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Associated Fungal Infections, Related to the Global Covid-19 Pandemic (Literature Review)

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Abstract

The 2019 coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept the globe. Based on a retrospective analysis of SARS and influenza data from China and around the world, we suggest that fungal co-infections associated with global COVID-19 may be missed or misdiagnosed. Although there are few publications, patients with COVID-19, especially severely ill or immunocompromised patients, are more likely to develop invasive mycoses. Aspergillus and Candida infections in patients with COVID-19 will require early detection by comprehensive diagnostic intervention (histopathology, direct microscopy, culture, (Arabian: 2004, Tilavberdiev: 2016) -β-D-glucan, galactomannan, and PCR assays) to ensure effective treatment. We consider it appropriate to assess risk factors, types of invasive mycoses, strengths and weaknesses of diagnostic methods, clinical conditions, and the need for standard or individual treatment.

Keywords: *Aspergillosis; COVID-19; Candidiasis; Fungal Coinfection; SARS-CoV-2*

Introduction

The global popularity of COVID-19 and the possibility of co-infection with fungal infections. As a person-to-person transmitted disease, Coronavirus Disease 2019 (COVID-19) caused by coronavirus 2 (SARS-CoV-2) severe acute respiratory syndrome has become a global public health emergency (Zhou: 2020, Gorbalenya: 2020). By May 18, 2020, COVID-19 had rapidly spread to 212 countries and caused nearly 5 million laboratory-confirmed cases and more than 310,000 deaths worldwide. Similar to SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV-2 is responsible for lower respiratory tract infections and can cause Acute Respiratory Distress Syndrome (ARDS) (Wang: 2019). In addition to diffuse alveolar lesions with pronounced inflammatory exudation, patients with COVID-19 always have immunosuppression with a decrease in CD4 + T and CD8 + T cells (Yang: 2019). In critically ill patients, especially in patients who were admitted to the intensive care unit (ICU) and who required mechanical ventilation, or who were in the hospital for a longer time, even up to 50 days, were more likely to develop co-morbid fungal infections (Yang X: 2020). Therefore, it is important

to note that patients with COVID-19 may develop further fungal infections in the middle and late stages of the disease, especially in severe form (Gangneux: 2020).

Discussion

Epidemiology of concomitant fungal infections in patients with COVID-19.

Unfortunately, very few articles have reported co-occurring fungal infections, not only that some studies have not provided detailed information on the pathogens. Nevertheless, patients with COVID-19 were found, especially seriously ill or immunocompromised, who had concomitant fungal infections (Guo L: 2019). In China, Chen et al. performed fungal culture on all 99 COVID-19 patients upon admission and found five (5%, 5/99) cases of fungal infection, including one case of Aspergillus flavus, one case of Candida glabrata and three cases of C. albicans (Chen: 2019). Young et al. Found concomitant fungal infection in three of 52 critically ill patients (3/52, 5.8%), including A. flavus, A. fumigatus, and C. albicans (Yang X: 2020). Other Chinese studies have found a higher percentage of secondary infections (8-15%) in patients with COVID-19, but it is unclear whether this is a bacterial or fungal infection (Huang: 2019, Ruan: 2020). In addition, one study mentioned that 2.8% (31/1099) of patients were treated with antifungal drugs, including 1.9% (18/926) of mild patients and 7.5% (13/173) of patients with a severe form, but there is no etiological evidence of fungal coinfection. (Guan: 2020)

Tilavberdiev Sh.A., Klimko N.N., Denning D.V. (2016) studying the use of the life program model to assess the prevalence of severe and chronic mycotic diseases in the Republic of Uzbekistan, note that in 2014 in the Republic of Uzbekistan the number of patients with severe and chronic mycotic diseases was 535 640 people. According to the results of the study, the author established a significant prevalence of mycoses in the Republic of Uzbekistan, which necessitates a deeper study of their epidemiological and clinical features and the improvement of preventive measures (Tilavberdiev: 2016).

Klimko N.N. et al. note that some changes in the chemical composition of sebum (a decrease in the squalene / triglyceride ratio) promotes hypercolonization of the skin by yeast-like fungi and their transition to a pathogenic - mycelial form (Zhou: 2020).

