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Sudden vision loss heralding COVID-19-associated aspergillosis. Report of 2 cases

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ABSTRACT

Purpose: To describe clinical, radiographic, laboratory and cytopathologic findings in 2 patients who developed vision loss due to endogenous aspergillus endophthalmitis during hospitalization for COVID-19 pneumonia.
Observations: Two unvaccinated sexagenarian male smokers lost vision within one month of contracting COVID-19 pneumonia. Initially, both received high dose steroids, nasal cannula oxygen and remdesivir. Immunomodulators tocilizumab or baricitinib were added during week 2 in case 1 and 2 respectively. Upon presentation after discharge from a post-COVID rehabilitation unit, visual acuities were light perception and hand motion. In both cases, inpatient blood and ocular fluid cultures were negative, serum 1,3-beta-D-glucan was positive, and vitreous cytopathology revealed filamentous fungi and PCR was positive for *Aspergillus fumigatus*. Large solitary intravitreal fungus balls were debulked in patient 1 and excised in patient 2. Final visual acuities were no light perception and 20/200 respectively. MRI revealed previously unsuspected brain and lung lesions consistent with disseminated aspergillosis in patient 2.
Conclusions: Vision loss due to fungal endophthalmitis may be the first or only sign of systemic aspergillosis associated with COVID-19 pneumonia. Aspergillosis should be suspected in patients who develop vision loss. Diagnosis limited by negative fungal cultures may be confirmed by vitreous cytopathology and PCR. Systemic imaging for disseminated aspergillosis is indicated. Ultimate visual acuity may depend upon surgical approach.

1. Introduction

Aspergillus, particularly *A. fumigatus*, is a recognized coinfection of COVID-19 pneumonia. SARS-CoV-2 damages respiratory epithelium, facilitating aspergillus invasion. COVID-associated pulmonary aspergillosis (CAPA) occurs in 10–33% of critically ill patients.[1] We report two patients without diagnosed CAPA in whom vision loss was the first indication of disseminated aspergillosis. The study was approved by the Geisinger Institutional Review Board (IRB) and granted exemption from full IRB review (reference number 2021-0879). It adhered to the Declaration of Helsinki. Since neither patient could be reached to provide written informed consent, the work was reviewed for HIPAA compliance and de-identification, and approved by the Geisinger Health System Security Officer for publication of this case report and accompanying images.

2. Case reports

2.1. Case 1

2.1.1. Inpatient course

A 60 year old unvaccinated Asian man with a history of smoking and gout developed dyspnea 5 days after testing positive for COVID-19. His PO_2 was 80. Admission chest X-ray demonstrated emphysematous changes with ground-glass opacities and bibasilar consolidation consistent with COVID pneumonia. At no time were pulmonary nodules reported.

Initial treatment included dexamethasone 4 mg IV daily, remdesivir 100 mg IV daily for 5 days and high flow nasal oxygen. Tocilizumab 560 mg was given on day 2. One week later he noticed painless vision loss in the right eye (OD). Visual acuity (VA) was 20/400. Moderate vitritis, 10% hypopyon and “inferotemporal retinal exudate” were observed (Fig. 1a).

Toxoplasma antibodies and serial blood cultures were negative.

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Serum 1,3-beta-D glucan was positive. Broad antibiotic coverage with oral azithromycin 500 mg daily, fluconazole 200 mg BID, valacyclovir 1 gm daily plus intravenous ceftriaxone 1 gm daily and voriconazole 4 mg/kg q12 were initiated for presumed endogenous endophthalmitis. Three weeks later, VA was 20/70 and vitritis cleared revealing a presumed fungal mass (Fig. 1b). Topical prednisolone was reduced and intravenous antibiotics were discontinued. One week later, the patient was discharged.

2.1.2. Outpatient course

Two weeks after discharge VA was light perception. There was no improvement following two successive weekly intravitreal voriconazole injections. The patient was referred for consultation.

On presentation, conjunctival injection was conspicuously mild with no chemosis. Hypopyon and dense vitritis obscured the posterior segment. B-scan revealed an intravitreal mass (Fig. 1c).

