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Exploring the pathogenesis of fungal infection in the gastrointestinal tract: Emerging insights and diagnostic challenges

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Abstract

In nature, fungi are abundant and can be found in extremely close contact to food, soil, mammals, and insects. These are among the most prevalent infections that can affect any organ in the body, including the gastrointestinal system in individuals with weakened immune systems, and they can have a serious negative impact on morbidity and death. The gastrointestinal system is regularly colonized and infected by various yeast and other fungus due to its constant exposure to fungi. In addition, it is the source of numerous disseminated fungal infections. The number of individuals with impaired immune systems has increased along with the occurrence of invasive fungal infections, especially in the gastrointestinal tract. Since the immunocompromised patients may exhibit unusual clinical characteristics, therefore diagnosis of fungal infections in these patients can be especially challenging. This review will focus on several significant emerging fungal infections on the GI tract in immunocompromised patients, even though *Aspergillus* and *Candida* species account for the majority of fungi diagnosed in this population of patients with compromised immune systems.

Keywords: *Aspergillus*, fungi, gastrointestinal system, immunocompromised, invasive infection

Introduction

Immunocompromised patients frequently experience fungal infections as a consequence, and endemic mycoses are among the leading infectious causes of morbidity and mortality in the general population. Over the past 20 years, as the number of individuals with impaired immune systems has climbed, so too has the incidence of invasive fungal infections in the gastrointestinal tract. Even with the advancements in laboratory technology, especially in the fields of molecular and serologic testing, it is still difficult to identify, diagnose, and classify fungal infections in this patient population^[1, 2].

Disseminated fungal disease is just as significant even if some gastrointestinal infections are caused by primary invasive fungal infections. Regardless of the kind of fungus causing the illness, the signs and symptoms of gastrointestinal fungal infections are similar and may include diarrhea, vomiting, melena, bleeding, abdominal discomfort, and fever. It can be challenging to diagnose fungal infections in immunocompromised patients since these patients may exhibit unusual clinical features. Additionally, it's crucial to keep in mind that gastrointestinal symptoms may be the first and only indications of a widespread illness.

Although most people who are described as "immunocompromised" have underlying medical conditions such as AIDS, chemotherapy, solid organ and bone marrow transplantation, or any combination of these, there are many other types of immunocompromise that can also lead to an increased risk of fungal infections. These include patients with primary immunodeficiencies, patients receiving long-term immunotherapy or steroids, very young or very old patients, diabetics, patients who are history of post-splenectomy, chronic alcoholism, malnutrition, or any other chronic debilitating disease^[3, 4].

While *Aspergillus* and *Candida* species account for most fungal infections in patients with weakened immune systems, other fungal species are becoming more prevalent and dangerous pathogens. Every patient has a different organism to which they are sensitive depending on a variety of circumstances, such as the underlying condition, the level of immunocompromise,

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and environmental factors including the patient's residence and the kinds and amounts of exposure^[5, 6].

Additionally, the host is the only source of the inflammatory response to the organism; the differential diagnosis for each given mycosis is created by the patient's surroundings, history of exposure, and particular immune system deficiencies. This analysis will concentrate on a number of significant new fungal infections that affect immunocompromised people.

Infection by filamentous fungi

Fungi in the order Mucorales are the source of the potentially fatal infection known as mucormycosis^[7]. As previously mentioned, *Aspergillus* species are known to be the most prevalent filamentous fungus in patients with impaired immune systems. Mucormycosis is becoming more common, especially in people with diabetes, hematologic cancers, and bone marrow transplant recipients. The Zygomycetes order was recently eliminated and replaced with the order Mucorales in the subphylum Mucormycotina^[8].

Diabetes and other metabolic acidosis-causing conditions, deferoxamine medication, organ or bone marrow transplant, neutropenia, deterioration of the skin and soft tissues, intravenous drug usage, neonatal preterm, and malnourishment are all linked to mucormycosis. Remarkably, there doesn't seem to be a correlation between this infection and HIV/AIDS. It seems that the incidence is rising, particularly among cancer patients. In general, the death rate is about 40%, and it is significantly greater for

patients who have hematologic malignancies and those who have had a bone marrow transplant^[9, 10].