Another study mentioned that in 149 cases, patients did not receive antifungal drugs (Yang W: 2019). A German study found that invasive pulmonary aspergillosis (IPA) associated with COVID-19 was found in five (26.3%) of 19 consecutive critically ill patients with moderate to severe ARDS [14]. In the Netherlands, 31 ICU patients had six patients (19.4%) with putative IPA, of which five were identified as A. fumigatus (Van Arkel: 2020). In addition, among the first 5 well-described French COVID-19 patients, an elderly, critically ill male was found to be coinfected with A. flavus by culture of tracheal aspirates (Lescure: 2020).

Abandoned fungal coinfection in patients with COVID-19 based on assumptions related with SARS and flu.

Studies have shown that SARS-CoV and SARS-CoV-2 belong to the same species and have similar prevalence, biological and clinical characteristics (Peeri: 2020). Looking back at SARS in 2003, it was found that the incidence of fungal infections in SARS patients was 14.8–27%, which was even higher in critically ill patients, up to 21.9–33% (Zhang Y: 2003). The main cause of death in SARS patients was fungal infection, accounting for 25–73.7% of all causes of death (Li: 2003). In addition, in recent decades, more and more reports of severe influenza pneumonia leading to ARDS complicated by fungal infection have been published (Thevissen: 2020). One study found that IPA was diagnosed in 83 (19%) of 432 patients hospitalized with influenza, which was higher in immunocompromised patients (32%), and in the

case of IPA, mortality increased from 28% to 51% (Schauwvlieghe: 2018). However, as far as fungal coinfection in COVID-19 patients is concerned, only a few studies have reported this and may have been neglected. Clinically, many COVID-19 patients did not have a sputum fungus assessment in the beginning, and the fungus is difficult to detect with fungal sputum culture alone (Guan: 2020). As the disease worsens, severe respiratory symptoms can be easily attributed to COVID-19, at best considering co-infection with bacteria or even mycoplasma (Chaturvedi: 2018), which usually leads to timely antibiotic use, and the diagnosis of a fungal infection is always delayed or ignored. Based on the experience of SARS in 2003 and cases of invasive aspergillosis combined with severe influenza, it is critically important to pay attention to the likelihood of COVID-19 accompanied by fungal infections.

Clinical and Diagnostic Perspective of COVID-19, associated with fungal coinfection.

With the ongoing COVID-19 pandemic, more and more experts are learning about joint fungal infections. The French High Council of Public Health has recommended systematic screening for fungal pathogens in patients with COVID-19 (Gangneux: 2020). Academician Lanjuan Li and her colleagues, who have accumulated experience in the severe treatment of COVID-19, reminded clinicians to focus on fungal infections in patients, especially those who are severe or immunocompromised (Xu K: 2020). At an early stage of the disease or in extrapulmonary fungal infections, atypical chest imaging may occur.

Therefore, in critically ill patients, it is necessary to observe for fungal pathogens, including (i) etiological examination: direct microscopy and culture; (Ii) histopathology; (Iii) serology: antigen and antibody, detection of (1,3) -β-D-glucan (BDG) (Lahmer: 2017) and galactomannan (GM) in serum should also be tested in suspicious patients, while bronchoalveolar lavage fluid (BALF)) and sampling of tracheal aspirate (TA) for inoculation and biomarker testing should be carried out in a well-protected environment due to the risk of aerosol spread and infection of health-care workers (Prattes: 2020); (Iv) PCR-based methods. If necessary, polymerase chain reaction (PCR) and molecular identification in real time can be performed to identify pathogens (Hage: 2019). Once the pathogen has been identified, an antifungal susceptibility test (AST) can be performed to select susceptible antifungal agents. If AST cannot be performed, it should be treated empirically. The main fungal pathogens of co-morbid fungal infections in patients with severe COVID-19 are Aspergillus and Candida. Other infrequent opportunistic fungi that cause lung infections, such as Mucor and Cryptococcus, must also be considered.

