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Emergomycosis: A Looming Fungal Threat of Public Health

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Abstract

Several infectious pathogens have emerged in the past posing a great challenge to the public health authorities throughout the world. Fungal infections are considered as a neglected threat to global human health. Emergomycosis, an emerging fungal infection caused by the genus Emergomyces within the family Ajellomycetaceae, presents significant problems in diagnosis and management, particularly among immunocompromised individuals. This thermally dimorphic pathogen, previously classified under Emmonsia, exhibits diverse clinical manifestations, including cutaneous lesions, pulmonary disease, and systemic dissemination. Diagnostic hurdles involve histopathology, fungal culture, and molecular techniques, thus underscoring the need for standardized diagnostic criteria. Treatment primarily relies on antifungal agents, emphasizing the importance of following established guidelines for endemic mycoses. Enhanced clinical awareness, collaborative efforts among healthcare providers and microbiologists, and robust public health strategies are essential for improving surveillance, diagnostics, and patient outcomes in emergomycosis.

Keywords: Emerging Dimorphic Fungi; Emergomyces; Emergomycosis; Public Health

Introduction

Fungi are living eukaryotic microbes that are widely prevalent in our environment, and are responsible for causing disease in humans and animals worldwide [1-5]. Fungal diseases affect approximately one billion people annually, resulting in more than 1.5 million deaths [6]. Recent years have witnessed the emergence of fungal pathogens, which cause significant morbidity and mortality in immunocompetent and immunosuppressed individuals, including with HIV infection, solid organ transplantation, hematological malignancies, diabetes, tuberculosis, and immunosuppressant use [2-11]. The infections due to emerging fungi are reported to occur in both sexes, all age groups, and in developed and developing nations [3-5]. Fungal infections are constantly evolving, with new genera and species increasingly implicated in human diseases, posing significant diagnostic and management challenges. Recently, a novel dimorphic fungus closely related to Emmonsia species has been observed in immunocompromised individuals, highlighting the dynamic nature of these pathogens [11]. Specifically, emergomycosis,

an emerging thermally dimorphic fungal infection, is caused by the genus Emergomyces formerly classified under the genus Emmonsia, which belongs to the order Onygenales and the family Ajellomycetaceae [12].

The genus Emergomyces comprises seven unique species: E. africanus, E. canadensis, E. crescens, E. europaeus, E. orientalis, E. pasteurianus, and E. sola, where except E. sola [non-pathogenic soil saprobe, not associated with human infections], all the other species cause infections [11-13]. Emergomycosis, prevalent among immunocompromised individuals, manifests primarily as widespread skin lesions and pulmonary disease [14]. Typically, patients with emergomycosis have underlying conditions such as HIV infection, solid organ transplantation, hematological malignancies, or are on immunosuppressant medications [11]. Infections with Emergomyces africanus frequently present with cutaneous lesions, including papules, plaques, nodules, or ulcers, often with extensive distribution [14,15]. Pulmonary involvement is also common, with 86% of patients in a South African series exhibiting abnormal chest X-rays, showing patterns such as diffuse reticulonodular disease, consolidation, effusions, and lymphadenopathy [14]. Additionally, emergomycosis can affect the gastrointestinal tract, liver, lymph nodes, and bone marrow [14]. However, limited pulmonary disease has been rarely reported, such as in the single documented case of Emergomyces europaeus infection [16].

Emergomycosis can be diagnosed through a biopsy of the afflicted tissue for histology and fungal culture. Histopathological findings often reveal tiny [2-5μm] yeasts with narrow-based budding, best visualized using fungal stains [15]. The diagnosis can be confirmed by cultivating Emergomyces species from clinical samples. In cases where fungal cultures are negative or not performed, PCR amplification and sequencing of the internal transcribed spacer [ITS] region from fresh, afflicted tissue can accurately identify the pathogen [12,14]. Emergomyces species thrive well on standard fungal media, such as Sabouraud agar, malt extract agar, or potato dextrose agar, incubated at 24-30°C. Initially, the colonies are glabrous and yellowish-white to tan, but after three weeks, they become powdery, slightly elevated, and wrinkled, with 2.5 to 3.5 cm diameters. Microscopically, the mold phase of Emergomyces species is characterized by thin conidiophores that branch off hyphae at an angle, forming “florets” of short secondary conidiophores, each bearing a single tiny subspherical conidium. The transition from the mold to the yeast phase is facilitated by spreading colonies onto potato dextrose agar or malt extract agar and incubating them at 35°C [11,12,17].

Current treatment guidelines for emergomycosis are based on observational studies and expert opinion, mirroring those for histoplasmosis [11]. When available, liposomal amphotericin B is preferred over deoxycholate for the initial 10 to 14 days treatment of immunocompromised patients due to its more favorable toxicity profile. Following immunological reconstitution, patients should continue treatment for an additional year with itraconazole or another newer azole. Fluconazole should be avoided due to the observed high minimum inhibitory concentrations [11,18,19].

