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Awareness on Tricky Fungal Infections Coexisting with COVID-19

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ABSTRACT

As we know that the whole world is fighting against SARS-CoV-2, here another new battle starts i.e., the fungal co-infections which throw a challenge to the world. In many cases, people who are recovered from COVID-19 are more prone to develop these co-fungal infections. Looking back on SARS-CoV in 2003, we found that the fungal infections was the main cause of death for SARS-CoV patients, accounting for 25% - 73.7% in all causes of death, while in COVID-19 patients, only few studies have been reported. The most common fungal infections associated with COVID-19 patients are mucormycosis (black fungus), candidiasis, aspergillosis and cryptococcosis. The main motto of this article is to present the detailed description about these fungal infections in aspects of their definitive species, associated risk factors, pathology, clinical manifestations, diagnosis, management, and their preventive measures.

Keywords: COVID-19, SARS-CoV-2, fungal co-infections, mucormycosis (black fungus), candidiasis, aspergillosis, cryptococcosis.

INTRODUCTION

Fungi are eukaryotic, heterotrophic (cannot make their own food) and unicellular or multicellular organisms [1]. Fungi are omnipresent in our living environment and are an integral part of all ecosystems, they have oppositional and symbiotic relationships with humans [2]. The infection caused by the fungi is called as mycosis. Fungal infections can occur any time after COVID-19 infection, either during the hospital stay or several days to a couple of weeks after discharge [3]. In COVID-19 condition, a life threatening phenomenon called a "cytokine storm" which is resulted from the overexpression of our immune system. So physicians are likely to prescribe steroids to reduce the immune response. But both this weakens the body's defenses and increases sugar levels, which funguses thrive off [4, 5].

COMMON RISK FACTORS FOR FUNGAL INFECTIONS:

According to CDC, people who are at high risk for developing this infection include those who [6]:

- Have spent a lot of time in the intensive care unit (ICU).
- Have a weakened immune system (for example- HIV, people on cancer chemotherapy, people who have had an organ transplant, allo-HSCT, SOT and people with low white blood cell counts).
- Have recently had surgery, especially multiple abdominal surgeries.
- Have recently received lots of antibiotics or steroids in the hospital.
- Receive total parenteral nutrition (food through a vein).
- Have kidney failure or are on hemodialysis.
- Have other disease conditions – Diabetes, cystic fibrosis, hemopoietic malignancy, COPD.
- Have a central venous catheter.

MUCORMUCOSIS (BLACK FUNGUS)

Mucormycosis (previously known as Zygomycosis) is a opportunistic fungal infection caused by fungi of the order mucorales in the class zygomycetes [7]. We call it as black fungus because of the black lesions observed in nasal and oral cavity [3].

PATHOLOGY: These fungi are angioinvasive, resulting in vessel thrombosis and tissue necrosis. It is caused by inhalation of sporangiospores (asexual) of mucorales which on favourable conditions settles within the nasal and oral mucosa [3]. The infection may then rapidly extend into adjacent tissues. The invading fungus may spread inferiorly to conquer the palate, posteriorly to conquer the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to conquer the brain. The fungus invades the cranium through either the orbital apex or cribriform plate of the ethmoid bone and finally kills the host. Black masses may be seen in the nasal cavity and oral cavity [8]. In immunocompromised patients, spores get germinate, hyphae outgrow and release destructive juices which digest the host tissue. Fungal asset of free iron supports growth of hyphal forms. In immunocompetent patients, mononuclear and polymorphonuclear cells clear spores and germlings. The spores can sometimes travel into the lower respiratory system and destroy lung parenchyma, from there it can roll out into circulatory system. Fungal growth overcomes host defenses and disseminates through bloodstream or direct invasion of contagious tissue [3]. In diabetic patients with ketoacidosis, the binding of iron to transferrin is inhibited and results in elevated iron levels, which promotes the growth of mucormycosis [9].