The most common gross manifestation of gastrointestinal zygomycosis is ulceration, which is often large and has rolled, irregular borders that may resemble like malignancies. These fungi can also superinfect previously ulcerated tissues, and disseminated disease can result from a primary gastrointestinal infection. While pulmonary disease is common, gastrointestinal zygomycosis is relatively uncommon and often fatal, with mortality reportedly approaching 40-50%^[11].

Studies have shown that the histological similarities between the lesions induced by *Mucor* and related species and aspergillosis are considerable^[12]. *Aspergillus* and *Mucor* are both angiogenic bacteria that cause necrosis, infarction, and thrombosis. Although the degree of inflammation varies, neutrophils are typically seen in large quantities. Spores are not produced by *Mucor*. Seldom observed are segmented aberrant forms with interior components and varying size, round to oval appearances.^[13] Differential diagnosis of Mucormycosis mostly involves various fungal illnesses. As previously mentioned, mucormycosis and aspergillosis can resemble one another quite a bit in terms of morphology and clinical presentation. *Aspergillus*, on the other hand, has uniformly widened septate hyphae that branch at acute angles, unlike *Mucor*. *Fusarium* is a newly discovered filamentous fungal infection that is also linked to neutropenia. It is morphologically identical to *Aspergillus* and closely resembles aspergillosis in both clinical and radiographic aspects^[14].

Name of organism	Distribution	Characteristics	Clinical presentation
<i>Aspergillus fumigatus</i> , <i>Aspergillus flavus</i> and <i>Aspergillus niger</i>	Globally	Septate uniform width is called hyphae. Acute angles with regular branching. Conidial head development in lesions of the cavity	Severe necrosis accompanied by angioinvasion acute inflammation Sometimes granulomatous
<i>Candida albicans</i> ; <i>Candida tropicalis</i>	Globally	Mixture of developing yeast cells with pseudohyphae; occasionally, septate hyphae can be visible using microscopy. When using gram staining, yeast forms are Gram positive.	Generally suppurative infection, with varying degrees of ulceration and necrosis Sometimes granulomatous Periodically, angioinvasion
Mucormycosis	Mucormycosis is linked to diabetes worldwide	It is characterized by hyphae-paraociseptate, ribbon- like thin walls, branching, and haphazardity.	Severe necrosis accompanied by angioinvasion acute inflammation Sometimes granulomatous
Basidiobolomycosis	Saudi Arabia, Africa, Some parts of Asia.	Like mucor, but with fewer organisms and a "cellophane ball" appearance	Granulomas, necrosis, and eosinophilia The Splendore-Hoeppli response to living things Generates mass

Accessory diagnostic measure

Since it greatly influences the usage of antifungal medications, accurate speciation of fungal infections is essential. For the diagnosis and speciation of fungal diseases, culture is still the gold standard; nevertheless, the growth and speciation of cultures might take a long period. More importantly, culture material is not always available because to the therapeutic situation. There is also growing availability for the direct identification of fungi using the 18S rRNA sequence using polymerase chain reaction and sequencing, which may be done straight from culture material. In the event that no culture material is available, either the patient should undergo another biopsy or molecular assays should be tried.

Two serological laboratory tests are useful for differentiating between the different filamentous fungus that can be seen on a slide, in addition to molecular testing. During growth, a component of the *Aspergillus* cell wall called galactomannan is released. Because the

galactomannan assay is positive for invasive aspergillosis but negative for other invasive fungal diseases, it is a useful serologic test for identifying invasive aspergillosis. However, *Penicillium marneffe* will cross-react with the galactomannan assay. Additionally useful is the beta D glucan assay, which is negative for mucormycosis but positive for almost all disseminated fungal diseases, including *Pneumocystis* infection^[15].