Emergomycosis

Etiology

Emergomycosis is an emerging thermally dimorphic fungal infection caused by the genus Emergomyces [formerly classified under Emmonsia], belonging to the order Onygenales and the family Ajellomycetaceae [12,17]. The taxonomy of fungal species within the Ajellomycetaceae is rapidly evolving through phylogenetic and phylogenomic approaches, leading to the description of multiple new species and genera. Furthermore, phylogenetic studies revealed that Emmonsia species were closely related to the genus Emergomyces and Blastomyces leading to its reclassification as either Emergomyces or Blastomyces [13]. Multi-gene phylogenetic analyses of Emmonsia and Emmonsia-like fungal species have revealed that the genus is polyphyletic [12,17]. Based on molecular phylogenetic analyses, seven species are currently placed in the genus Emergomyces: Emergomyces africanus, Emergomyces canadensis, Emergomyces crescens, Emergomyces europaeus, Emergomyces orientalis, Emergomyces pasteurianus, and Emergomyces sola [12,17].

Geographical Distribution

The fungus is widely spread across the globe, with the type species, Emergomyces pasteurianus reported from Europe [including Italy [20], Spain, France [ex-Georgia] [21], and the Netherlands [22]], Asia [China [23] and India [ex-Nepal] [24]], and Africa [Uganda [ex-Rwanda] and South Africa [12]]. Emergomyces africanus has been reported from South Africa and Lesotho [12,14]. Emergomyces canadensis has been reported from Canada [Saskatchewan] and the United States [Colorado and New Mexico] [11]. Emergomyces orientalis has been reported from China [25], and Emergomyces europaeus has been reported once from Germany [16]. However, given the increasing prevalence of HIV/AIDS, it is assumed that the disease has a global distribution (Figure 1), with many cases going undetected [26]. The classification and distribution of emergomycosis are summarized in Table 1 and Figure 1.

Species	Regions Reported
Emergomyces pasteurianus	Europe [Italy, Spain, France [ex-Georgia], Netherlands], Asia [China, India [ex-Nepal]], Africa [Uganda [ex-Rwanda], South Africa]
Emergomyces africanus	South Africa, Lesotho
Emergomyces canadensis	Canada [Saskatchewan], USA [Colorado, New Mexico]
Emergomyces orientalis	China
Emergomyces europaeus	Germany

Table 1: Classification and geographic distribution of Emergomyces species.
Source: [12,17,19].

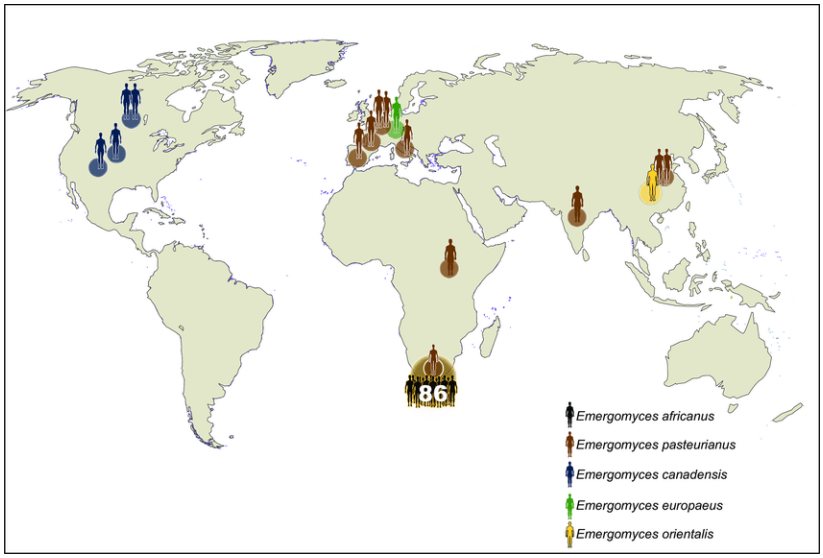

Figure 1: Global geographic distribution of reported cases of emergomycosis.
Note: Each icon represents a single case except for Emergomyces africanus in South Africa.
Source: Map created by Institute of Tropical Medicine, Antwerp.

Pathogenesis

Emergomyces species discharge aerosolized conidia into the environment during the mold phase of their life cycle. In a murine model of pulmonary infection established using a clinical isolate of E. africanus [CBS 136260], it was observed that both conidia and yeast forms caused pulmonary and disseminated infection with organisms isolated from the lung, spleen, liver, and kidney [27]. Inhaling these conidia can cause lung disease in individuals who are susceptible to the temperature-dependent budding process that turns conidia into yeast-like cells. When yeast-like cells spread hematogenously across the body's macrophages, extrapulmonary sickness results. The most commonly reported symptom is cutaneous involvement, while practically any area of the body can be impacted [11]. Experimental infections have demonstrated susceptibility of golden hamsters and mice [28,29]. In one study, it was found that intraperitoneal inoculations with Es. africanus were fatal to wild-type mice at doses of 106 conidia, whereas lower doses did not cause disease [although the organism could still be cultured from their livers and spleens with inoculae as low as 102 conidia] [29]. C57BL/6 mice were more susceptible to disease than BALB/c mice [28]. Further work is underway to understand the pathogenesis of disease and the immunology of infection.