Invasive aspergillosis (IA). Aspergillus species can be an important cause of life-threatening infection in COVID-19 patients, especially those with high risk factors. Potential risk factors for patients include GC use, long-term neutropenia, chronic obstructive pulmonary disease (COPD), allogeneic hematopoietic stem cell transplantation (allo-HSCT) (Miceli: 2017), solid organ transplant (SOT) (Fishman: 2020), hereditary immunodeficiencies, hematopoietic disorders, malignant neoplasms (HM), cystic fibrosis (CF) (Poli: 2020), etc. The diagnosis of IA requires microbiological and or histopathological findings, although specimen collection is challenging for many patients because lung biopsy may be contraindicated in patients with clotting disorders or severe respiratory failure (Van Arkel: 2020). Histopathological examination is mainly based on the detection of specific fungal patches on the lung fluid or tissue when a fungal infection is suspected and may reveal the characteristic acute angular branching septa of Aspergillus spp., As well as Grocott-Gomori methenamine silver (GMS) and periodic acid staining, staining fixed tissue Schiff (PAS) would be beneficial, while Aspergillus spp is difficult to distinguish from other filamentous fungi such as Fusarium spp. and Scedosporium spp. (Blot: 2012). Therefore, definitive confirmation by culture or non-culture method should be obtained, including (i) direct microscopic examination using optical brightener, Calcofluor or Blankophor methods, which can increase the sensitivity and specificity for the detection of Aspergillus-like traits; (Ii) culturing on fungal-specific medium at 37 ° C for 2-5 days, if positive, Aspergillus morphological traits can be identified under a microscope or DNA sequencing can be used in reference laboratories to accurately identify species, but usually yields cultures are low, and a negative result does not exclude the diagnosis of IA;

(Iii) molecular assays targeting ribosomal DNA (rDNA) sequences can also be used to detect Aspergillus in tissues or BALF, especially to detect Aspergillus spp. and mutations of resistance to CYP51A in A. fumigatus, although these methods have not been standardized or limited by laboratory conditions or validated commercial reagents in some countries (Patterson: 2016); (Iv) Serum and BALF GM testing is also recommended as an early and accurate marker using less invasive diagnostic methods, especially in neutropenic patients, with the benefits of fewer trauma and time savings, although sometimes this test in blood samples is less sensitive. than cultured respiratory specimens (Hage: 2019).

Treatment recommendations can be supported by updated guidelines from the Society of Infectious Diseases of America 2016, according to which the prevention, therapeutic treatment, combination and alternative treatment of Aspergillus infection received more detailed recommendations (Patterson: 2016). Typically, drugs recommended for the treatment and prevention of IA include triazoles (itraconazole, voriconazole, posaconazole, ezaconazole), amphotericin B and its liposomes, and echinococins (micafungin or carpofening). Most patients can choose triazole drugs for the treatment of AI, however, therapeutic drug monitoring (TDM) is recommended and interactions between azoles and other drugs should be fully considered.

Invasive candidiasis (IC). For patients with severe COVID-19 who are more likely to be treated with broad-spectrum antibiotics, parenteral nutrition and invasive examinations, or patients with prolonged neutropenia and other immune deficiencies, the risk of contracting Candida species may be significantly increased. (Clancy: 2018). Diagnosis of IC depends on culture methods, including culture of blood or other specimens collected under sterile conditions, which are generally considered the gold standards for IC, and diagnostic tests not related to culture, including tests for mannan and anti-mannan IgG, antibodies to C. albicans from germ tube (CAGTA), BDG. and PCR-based assays, which are now included in clinical practice as an adjunct to cultures (Ibanez-Martinez: 2017). Basically, there are two drawbacks to blood culture, on the one hand, the blood culture time is long because the average time for a positive alarm is 2–3 days (range 1 to ≥ 7 days), plus the duration of the ID and sensitivity test is 4 to 6 days, on the other hand, it is less sensitive than PCR, with a much lower detection limit when Candida concentration is ≤ 1 CFU / ml, and cannot detect candidiasis in extremely low concentrations, intermittent candidiasis, or deep Candida infection that has not been trapped into the blood. Therefore, several non-cultural diagnostic tests are recommended, but there is also widespread uncertainty about their usefulness in clinical practice (Clancy: 2018). β-D-glucan (BDG) is a major component of the cell wall of Candida and most pathogenic fungi, with the exception of Cryptococcus, Blastomyces and Mucorales species, which is widely used in clinical practice and is well recommended for detection in serum, but cannot distinguish Candida from other fungi (Hage: 2019). In addition, IgG mannan and anti-mannan tests, CAGTA are used in many European centers, and higher sensitivity and specificity are observed when combined with the mannan / anti-mannan assay (Mikulska: 2010).

