

Endogenous fungal endophthalmitis in COVID-19 patients: An unexplored possibility

There has been an increase in literature on endogenous endophthalmitis (EE) in COVID-19 patients. By using the terms “endogenous endophthalmitis” and “COVID-19,” 10 articles could be found in PubMed that reported 54 patients of EE from India. More than 80% of these patients were due to fungal etiology or responded to empirical antifungal treatment when treated as presumed fungal EE [Table 1]. Almost all these patients had been hospitalized for severe COVID-19 disease. One of the six patients with EE in a case series by Agrawal M. *et al.*^[1] had no history of hospitalization and culture from vitreous aspirate of that patient-isolated *Staphylococcus aureus*. In another large case series of 24 patients with EE, 90% of the patients had various systemic comorbidities; all patients had a history of hospitalization, with 66.6% requiring intensive care unit support.^[2] Fourteen of 19 vitreous biopsies (73.6%) were microbiologically positive, and a fungal etiology was established in 78.6% of them (11 out of 14).^[2] While trying to identify the systemic focus of infection, the authors could detect candidemia only in five patients. *Aspergillus spp.* isolated from renal biopsy and paranasal sinus biopsy of two patients, and one patient had mucormycosis.^[2] The spread of fungal infection from other organs has been identified in other case series, but in a significant number of cases, the source of infection remains unidentified.^[3-6] Various hypotheses have been put forward to this sudden uptick of EE cases in COVID-19 patients and also to answer this gap in identifying the source of infection. Many of these patients had diabetes and required a high dose of systemic corticosteroid and/or further immunomodulation to combat “cytokine storm.” Thus, a state of immunosuppression

and the presence of systemic comorbidity were the prime suspects in these patients with EE. A decrease in the peripheral distribution of CD4+ T and CD8+ T cells has been reported in COVID-19 patients.^[7]

Fungal EE has been considered more common in the Western hemisphere compared to the Eastern hemisphere.^[12,13] Several large case series from the western world countries reported high rates of pulmonary and systemic fungal infections among COVID-19 patients,^[14] but surprisingly, there is a relative paucity of literature on fungal EE in a similar cohort of patients. All cases of EE in COVID-19 patients reported from the western world are of bacterial etiology.^[15,16] Bilgic A *et al.*^[15] reported three patients of EE and vitreous biopsy isolated *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus*. In another report, a 35-year-old with diabetes and cirrhosis developed a prostatic abscess, and urine culture grew *Klebsiella pneumoniae*. He was found to be COVID-19 positive, and during treatment, the patient developed endogenous *Klebsiella* endophthalmitis. In a recently presented paper, the rate of bacterial or fungal coinfection and associated EE among inpatients with COVID-19-associated pneumonia at seven general hospitals in Louisville, Kentucky, from March to May 2020 were assessed.^[17] Among 632 patients in this study, 10.3% had a systemic, culture-positive bacterial or fungal coinfection (60 bacterial, 5 fungal). Only one patient with Streptococcal bacteremia developed EE in one eye (0.16% of total COVID-19 inpatients). It is important to emphasize here that the history of hospitalization remained an important risk factor for fungal EE in the literature from the western world.^[18,19] In a study of fungal EE from Bascom Palmer Eye Institute published in 2012, 69% of the patients had a history of hospitalization.^[19] Thus, the exact epidemiology of fungal EE in COVID-19 patients from these countries remains confusing.

Table 1: Literature of review of patients with endogenous endophthalmitis (EE) following COVID-19 from India