Pars plana vitrectomy with amphotericin 5 μg/0.1ml injection was performed. Over 70% of the fungal mass was debulked. Vitreous culture was negative. Cell block preparation demonstrated numerous filamentous fungal hyphae with acute angle branching, which was highlighted with Grocott methenamine silver (GMS) stain, in a background of neutrophils and necrosis (Fig. 1g and h).

In spite of three weekly intravitreal injections with voriconazole and amphotericin plus oral fluconazole, the mass enlarged and a tractional retinal detachment developed. VA was light perception. Aqueous PCR was negative. Vitreous aspirate PCR was lost during transport, however PCR of the vitreous cell block demonstrated *Aspergillus fumigatus* confirming the diagnosis of Aspergillus fungal endophthalmitis. The patient declined additional surgery.

Four months later, VA was no light perception. The patient no longer required supplemental oxygen. Systemic surveillance with CT of chest, abdomen and pelvis 5 months after discharge showed mild atelectasis. There was no additional evidence of disseminated aspergillosis on comprehensive infectious evaluation including brain MRI.

2.2. Case 2

2.2.1. First inpatient course

A 69 year old unvaccinated Caucasian man with a 50-year smoking history and moderate emphysema developed COVID-19 pneumonia. Admission X-ray demonstrated right perihilar and bibasilar pneumonia with hyperinflation consistent with emphysema. Initial treatment included dexamethasone 4 mg IV daily, remdesivir 100 mg IV daily for 5 days, and high flow nasal cannula oxygen. On day 6, "tree-in-bud" nodularity was recorded on repeat X-ray and baricitinib 4 mg po daily for one week was added. Ocular symptoms including redness, photophobia, discomfort and vision loss OD developed 2 weeks later and worsened in spite of topical ocular antibiotic drops and ointment. He was discharged two weeks later and presented to ophthalmology the next day.