There are promising PCR tests, including multiplex PCR platforms, while there are some limitations due to the lack of multicenter validation of assay performance, so there are no FDA approved PCR tests for Candida, but there are commercial and proprietary tests that are widely available. In addition, T2 magnetic resonance can also be used to enhance and detect Candida DNA, but its potential for early diagnosis of candidemia remains unclear. MALDI-TOF technology is available in more hospitals with the greatest advantage of its speed, requiring no more than 5 minutes to identify a microorganism in isolated colonies, even researchers have developed protocols for identifying yeast directly from bottles with positive blood cultures for half an hour without performing subcultures (Ibanez-Martinez: 2017). In general, not only must the benefits of combining culture and non-culture methods be fully understood, but also, clinicians must take into account the IC types, the advantages and limitations of each study method, and the context of the clinical setting in order to make a reasonable interpretation. In addition, a susceptibility test is recommended for all bloodstream Candida isolates and other clinically relevant Candida isolates, especially C. glabrata or C. parapsilosis.

Treatment recommendations can be supported by the updated Infectious Disease Society of America recommendations from 2016, according to which therapeutic and alternative drugs for candidal infection received more detailed recommendations (Pappas: 2016). As a rule, patients with suspected or confirmed CI should receive echinocandin (caspofungin, micafungin, and anidulafungin), azoles (fluconazole, voriconazole, itraconazole), and amphotericin B and its liposomes, moreover, TDM should be used for azoles. optimize efficacy and limit toxicity.

Invasive mucormycosis. Patients with COVID-19 with trauma, diabetes mellitus, intake of GC, malignant neoplasms (HM), prolonged neutropenia, allo-HSCT, SOT are more likely to develop mucormycosis (Cornely: 2019). The suspicion of mucormycosis is usually based on direct microscopy or fluorescent whiteners from clinical specimens such as sputum, BALF, and skin lesions in which Mucorales hyphae do not have septa or small septa with variable widths of 6–16 μm. To confirm the diagnosis, unpigmented hyphae showing tissue invasion should be shown on tissue sections stained with hematoxylin-eosin (HE), PAS, or GMS (Skiada: 2018). For genus and species identification, specimen cultivation is strongly recommended, as well as AST. Moreover, it is recommended to cultivate at 30 ° C and 37 ° C separately to obtain cottony white or grayish-black colonies, and then morphologically identify fungi or DNA sequencing based on barcode genes such as 18S, ITS, 28s, or rDNA. MALDI-TOF identification is moderately supported because it depends mainly on internal databases, and many laboratories do not have this capability (Dadwal: 2018). In addition, the detection of fungal DNA in serum, as well as in other body fluids, even in paraffin-embedded tissue, is promising, however, due to a lack of standardization, it is only supported with moderate efficacy.

Treatment recommendations can be supported by the 2019 global guidelines for the diagnosis and treatment of mucormycosis by the European Confederation for Medical Mycology (ECMM) and the Consortium for Mycosis Education and Research, which provided more detailed guidance on therapeutic and alternative drugs for mucormycosis (Cornely: 2019). It generally strongly supports early, complete surgical treatment of mucormycosis whenever possible, in addition to systemic antifungal treatment. Patients with neutropenia, patients with graft versus host disease, or those with a high-risk factor may be advised to use posaconazole for primary prophylaxis. Amphotericin B Lipid Complex, Amphotericin B Liposomal and Posaconazole Oral Suspension are considered first-line antifungal monotherapy, while isavuconazole is strongly supported as a therapeutic agent. There is no conclusive evidence to guide the use of antifungal combination therapy of polyenes and azoles or polyenes with echinocandins.