CLINICAL MANIFESTATION: this can be classified into [8]-

Rhino cerebral mucormycosis	Pulmonary mucormycosis	Cutaneous mucormycosis	Gastrointestinal mucormycosis	Disseminated mucormycosis
One sided facial swelling, Headache, Nasal or sinuses congestion, Blepharoptosis, Acute vision loss, Fever, Black necrotic eschar.	Fever, Cough, chest pain, Shortness of breath.	Necrotic eschar with surrounding erythma and induration, Targetoid Plaque with blacken necrotic center, Blisters or ulcers.	Abdominal pain, Peritonitis, GI bleeding, Hematochezia.	It reflects the host as well as the location and degree of vascular invasion and tissue infraction in the effected organs.

DIAGNOSIS: Mucormycosis is identified by following tests-

1. Direct microscopy using fluorescent brightener and histopathology with special stains [10] (PAS {Periodic acid – Schiff} and GMS {grocott – gomori's methenamine- silver stain})
   Typical findings: non-septate / pauci-septate, ribbon like hyphae (at least 6-16 µm wide).
2. Culture – routine media at 30ºC and 37ºC [10].
   Typical finding: cottony white or grayish black colony
3. Molecular identification: PCR based-assays, HRM {high resolution melting, Target gene: 18s, ITS, 28s or rDNA [10].
4. Imaging techniques: CT scan of sinuses, lungs and chest [7].
5. Blood test – CBP: neutropenia, iron levels, blood glucose, bicarbonates, and electrolytes [7, 9].

MANAGEMENT: It includes [10] –

- Surgical treatment if possible.
- Primary prophylaxis: Posaconazole, Itraconazole, Voriconazole.
- First line treatment: Amphotericin B (AmB) lipid complex, liposomal AmB, posoconazole oral suspension.
  - Combination of liposomal AmB and posoconazole showed synergistic effect against fungal hyphae formation.

- Salvage therapy: Isavuconazole.

CANDIDIASIS

Candidiasis is caused by a type of fungus (yeast) called as "Candida". Candida can usually live inside the body, in places like the mouth, throat, conjunctival flora, gut and vagina (vulvovaginal candidiasis) without causing infection [6].

PATHOLOGY: Systemic medications such as antibiotics, anti-cancer, immunosuppressive, and Anti-cholinergic drugs are associated with oral candidiasis due to the alteration of the oral microbial flora that normally inhibits candidial growth [9]. Candida albicans are the most common infective oral candidiasis and also the source of thrush when healthy host immunity is compromised. Abnormal growth of yeast on the oral mucosa leads to desquamation of epithelial cells and results in accumulation of bacteria, keratin and necrotic tissue. This debris combines to form a pseudo membrane, which may closely adhere to the mucosa [11]. During hyposalivation, decreased anti microbial proteins leads to reduce anti fungal properties [9]. When the host defense mechanism become altered, the Yeast form converts into Hyphae form and shows its virulence traits by establishing a robust biofilm layer that strongly adhere and then penetrates into the outermost layer of the vaginal epithelium which recruits inflammatory cells, debris from lysed cell and vaginal fluid account for the vaginal discharge [12,13]. In contrast to oral thrush and vaginal yeast infection, systemic/ disseminated candidiasis is a critical infection that can affect the blood and also other vital organs which leads to mortality [14].

CLINICAL MANIFESTATIONS:

Oral cavity[15]	**Vaginal candidiasis[13]**	**Disseminated candidiasis [14]**
Whitish creamy plaques on tongue , roof of the mouth and buccal mucosa, Redness on the dorsum of the tongue and palate, Burning sensation or soarness, Pain while eating or swallowing, Cracking and redness at the corners of the mouth.	Vaginal itching , Burning, Pain or discomfort when urinating, Abnormal viginal discharge.	Hyper and / or hypothermia, Tachycardia, Hypotension, High WBC count.

DIAGNOSIS: Candidiasis is identified by following tests-

1. Direct microscopy using calcofluor or blankophor, PAS, KOH staining.
   Typical finding: pseudo hyphae [10].
2. Culture: blood or other sterilizes samples.
   Typical findings: cream like [10].
3. Serology: mannan and anti –mannan IgG tests, CAGTA (C.albicans germ tube antibody), BDG (β-D-glucan) [10].
4. Molecular identification: PCR-based assays, target gene: rDNA, ITS [10].
5. New methods: T2 magnetic resonance and MALDI-TOF technology [10].
6. Oral mucosal biopsy procedure is recommended in chronic hyperplastic candidiasis to differentiate it from leukoplakia [9].
7. Salivary assays [9].

