogenous endophthalmitis. The etiology has mostly been related to fungal infections, especially *Candida*, as in the pre-COVID-19 era. Other notable pathogens have been *Aspergillus* and *Mucor*, in particular in diabetics. *Mucor* infections have been associated with concomitant orbital and sinus involvement and a much poorer prognosis for life and sight. Bacterial pathogens have been cultured more infrequently. The prolonged use of systemic antibiotics should also theoretically have a role. The rates of postoperative endophthalmitis generally seem not to have increased.

Concerning post-traumatic cases, some authors report a decrease, whereas others – a higher rate due to domestic violence-related traumas and late presentation. With regard to therapy, there has been a tendency to perform PPV with intravitreal medications as the primary procedure, but the results have been mixed.

3. References

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