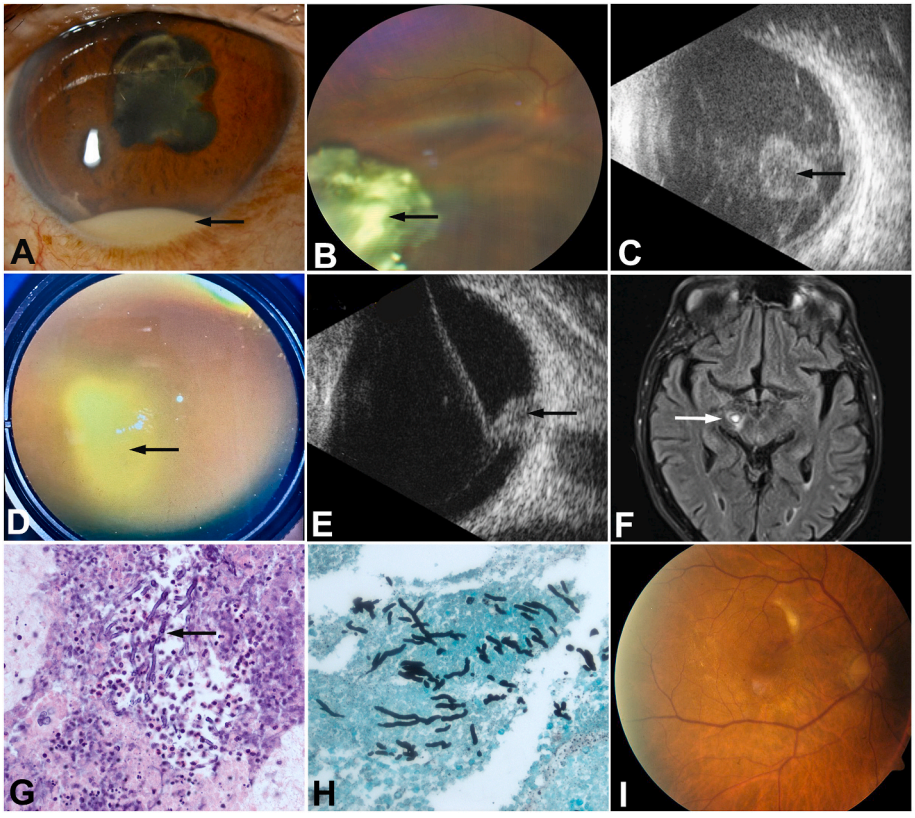

Fig. 1. Clinical and cytopathologic findings of two patients with COVID-19-associated endogenous *Aspergillus fumigatus* endophthalmitis.
A. Hypopyon (arrow) with disproportionately mild conjunctival injection (patient 1).
B. Vitritis improved and intravitreal mass (arrow) was visible after treatment with systemic voriconazole during initial hospitalization (patient 1).
C. B-scan ultrasound of patient 1 upon presentation demonstrates dense vitritis and large solitary spherical intravitreal mass (arrow).
D. Vitritis with posterior vitreous mass (arrow) at presentation in patient 2.
E. B-scan ultrasound of patient 2 demonstrates solitary spherical mass over optic disc (arrow) with associated traction detachment.
F. One of several rim enhancing lesions (arrow) on brain MRI of patient 2.
G. Cell block preparation of vitreous fluid demonstrates filamentous fungal hyphae (arrow) in a background of neutrophils and necrosis (hematoxylin-eosin; ×400).
H. Grocott methenamine silver (GMS) stain highlights fungal forms (GMS; ×400).
I. Post-operative appearance patient 2 with residual preretinal fibrous material. No change was observed during follow-up.

2.2.2. Outpatient course

On presentation, VA was hand motion. External exam was remarkable for 2+ conjunctival injection without chemosis. There were Descemet's folds, 3+flare with suspended cells, and multiple posterior synechiae. Vitreous was hazy. A large posterior white mass prevented visualization of the optic disc (Fig. 1d). The left eye was unremarkable. B-scan ultrasound revealed a posterior spherical mass consistent with a fungus ball (Fig. 1e). Diagnostic paracentesis was performed.

2.2.3. Second inpatient course

The patient was admitted for intravenous voriconazole treatment of presumed endogenous fungal endophthalmitis. Admission X-rays revealed bibasilar consolidation, multifocal ground glass opacities on a background of moderate emphysema. Rim enhancing lesions were evident on brain MRI (Fig. 1f). Cultures of blood and aqueous fluid and serum aspergillus antibody EIA were negative. Serum 1,3-beta-D-glucan was positive. Aqueous PCR revealed *Saccharomyces cerevisiae*, a contaminant specific to the eSwab which masked identification of other fungal species.

Pars plana vitrectomy was performed and the entire fungus ball was resected. As it was debulked, retinal traction relaxed. There was no hemorrhage as the capsule was peeled from the retinal surface. Intravitreal amphotericin 5 μg/0.1ml was injected. Cytopathologic examination of the cell block preparation with GMS stain demonstrated fungal elements with septate morphology. Vitreous cultures were negative; vitreous PCR revealed *Aspergillus fumigatus* and confirmed the diagnosis of disseminated Aspergillosis.

The patient was discharged 10 days later. Follow-up CT-scan one month later revealed improvement in lung lesions. The patient required no supplemental oxygen and continued oral voriconazole 200 bid. VA was 20/200. The retina was attached with no recurrent infection. OCT thinning was apparent in the area of previous fungal invasion. MRI of the brain 2 months after discharge demonstrated complete resolution of CNS lesions. Voriconazole was discontinued.

3. Discussion

Fungal endophthalmitis has been reported around the globe in patients who have been hospitalized for COVID 19.[2,3] Our cases illustrate that vision loss in patients with active or recent COVID-19 pneumonia may indicate endogenous endophthalmitis and herald disseminated aspergillosis. A high index of suspicion may reduce both systemic and visual morbidity.

Risk factors for pulmonary aspergillosis include immune suppression with targeted immunomodulators[1] including tocilizumab[4–6] and baricitinib,[6,7] and prolonged high dose steroids[6,8] and COVID-associated decreased T-cell population[9] which may cause transient neutropenia. Transient fungemia, even in the absence of CAPA, may have promoted invasive fungal infection (IFI) by ocular and systemic seeding.