Differential diagnostic measure of yeast

When one thinks of gastrointestinal infections involving yeast forms, one typically thinks of species of *Candida*, and the most common cause of fungal infection-related death in the HIV community is still *Cryptococcus*^[16]. But in the population of immunocompromised patients, numerous other important but less prevalent yeasts are becoming recognized as serious infections.

The dimorphic fungus *Penicillium marneffe* is native to several regions of East Asia^[17]. One of the most prevalent

opportunistic illnesses among Asian AIDS patients is *Penicilliosis*. Rarely have cases of this virus been reported in immunocompetent individuals, and patients with it who are HIV-negative frequently also suffer from other immunocompromising illnesses such autoimmune diseases, hematologic malignancies, malnourishment, or other incapacitating infections. The lungs and liver are the organs most frequently affected by *P. marneffei*, then the GI tract. Within a few weeks, dissemination can happen and can be lethal very quickly, particularly in people with impaired immune systems [18, 19].

After infecting the mononuclear phagocyte system, the organism grows inside histiocytes, which expand to hold more and more organisms. There are three possible inflammatory responses: granulomatous, suppurative, and mixed. The spherical to ovoid creatures pack and spread out the macrophages that are engaged. Necrosis becomes more prevalent as the lesions enlarge, and the macrophages may lyse and release free organisms. The fungus is usually small (2-5 microns), resembling *Histoplasma*; however, occasionally, they can be up to 20 microns long, elongated, or curved, with a central septum and rounded ends. Furthermore, *P. marneffei* split by fission at their central septum, meaning they do not bud [20].

Differential diagnosis of some common fungi

Histoplasmosis: Since both organisms can be intracellular and have comparable sizes, *Histoplasma capsulatum* is the frequent organism in the morphological differential diagnosis. Although *Histoplasma capsulatum* is occasionally endemic in certain regions, it is also known to occur in other nonendemic places. Over 80% of individuals with disseminated infection experience GI involvement. Diffuse lymphohistiocytic infiltrates and nodules, typically affecting the mucosa and submucosa with ulceration, are among the histologic findings. Numerous organisms may be observed in immunocompromised patients with almost no tissue reaction. *Histoplasma*, on the other hand, can be distinguished from buds by their pointed pole [21, 22].

Cryptococcosis: In the population of immunocompromised patients, *Cryptococcus neoformans* is a yeast that is frequently found and is an uncommon but significant source of gastrointestinal infection [23]. The majority of patients with GI cryptococcosis also have meningeal and pulmonary diseases that are related with their multisystem organ involvement and hematogenously disseminated disease. The type and degree of the inflammatory response vary depending on the host's immunological status; it can be suppurative, necrotizing, and frequently granulomatous, or it might be almost nonexistent, as in the case of anergic hosts. Compared to *P. marneffei*, *Cryptococcus* is bigger and usually exhibits a wide range of sizes. Round to oval in shape, *Cryptococcus* frequently has a clearing "soap-bubble" surrounding it, which on H&E sections represents the capsule's weak staining. In addition, it lacks *P. marneffei*'s transverse septum and frequently budding. However, mucicarmine staining will frequently yield a negative result for capsule-deficient *Cryptococcus neoformans* and *Cryptococcus gattii*, a new variety of *Cryptococcus* [24, 25].

Pneumocystosis

Another significant entity in this patient cohort is *Pneumocystis jirovecii*. Even though *P. jirovecii*'s life cycle

more closely resembles that of a protozoan, there is strong molecular evidence that *P. jirovecii* is more similar to fungi. In addition to patients with AIDS, *Pneumocystis* infection has infrequently been recorded in the context of organ transplant, hematologic malignancy, other immunodeficiency conditions, and steroid therapy. Extrapulmonary, or GI, involvement is not uncommon in the immunocompromised population. Additionally, there have been reports of a correlation between *pneumocystis* infection and infliximab therapy, an immunosuppressive medication used to treat rheumatoid arthritis and Crohn's disease [26, 27].

Mucosal arteries or the lamina propria may exhibit microscopic, granular, foamy eosinophilic casts resembling those observed in lung *Pneumocystis* infection. Similar to the lung, a wide range of inflammatory reactions could manifest, such as necrosis, granulomatous inflammation, and significant macrophage infiltrates. Many have distinctive interior structures that are paired or single comma-shaped [27].