Authors	Number of Patients	Etiologies
Nakhwa C ^[8]	One patient	<i>Candida Tropicalis</i>
Nayak S <i>et al.</i> ^[2]	33 eyes of 24 patients	Microbiologically positive samples: 73.68% (19), fungus 78.6% (11)*, bacterial 2, virus 1
Sahu ES <i>et al.</i> ^[9]	Five patients	<i>Aspergillus niger</i> 2, <i>Aspergillus fumigatus</i> 2, Presumed fungal etiology 1
Mehta S <i>et al.</i> ^[4]	One patient	<i>Rhizopus microsporus</i> (Lung)
Khatwani PR <i>et al.</i> ^{[3]**}	Nine eyes of 7 patients	Mucormycosis-associated sinusitis and orbital cellulitis 3 Aspergillosis (Lung) Systemic fungal infection 2
Agarwal M <i>et al.</i> ^[1]	Eight eyes of 6 patients	Fungus 2 : <i>Candida sp</i> 1 , <i>Bipolar sp</i> 1 <i>Staph. aureus</i> 2 Microbiologically negative: 2
Shroff D <i>et al.</i> ^[10]	Seven eyes of 5 patients	<i>Candida sp.</i> 4 <i>Aspergillus sp.</i> 1 Presumed 2
Shah KK <i>et al.</i> ^[11]	Four patients	Presumed fungal etiology :4†
Goyal M <i>et al.</i> ^[5]	Two patients	Presumed: 1 <i>Candida tropicalis</i> : 1 (blood and urine)
Kamath SD <i>et al.</i> ^[6]	One patient	Pleural fluid: <i>Pseudomonas aeruginosa</i> , Blood: <i>Staphylococcus aureus</i>

* systemic antifungal was used in 19 patients, **vitreous biopsy was not done; † vitreous biopsy was negative, but EE responded to antifungal

Diagnosis of fungal EE requires a high index of suspicion. Irrespective of immune status, the ophthalmologist should investigate and explore the possibilities of dissemination of fungus in the bloodstream of patients with fungal EE. The contaminated intravenous fluid remains an important source of fungal EE in India. Several reports of fungal EE secondary to presumably contaminated intravenous fluid from India were reported in the pre-COVID-19 era.^[20-23] In a case series from North India, 12 patients developed fungal EE after each of them received a single intravenous dextrose infusion for some minor ailments.^[20] Microbiological investigation of the vitreous aspirates of these patients isolated five cases of *Aspergillus fumigatus*, four cases of *Aspergillus niger*, two cases of *Candida albicans*, and one case of *Mucor*. To prove their hypothesis, the authors subjected the sealed bottles of dextrose to microbiological analysis, and 11 of these 72 bottles were found to be culture-positive for fungi.^[20] In another report, the authors described a case of bilateral simultaneous onset of fungal EE in a 26-year-old woman who was treated with multiple intravenous dextrose infusions because of fever. The vitreous aspirate from her left eye grew *Aspergillus fumigatus*. These cases were not from a particular center and reflect the magnitude of a serious public health hazard in developing countries. In two other separate case reports, the authors reported fungal EE with posterior hypopyon in patients who had received presumably contaminated dextrose infusions for febrile illness^[21,23] Interestingly, none of these patients had developed fungal infections in other organs following the infusion of contaminated intravenous infusions.^[20-23] Thus, it is important to realize that contaminated intravenous fluid can be a major source of infection in patients with fungal EE in addition to other risk factors attributed in COVID-19 patients.

Parthoprati Dutta Majumder

Senior Consultant, Medical and Vision Research Foundations,
Sankara Nethralaya, Chennai, Tamil Nadu, India.
E-mail: drparthoprati@gmail.com

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About the author



Dr. Parthoprati Dutta Majumder

Dr. Parthoprati Dutta Majumder is working as a senior consultant in the Department of Uvea, Sankara Nethralaya, Chennai, India. He has attended and presented papers in various national and international conferences. His areas of interest include scleritis, pediatric uveitis, medical management of uveitis and scleritis, and phacoemulsification in uveitic cataract. He has published many articles in various peer and non-peer reviewed journals. He has authored several chapters in various ophthalmology books and has edited four books – *Recent Advances on Uveitis, Retinal and Choroidal Imaging in Systemic Diseases, Modern System of Ophthalmology (Uvea)* and *Essentials in Ophthalmology for the Post-graduates*. He has authored two scientific monographs on *Polymerase Chain Reaction in Ophthalmology* and *Scleral Inflammations*, published by the All India Ophthalmology Society. He is the founder and chief editor of the popular ophthalmology portal www.eophtha.com