MANAGEMENT: It includes [10]-

- Echinocandin- ex: caspofungin, micafungin, anidulafungin
- Triazoles – ex: fluconazole, voriconazole, itraconazole, clotrimazole
- Polyenes – Nystatin, Amphotericin B and its liposomes.

ASPERGILLOSIS

Aspergillosis is an opportunistic infection caused by a type of fungus called aspergillus fumigatus, which is most common species causing co-infection in COVID-19 patients, followed by aspergillus flavus [16]. The major species known to cause disease in humans are found in five aspergillus sections: Fumigati, Flavi, Nigri, Terrei and Nidulante [17].

PATHOLOGY: The infectious lifecycle of aspergillus starts with the inhalation of

airborne conidia (asexual spores), followed by conidial accumulation in the bronchial or alveolar spaces. Due to the presence of sialic acid residues on conidia, aspergillus species are found to be bind and engulfed by variety of epithelial cells including tracheal epithelial cells, alveolar type 2 cells, human nasal epithelial cells and the A549 lung epithelial cell line responsible for pathogenicity by colonization of epithelia. In healthy individuals, conidia which is not cleared by mucociliary defense mechanism reaches epithelial cells or alveolar macrophages which are mainly responsible for the phagocytosis of aspergillus conidia as well as the initiation of pro-inflammatory response that recruits neutrophils to the site of infection. Conidia that escape from macrophage associated phagocytosis can grow and become the target of infiltrating neutrophils that are able to destroy hyphae [18].

CLINICAL MANIFESTATION:

Allergic Broncho pulmonary Aspergillosis (ABPA) [19]	**Invasive Pulmonary aspergillosis (IPA) [19]**	**Aspergilloma (fungus ball develops in the air spaces of lung) [19]**	**CNS aspergillosis [19]**	**Cutaneous aspergillosis [20]**
Fever, Wheezing, Expectoration of sputum with brown plugs, Pleuritic chest pain.	Chest pain, Cough, Hemoptysis, Shortness of breath, Inflammation trachea bronchial tree.	Fever, Cough, Hemoptysis, Dyspnea.	Seizures, Cerebral infarction, Intracranial haemorrhage, Meningitis, Epidural abscesses, Ring-enhancing lesions.	Macules, Papules, Nodules, Plaques, Hemorrhagic bulla, Fever, Swelling, Induration, Tenderness.

DIAGNOSIS: Aspergillosis can be identified by the following tests –

1. Direct microscopy using calcofluor or blankophor and histopathology with special stains (ex: PAS and GMS {grocott – gomori's methenamine- silver stain})
   Typical findings: acute angle branching septate hyphae [10].
2. Culture - 37º for 2-5 days, morphological features of aspergillus [10].
3. Molecular identification – PCR-based assays, target gene: BenA, CAL and ITS [10].
4. GM test: serum and BALF (bronchoalveolar lavage fluid) [10].
5. Serology – galacto mannan test, BDG (β-D-glucan) test [10].
6. Imaging techniques – CT scan of chest [19].

MANAGEMENT: it includes –

- Surgical treatment if possible [19].
- Triazoles – ex: voriconazole, posaconazole, isavuconazole, itraconazole [10]. Posaconazole or itraconazole can be used as prophylactic treatment for organ transplantation and prolonged neutropenia patients [10].
- Polyenes- amphotericin B and its liposomes [10].
- Echinocandins – ex: micafungin, caspofungin. It can be used for salvage therapy [10].

CRYPTOCOCCOSIS

Cryptococcosis is caused is caused by a type of fungus called Cryptococcus neoformans and Cryptococcus gattii which primarily target lungs and leads to meningitis in later stages. Cryptococcus neoformans mostly commonly observed in immunocompromised individuals while Cryptococcus gattii is isolated in immunocompetent individuals and healthy hosts [20].