Invasive cryptococcosis. Patients with COVID-19, with human immunodeficiency virus (HIV) infection with CD4 + T-lymphocyte count <200 cells / μL, allo-HSCT, SOT or other immune disorders are susceptible to cryptococcosis, which manifests itself predominantly as meningoencephalitis (Setianingrum: 2019) ... Considering the difficulties associated with the diagnosis of cryptococcosis and the identification of Cryptococcus species, including C. neoformans and C. Gattii. The diagnosis of cryptococcosis is usually based on a combination of clinical and laboratory confirmation. The following methods are used to confirm infection: culture, direct microscopy, histopathology, serology, and molecular detection. To diagnose cryptococcosis, a sample of cerebrospinal fluid (CSF) is mixed with India Ink and under a microscope, Cryptococcus spp. with narrow kidneys. Encapsulated yeast is commonly found. Culture samples should be plated on Sabouraud Dextrose Agar at 30 ° C for 7 days under aerobic conditions and observed daily. Moreover, cultures from patients receiving systemic antifungal therapy may take longer to grow. Cryptococcus looks like slimy, creamy colonies. Cryptococcus capsular polysaccharides can be detected and quantified in body fluids such as serum, cerebrospinal fluid, BALF or abnormal tissue. Three formats of cryptococcal antigen (CrAg) detection tests are currently available: latex agglutination test (LAT), enzyme-linked immunosorbent assay (EIA), and lateral flow immunoassay (LFA). These methods are rapid, sensitive and specific, but they are not standardized for respiratory specimens such as BAL fluid, pleural fluid, or sputum (Ibanez-Martinez: 2017). Molecular detection of cryptococcus is required in certain situations where other diagnostic tools

have failed to confirm the diagnosis of cryptococcosis. These molecular methods include pan-fungal PCR, DNA sequencing for identification, multiplex PCR, isothermal amplification, and probe microarrays. Once a diagnosis of cryptococcosis is made, lumbar puncture and examination of cerebrospinal fluid (including antigen) are recommended for all patients (Gassiep:2018). Cryptococcus can spread to the central nervous system, causing cryptococcal meningitis.

Treatment recommendations can be supported by the World Health Organization guidelines for the diagnosis, prevention and treatment of cryptococcal infection in HIV-infected adults, adolescents and children in 2018 (from: https://www.who.int/hiv/ pub / guidelines / cryptococcal disease / en /). Typically, the following is recommended as the preferred regimen: (i) an induction phase for amphotericin B and + flucytosine deoxycholate followed by fluconazole; alternatives: fluconazole + flucytosine or amphotericin B deoxycholate + fluconazole. (II) The phase of consolidation of fluconazole. (III) Maintenance (or secondary prevention) phase of fluconazole.

Conclusion

Thus, by analyzing retrospective analyzes of SARS and influenza data in China and around the world, we hypothesize that co-occurring fungal infections associated with global COVID-19 may be overlooked or misdiagnosed. In addition, as a life-threatening infectious disease, COVID-19 patients exhibited overexpression of inflammatory cytokines and impaired cell-mediated immune response with decreased CD4 + T and CD8 + T cell counts, indicating its susceptibility to co-fungal infection. Moreover, COVID-19 patients with an immunocompromised condition such as prolonged neutropenia, HSCT, HA use, SOT, hereditary or acquired immunodeficiencies, and tumor are more likely to develop fungal coinfection. Here we have summarized updated diagnostic information (histopathology, direct microscopic examination, culture, (1,3) -β-D-glucan, galactomannan, PCR assays, MALDI-TOF technology, etc.) and recommendations for the treatment of invasive mycosis ... We believe that it is appropriate to assess risk factors, types of invasive mycosis, strengths and weaknesses of diagnostic methods, clinical parameters and the need for standard or individualized treatment of patients with COVID-19. Finally, a clinical outline (Figure 1) was provided to assist clinicians and laboratory experts in treating aspergillosis, candidiasis, mucormycosis, or cryptococcosis as comorbidities in COVID-19 patients.

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