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Case Report

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RHINO-ORBITO-CEREBRAL MUCORMYCOSIS ASSOCIATED WITH COVID 19

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ABSTRACT

COVID-19 disease presents with wide variety of extra-pulmonary manifestation and may be associated with number of bacterial and fungal co-infections. We report the case of a patient with COVID-19 disease, which, during the course of the treatment, developed rhino-orbito-cerebral mucormycosis. A 49 year old female patient, a longstanding diabetic and hypertensive, with a positive reverse transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was admitted for treatment. She received intravenous piperacillin-tazobactum, methyl prednisolone and remdesivir. Over the course of the admission, she developed signs of orbital cellulitis. She had right opthalmoplegia with Left sided hemiplegia. Histopathologic examination from maxillary sinus was suggestive of mucormycosis. CT brain contrast with CT angio showed complete occlusion of Right middle cerebral artery and Right cavernous sinus thrombosis. She responded to liposomal Amphotericin B. Extensive use of steroids and broad-spectrum antibiotics may lead to the development or exacerbation of a preexisting fungal disease. Physicians should be aware of the possibility of secondary invasive fungal infections in patients with COVID-19 infection.

KEYWORDS: Mucormycosis, Diabetes, Cavernous sinus thrombosis, Amphotericin B.

INTRODUCTION

As a person-to-person transmitted disease, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been an emergency global public health event.[1,2] Besides, the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients always have immunosuppression with a decrease in CD4 + T and CD8 + T cells.[3] Critically ill patients, especially the patients who were admitted to the intensive care unit (ICU) and required mechanical ventilation, or had a longer duration of hospital stays were more likely to develop fungal co-infections.[4] Hence, it is important to notice that COVID-19 patients can develop further fungal infections during stages of this disease, especially severely ill patients.[5] We report the case of a patient with COVID-19 disease, which, during the course of the treatment, developed rhino-orbito-cerebral mucormycosis. Mucormycosis is an opportunistic and frequently fulminating fungal infection caused by members of the family Mucoraceae, order Mucorales and class Zygomycetes. It is commonly reported in immunocompromised patients such as poorly controlled diabetes mellitus, blood dyscrasias, malnutrition, neutropenia, iron overload, organ transplant, and immunosuppressive therapy. Diagnosis is confirmed by histopathological demonstration of the organism in the affected tissue. Early diagnosis and treatment of mucormycosis is extremely important due to the aggressive course of the disease. The disease may manifest in six different ways as rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system or disseminated forms. Rhino-orbito-cerebral mucormycosis is the most common type accounting for 30% to 50% of the cases and its extension to the orbit and brain is quite usual making it potentially life-threatening disease.

CASE REPORT

A 49 year old female patient was admitted with a 4 days history of breathlessness, fever and generalized weakness. She was diabetic since 15 years and on oral tablet metformin 500 mg BD. On examination, her pulse rate was 100/minute, blood pressure was 150/90 mmHg, she was afebrile on admission, respiratory rate was 30/minute, with a specific oxygen saturation of 86% on oxygen (10 -12 liters/min). The physical examination revealed bilateral crepitations at the lung bases with a normal cardiovascular and neurological exam.

A reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab was positive for the SARS-CoV-2 virus. A x-ray chest showed multiple patchy consolidation in both lungs involving both lower

lobes, the right middle lobe, and the lingula predominantly in a peripheral distribution strongly suggestive of COVID-19 disease (Figure 1).

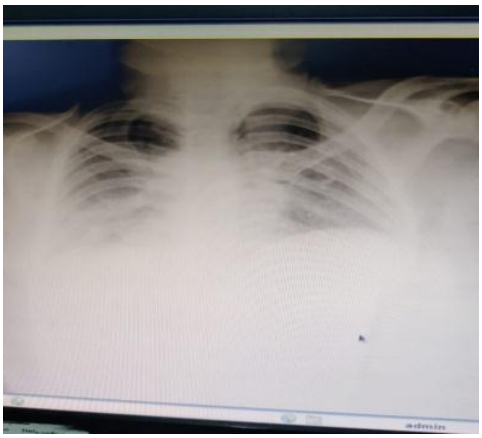

Figure 1: xray chest PA view.

She was started on intravenous piperacillin-tazobactam 4.5 gm TDS, oral, with intravenous methylprednisolone 40 mg BD, injectable remdesivir loading dose 200 mg intravenous over 30-120 min thereafter 100mg once a day and in compliance with the local protocol, along with general supportive care. Her diabetes mellitus was managed with insulin adjusted as per a sliding scale based on her random blood sugar levels adjusted to maintain 180-200 mg/dl. She also received subcutaneous enoxaparin (40mg/0.4 ml) twice daily.

She gradually deteriorated with the onset of acute respiratory distress syndrome over the next few days. On day 4, she was shifted on non-invasive ventilation to maintain her oxygen saturation. On day 6 she received was started on subcutaneous insulin glargine (10 units) at night with regular insulin as needed to continue to maintain a blood sugar level of 180-200 mg/dl.