Candida glabrata, which has microscopic budding yeast forms comparable in size to *Histoplasma* and *P. marneffei* but without hyphae or pseudohyphae, is one of the other organisms in the differential diagnosis. In addition, *C. glabrata* have more buds than *Histoplasma*, are frequently extracellular, and do not have the "halo" that *Histoplasma* has in tissue slices. Unlike *P. marneffei*, *C. glabrata* does not normally pack and spread out macrophages and does not have a transverse septum. On Gram stain, yeast forms of the *Candida* species will also stain Gram positive [12].

Subjective diagnostic measure

Similar to filamentous fungi, precise speciation of these invasive yeasts is essential, as it greatly impacts therapy; cultures are very useful when material is available, but tissue sections may have diagnostic features that enable therapy to be instituted without waiting for the results of mycological cultures; molecular assays are becoming more and more accessible for many of these yeasts, and they can frequently be carried out straight from the paraffin block; immunohistochemistry and in-situ hybridization assays are available for some of these entities, but they are not easily obtained.

Serologic testing may also be useful in this type of fungal infections, as previously mentioned [15]. Due to their distinct tissue appearances, *P. marneffei* and *Aspergillus* will cross-react in the galactomannan assay used to diagnose *Aspergillus* infections. This could be useful. Because the beta D glucan assay is positive for *pneumocystis* infection, it is also beneficial [28].

Advance serological diagnostic measure

Making diagnostic decisions is made easier by serological testing, which offers a speedier method of identifying the fungi causing the disease. These tests are performed to show the presence of an antigen or antibody in serum or other bodily fluids related to a possible fungal infection. As a potential prognostic marker, serology-based tests have the benefit of being non-invasive and providing fast findings, in contrast to culture procedures [29]. Samples such as blood, urine, sputum, etc. can be used for these tests. Even in cases when the fungus species is nonculturable, the culture test is negative, or the patient is difficult to obtain a sample from because of an underlying medical condition, a serology test may yield a positive result [30, 31]. Immunocompromised or

immunosuppressive patients are a key factor in restriction for antibody-based testing as they are unable to elicit enough amounts of antibodies and may produce false negative results. Fungal antigen detection in these cases, however, provides the answer. Secreted during fungal growth, polysaccharides or proteins (fungal antigens) can end up in a variety of physiological fluids, which makes them excellent for detecting as potential disease markers in both immunocompetent and immunocompromised individuals. However, there is still significant space for improvement in serology-based testing, as has been addressed under each subheading^[32].

Advance molecular based diagnostic measure

Recently, the science of mycology has witnessed significant advancements in molecular techniques to support the diagnosis and identification of fungi. Compared to culture tests, molecular methods offer a detection approach with fewer variances and a high-performance output, providing data faster. The fact that there are numerous commercial assays for fungal identification demonstrates how well-developed, standardized, and validated fungal PCR tests have become. The current section will go over the latest advancements in molecular-based methods that make them more accurate in the identification of fungal pathogens, step-by-step. From talking about the new PCR assays and related advances to using newer approaches like DNA metabarcoding, evolution of new sequencing, and bioinformatic tools.

Conclusion

The literature on fungus-related infections of the gastrointestinal tract is the primary topic of the present study. It offers fundamental knowledge about causes, symptoms, and treatment options and is simple to utilize in therapeutic settings. When patients experience colonic symptoms, especially in cases when there is immunocompromised patient, physicians should be mindful of this fungal organism. While numerous fungal infections, such as aspergillosis, candidiasis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, penicilliosis, pneumocystosis, scedosporiosis, and zygomycosis, have been linked to colonic disease, understanding the variations in epidemiology, risk factors, clinical manifestations, and pathological findings will assist medical professionals in diagnosing and treating these infections. Even while appropriate antifungal medication substantially improves results, cases of aspergillosis and zygomycosis still have high fatality rates.

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