PATHOLOGY: The infectious Cryptococcus begins primarily by inhalation of the infectious propagules (poorly encapsulated yeast cells) from environmental vectors. Later on, yeasts are deposited in alveoli where they are encountered by alveoli macrophages. The

virulence factors of C.neoformans include capsule formation, melanin pigment production, phospholipase & urease production and thermo tolerance. The mechanism of cytotoxicity include lytic exocytosis, organelle dysfunction, phagolysosomal membrane damage and cytoskeletal alteration [21]. Host response to cryptococcal infection, mainly involves Th cells response with cytokine including human necrosis factor (TNF), interferon γ and IL-2 resulting in granulomatous inflammation. In many cases dormant yeast within the thoracic lymph nodes or a pulmonary granuloma that can persist in an asymptomatic individuals for years. In compromised cellular immunity, the yeast can reactivate and grows at the site of initial infection and also disseminate within the phagocyte which gain access to other body sites. Both direct invasion of blood brain barrier via transcytosis of free yeast forms and transport via macrophages into the CNS (the 'Trojan horse' mechanism) can be seen [20].

CLINICAL MANIFESTATION:

PULMONARY CRYPTOCOCCOSIS [20,22]	CNS CRYPTOCOCCOSIS [23]	CUTANEOUS CRYPTOCOCCOSIS [23]	EYE INFECTION [24]
Chronic cough , Hemoptysis, Low grade fever, Dyspnea, Acute respiratory distress syndrome (ARDS).	Headache, Confusion, Memory loss, Tremors, Muscle weakness, Disorientation.	Papules, Acneiform lesions, Nodules, Ulcers.	Ocular palsies, Papilledema, Irreversible, blindness.

DIAGNOSIS: Cryptoccocosis is identified by following tests –

1. Direct microscopy – CSF mixed with India ink, narrow budding encapsulated yeast [10].
2. Culture - 30º C for 7 days, in aerobic condition, urine and sputum culture.
   Typical finding – mucoid creamy colonies [10].
3. Serology – CrAg, LAT (latex agglutination test), EIA (enzyme linked immune assay), LFA (lateral flow immune assay) [10].
4. Molecular identification: Pan-fungal PCR, DNA sequencing, multiplex PCR, isothermal amplification, probe-based microarrays, target gene –IGS1, CAP5, ITS [9].
5. Biopsy – cutaneous lesions [23].
6. Radiographic findings – in case of immunocompetent patients-
   Typical findings: intrapulmonary mass up to 3 cm in size, lung consolidation or a reticulonodular pattern [22].

MANAGEMENT: it includes [10]-

Generally, the following is recommended as the preferred regimen:

(i) Induction phase - amphotericin B deoxycholate and + flucytosine, followed by fluconazole; alternative options for fluconazole + flucytosine or amphotericin B deoxycholate + fluconazole.
(ii) Consolidation phase - fluconazole.
(iii) Maintenance (or secondary prophylaxis) phase – fluconazole.

PREVENTIVE MEASURES FOR FUNGAL INFECTIONS [25]-

- Control high sugar and Monitor blood glucose levels particularly during and post COVID-19 condition.
- Use corticosteroids, antibiotics, antifungals wisely –correct timing, dose, and duration.
- Use clean, sterile water for humidifiers during oxygen therapy.
- Maintain personal hygiene.
- Wear face masks and face shields to avoid being exposure to airborne infectious agents.

- Stay away from the places where you are likely to contact molds like construction sites, compost pile and buildings that store grains.
- Ensure proper ventilation to breath fresh air.

CONCLUSION

Many studies have been shown that the common risk factors for the fungal co-infections in COVID -19 patients are reported mainly due to immune compromised conditions, high blood glucose levels, over usage of steroids & antibiotics, poor hygienic conditions and usage of tap water in humidifiers of oxygen cylinders which may leads to fatal conditions. So, Lets say BIG NO to these opportunistic infectious agents by habituating the precautionary measures.

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