Positive blood cultures are rare for patients with IFI. In our cases, aqueous PCRs were negative, possibly due to previous antifungal therapy (case 1) and a collection medium contaminant (case 2). Positive serum 1,3-beta-D glucan supported clinical diagnosis which was confirmed by cytopathologic examination and PCR of pars plana vitrectomy specimens. Serum fungal antigens, including1,3-beta-D glucan may aid in detection of IFI caused by Candida or Aspergillus spp. Although positive and negative predictive values may vary, 1,3-beta-D glucan is recognized as an important diagnostic in immunosuppressed, neutropenic patients.[10]

There is no standard treatment of endogenous aspergillus endophthalmitis. Resistant strains, macular abscess and late recurrence contribute to poor visual outcomes.[11] Better outcomes have been reported with early pars plana vitrectomy versus vitreous tap.[12] Both cases presented with a spherical vitreal mass unlike macular abscesses previously reported.[11] Fungal ball excision was superior to debulking as residual fungal mass quickly enlarged in spite of intravitreal and oral antimicrobials. Similarly, survival is improved with resection of pulmonary abscess.[13] Prolonged uninterrupted voriconazole may have contributed to better outcome in patient 2. Alternatively voriconazole resistance may have developed in patient 1.[14,15]

In summary, visual loss in the setting of COVID-19 pneumonia may indicate endogenous aspergillus endophthalmitis and potentially life threatening disseminated aspergillosis. Systemic imaging is warranted especially if patients have received high dose steroids and immunomodulators. Pars plana vitrectomy specimens may confirm diagnosis. Complete fungus ball excision achieved a better visual outcome.

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Author order and contributions

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Janssen N, Nyga R, Vanderbeke, et al. Multinational observational cohort study of COVID-19–associated pulmonary aspergillosis. *Emerg Infect Dis*. 2021;27:2892–2898.
2. Shroff D, Narula R, Atri N, et al. Endogenous fungal endophthalmitis following intensive corticosteroid therapy in severe COVID-19 disease. *Indian J Ophthalmol*. 2021;69(7):1909–1914.
3. Fekri S, Khorshidifar M, Esfahanian F, et al. Endogenous fungal endophthalmitis following COVID-19 hospitalization: evidence from a year-long observational study. *J Fr Ophtalmol*. 2023;46(5):461–467.
4. Burger B, Epps S, Cardenas VM, et al. Tocilizumab is associated with increased risk of fungal infections among critically ill patients with COVID-19. *Am J Respir Crit Care Med*. 2021;203:A2635.
5. Machado M, Valerio M, Álvarez-Uría A, et al. Invasive pulmonary aspergillosis in the COVID-19 era: an expected new entity. *Mycoses*. 2021;64:132–143.
6. Ezeokoli OT, Gcilitshana O, Pohl CH. Risk factors for fungal Co-infections in critically ill COVID-19 patients, with a focus on immunosuppressants. *J Fungi (Basel)*. 2021;7:545.
7. Shimada A, Ohnaka S, Kubo K, et al. COVID-19-Associated pulmonary aspergillosis in a patient treated with remdesivir, dexamethasone, and baricitinib: a case report. *Cureus*. 2022 Apr 2;14(4), e23755.
8. Dellière S, Dudoignon E, Fodil S, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. *Clin Microbiol Infect*. 2021;27:790.e1–790.e5.
9. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID 19 in Wuhan China. *Club Inf Dis*. 2020;71:762–768.
10. Theel ES, Doern CD. β-D-glucan testing is important for diagnosis of invasive fungal infections. *J Clin Microbiol*. 2013;51(11):3478–3483.
11. Weishaar PD, Flynn HW, Murray TG, et al. Endogenous aspergillus endophthalmitis, clinical features and treatment outcomes. *Ophthalmology*. 1997;105:57–65.
12. Behera UC, Budhwani M, Das TP, et al. Role of early vitrectomy in the treatment of fungal endophthalmitis. *Retina*. 2018;38:1385–1392.
13. Matt P, Bernet F, Habicht J, et al. Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. *Chest*. 2004;126(6):1783–1788.
14. Lestrade PP, Bentvelsen RG, Schauwvlieghe AFAD, et al. Voriconazole resistance and mortality in invasive aspergillosis: a multicenter retrospective cohort study. *Clin Infect Dis*. 2019;68(9):1463–1471.
15. Salmanton-García J, Sprute R, Stemler J, et al. Fungi Scope European confederation of medical mycology/the International society for human and animal mycology working group. COVID-19-Associated pulmonary aspergillosis. *Emerg Infect Dis*. 2021;27(4):1077–1086.