On day 13, right lid edema with right eye prominence was noted and topical antibiotic drop was prescribed. On examination she had ptosis of right eye with external ophthalmoplegia and absent direct and consensual light reflex. Redness over right cheek region and oral cavity examination showed white ulcerative necrotic oval patch on hard palate (Fig. 2 and 3).

Figure 2: shows ptosis of right eye.

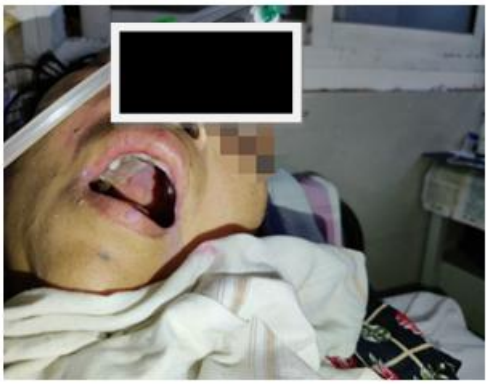

Figure 3: shows palatal ulcer with erosion.

Systemic examination was within normal limit. On investigations, TLC was 13,000/cmm.KFT, LFT and electrolytes were normal.

An ophthalmic evaluation was requested the next day. On examination, the right eye was proptotic with extensive areas of edema in the periorbital region with soft tissue necrosis along the medial half of the upper and lower lids. The right eye was congested with conjunctival edema and signs of exposure keratitis. The right eye appeared fixed and had a dilated non-reactive pupil either due to extension of infection to the other cavernous sinus or due to COVID-19 coagulopathy. Visual acuity and detailed ocular movements could not be assessed, as the patient was drowsy and not responsive.

She developed left hemiplegia by 14th day. Keeping high suspicion of mucormycosis, nasal biopsy from the middle turbinate sent for histopathological study revealed broad aseptate filamentous fungal hyphae suggestive of mucormycosis, which was confirmed on a Sabourauds Dextrose Agar culture. CT angio of brain showed complete occlusion of right internal carotid artery by an extensive thrombus with right middle cerebral artery territory large infarct and right cavernous sinus thrombosis with infarction of right ganglio-capsular region (figure 4).

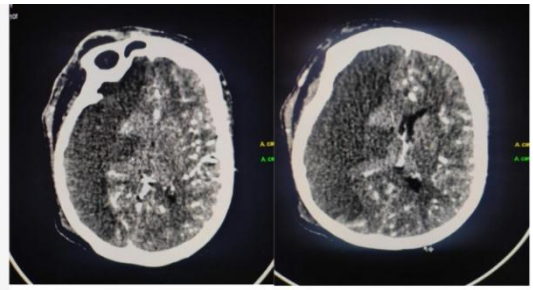

Figure 4: Large gangliocapsular infarct in right MCA terriotory.

ENT, Neuro surgery opinion was taken - and was advised to manage conservatively. As Liposomal Amphotericin B is the drug of choice she was started on Liposomal amphotericin B – IV 5mg/kg/day dose. In

view of cavernous sinus thrombosis, she was also given LMWH & overlapped with warfarin 5 mg OD. Histopathological report came after 7 days as sinonasal mucormycosis. Therapy planned to be given for total 6 weeks with monitoring of vitals and laboratory parameters. No any deterioration in signs or symptoms after 7th dose of Amphotericin B drug.

A complex interaction of factors, including preexisting diseases, such as diabetes mellitus, previous respiratory pathology, use of immunosuppressive therapy, the risk of hospital-acquired infections, and systemic immune alterations of COVID-19 disease itself may lead to secondary infections, which are increasingly being recognized in view of their impact on morbidity and mortality.[6] In a recent review, 62/806 (8%) patients had secondary bacterial or fungal infections during hospital admission. There was widespread use of broad-spectrum antibiotics, with as many 1450/2010 (72%) of patients receiving these drugs, often with no underlying evidence of infection.[7]

COVID-19 patients with trauma, diabetes mellitus, glucocorticoid use, prolonged neutropenia, are more likely to develop mucormycosis.[8] Mucormycosis is usually suspected based on results of direct microscopy or fluorescent technique from clinical specimens such as sputum, bronchoalveolar lavage, and skin lesions that *Mucorales* hyphae are non-septate or pauci-septate with a variable width of 6 –16 μm. To confirm the diagnosis, non-pigmented hyphae showing tissue invasion should be shown in tissue sections stained with hematoxylin–eosin (HE), PAS, or GMS (Grocott-gomori's methamine silver staining).[9] Culture of specimens is strongly recommended for identification of genus and species. What's more, it is suggested to be cultured at 30 °C and 37 °C separately that typically cottony white or grayish black colony usually will be found, afterward morphological identification of fungi or DNA sequencing based on bar code genes, such as 18S, ITS, 28 s, or rDNA. MALDI-TOF identification is just moderately supported because it depends mainly on in-house databases, and many laboratories do not have this capacity.[10] Further, it is promising to detect fungi DNA, in serum as well as in other body fluids, even in paraffin-embedded tissue, however, because of lack of standardization supported it is only with moderate strength. Mucor is attracted to blood vessels and invasion of their wall (particularly arterial) is the pathological trademark of the infection. The integrity of host defense mechanisms plays a key role. The presence of certain underlying diseases and immunosupression provides a favourable microenvironment for fungal growth. The disease usually spreads to the cavernous sinus, internal carotid artery and subsequently to the brain. Vascular manifestations of mucormycosis include pseudoaneurysms, partial thrombosis, narrowing and arteritic irregularities of intracranial arteries. Their pathologic basis is believed to be a combination of direct endothelial injury and growth of hyphae into the lumen, with resultant distal infarcts and mycotic emboli. Vasculitis usually occurs in the internal carotid artery. Mycotic pseudoaneurysms, arterial dissection, or venous congestion could lead to intracranial hemorrhages. Rapid thickening and enhancement of the carotid artery wall on serial MRI establishes the nature of the arterial involvement by mucormycosis rather than atherosclerosis.[11]

The treatment recommendations can be supported by the global guideline for the diagnosis and management of mucormycosis in 2019 by European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium that the therapeutic and alternative medication of mucormycosis have been given more detailed guidance opinions.[12] Generally, it strongly supports an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment. In neutropenic patients, those with graft-versus-host disease or high risk factor, primary prophylaxis with posaconazole may be recommended. Amphotericin B lipid complex, liposomal Amphotericin B and posaconazole oral suspension are treated as the first-line antifungal monotherapy, while isavuconazole is strongly supported as salvage treatment. There are no convincing data to guide the use of antifungal combination therapy of polyenes and azoles or polyenes plus echinocandins. Mehta et al. have reported case of 60 year old male with Rhino-Orbital Mucormycosis Associated With COVID-19.[13] White et al. screened 135 adults with COVID-19 infection and reported an incidence of invasive fungal infections of 26.7% (commonly aspergillosis (14.1%), or yeast, usually candida (12·6%)). Patients with invasive fungal diseases had higher mortality (53% with vs 31% without), which was significantly reduced by appropriate therapy. Corticosteroid therapy and a past history of chronic pulmonary disease were associated with a higher risk of invasive fungal disease.[14] All the patients that died presented with diabetic ketoacidosis. Hemiplegia as a neurological complication of the disease was seen in 66.6% (2/3) of the deaths.[15]

The patient we describe with severe COVID-19 was a long-standing diabetic. The signs of orbital infection were noticed only after 12 days of admission for COVID-19 infection during which time she was treated with both broad-spectrum antibiotics and steroids. All these factors tend to facilitate fungal coinfection, along with any possible COVID-19 pathophysiological mechanisms. In our case, either a previously undiagnosed mucor infection may have been aggravated or it may have subsequently developed.

CONCLUSION

COVID-19 patients showed overexpression of inflammatory cytokines, and impaired cell-mediated immune response with decreased CD4 + T and CD8 + T cell counts, indicating its susceptibility to fungal co-infection. Moreover, COVID-19 patients accompanied

with immunocompromised state, such as prolonged neutropenia, glucocorticoid use, inherited or acquired immunodeficiencies, and tumor are more likely to develop fungal co-infection. We suggest it is priority to assess the risk factors, the types of invasive mycosis, the strengths and limitations of diagnostic methods, clinical settings, and the need for standard or individualized treatment in COVID-19 patients.

Clinical suspicion should be maintained for such dangerous infection when presents in diabetic patients. Due to lethal nature of disease, early initiation of therapy helps in rapid reversal of disease process.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020; 579(7798): 270–3.
2. Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol, 2020; 5(4): 536–44.
3. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect, 2020.
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med, 2020.
5. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med, 2020.
6. Chen N, Zhou M, Dong X, et al.: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395: 507-513. 10.1016/S0140-6736(20)30211-7
7. Rawson TM, Moore LSP, Zhu N, et al.: Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis, 2020. [Epub ahead of print]:ciaa530. 10.1093/cid/ciaa530
8. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis, 2019; 19(12): 405–21.
9. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol, 2018; 56(suppl 1): 93–101.
10. Dadwal SS, Kontoyiannis DP. Recent advances in the molecular diagnosis of mucormycosis. Expert Rev Mol Diagn, 2018; 18(10): 845–54.
11. Calli C, Savas R, Parildar M, Pekindil G, Alper H, Yunten N. Isolated pontine infarction due to rhinocerebral mucormycosis. Neuroradiology, 1999; 41: 179-181.
12. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis, 2019; 19(12): 405–21.
13. Mehta S, Pandey A (September 30) Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus, 2020; 12(9): e10726. DOI 10.7759/cureus.10726
14. White PL, Dhillon R, Cordey A, et al.: A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis, 2020. [Epub ahead of print]:ciaa1298. 10.1093/cid/ciaa1298
15. Abbas Z, Jafri W, Rasool S, Abid S, Hameed I. Mucormycosis in patients with complicated cirrhosis. Singapore Med J, 2007; 48(1): 69-73. PMID: 17245519.