Clinical Signs

The primary route of infection is presumed to be the inhalation of airborne conidia released from saprophytic mycelia in soil [11]. Once inside the human host, these conidia transform into yeast-like cells capable of replication and dissemination beyond the lungs. All reported cases of disseminated infection caused by Emergomyces species have occurred in immunocompromised adults, predominantly those with advanced HIV infection. Other underlying risk factors include neutropenia, solid organ transplantation, hematological malignancies, and the use of immunosuppressive drugs [29].

Emergomycosis manifests as a multisystem disease involving the skin, lungs, liver, spleen, bone marrow, lymph nodes, brain, and cervix. In a study from South Africa, 96% of patients with disseminated disease exhibited cutaneous lesions, all of whom had severely low CD4+ T cell counts [median CD4 count of 16 cells/mm3] and significant anemia [14]. Cutaneous involvement presents as umbilicated papules, nodules, ulcers, verrucous lesions, crusted plaques, and erythema [14,30]. Pulmonary manifestations include diffuse and focal reticulonodular infiltrates, consolidations, lobar atelectasis, effusions, and hilar lymphadenopathy. Limited pulmonary disease has been noted in the single reported case of emergomycosis caused by Emergomyces europaeus [16]. The diverse clinical presentations of disseminated emergomycosis are summarized in Table 2.

System Involved	Clinical Manifestations, Laboratory, and Imaging Findings
Skin	Umbilicated papules, nodules, ulcers, verrucous lesions, crusted hyperkeratotic plaques, erythema
Respiratory system	Upper respiratory: epistaxis, nasal congestion, oroantral fistula Lower respiratory: pneumonia, lobar atelectasis Imaging findings: diffuse and focal reticulonodular infiltrates, consolidations, lobar atelectasis, effusions, and hilar lymphadenopathy
Hematologic system	Anemia, thrombocytopenia
Central nervous system	Altered mental status, headache, seizure, ataxia, loss of visual acuity, personality changes Laboratory findings: Cerebrospinal fluid pleocytosis, low Cerebrospinal fluid glucose, elevated Cerebrospinal fluid protein
Gastrointestinal system	Laboratory findings: elevated levels of serum bilirubin, alkaline phosphatise, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase Imaging findings: hepatomegaly, abnormal echogenicity of liver, splenic lesions, lymphadenopathy, abdominal mass
Genital system	Endocervical mass

Table 2: Clinical manifestations of Emergomycosis.
Source:[29,30].

Diagnosis

The diagnosis of emergomycosis poses a challenge for clinicians and microbiologists. Studies indicate that three-quarters of patients with emergomycosis get misdiagnosed as tuberculosis and receive treatment for the latter. Among the mycoses, emergomycosis should be considered in the histoplasmosis differential diagnosis because the two diseases have significant clinical and histopathological findings that overlap [7]. The cases are diagnosed by microscopy, histopathology of sample and isolation of fungus from skin lesion, bone marrow and sputum etc. The identification of the isolates is confirmed by sequencing internal transcribed spacer region of rDNA, beta-tubulin, actin and intein PRP8. Internal transcribed spacer [ITS] sequencing of ribosomal DNA is the gold standard for identification but its application is jeopardised in resource limited settings [8]. Blood, skin tissue, bone marrow aspirate and/or trephine biopsy, lymph node aspirate, induced sputum, or bronchoalveolar lavage [BAL] specimens are appropriate for mycological investigations [31]. Pal sunflower seed medium, which was initially developed in 1980 for the rapid diagnosis, and epidemiological investigation of cryptococcosis, should be tried for the cultivation of fungi, which are implicated in the etiology of emergomycosis [4,5].

Treatment

The management of the infection is complicated due to the lack of defined diagnostic and therapeutic guidelines. However, systemic antifungal therapy is the most important method for restoring severely infected skin to health. Currently, there are four classes of antifungal drugs used for treating systemic mycoses: polyenes [such as amphotericin B], azoles [including fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazole], echinocandins [such as caspofungin, micafungin, and anidulafungin], and antimetabolites [like flucytosine]. Among these, Amphotericin B, a nephrotoxic antifungal, is usually the first-line therapy for emergomycosis, usually for 1-2 weeks, followed by itraconazole or another azole for maintenance [32]. However, liposomal amphotericin B is favoured due to its low toxicity and can be used instead of deoxycholate amphotericin B in treating emergomycosis, according to the WHO guideline for cryptococcosis [33]. However, it is either prohibitively expensive or unavailable in most resource-poor situations. Thus far, liposomal amphotericin B is available in just 7 African nations [Benin, South Africa, Egypt, Tanzania, Mauritania, Eswatini, and Ethiopia] [34]. Hence, specific treatment guidelines for emergomycosis are not yet established due to the lack of randomized controlled

trials. In the absence of such guidelines, it is recommended to follow the Infectious Diseases Society of America guidelines for managing endemic mycoses in immune compromised individuals [35]. However, it is advised that further research should be conducted to develop safe, effective, and low-cost drugs for the treatment of emergomycosis.

Conclusion and Recommendations

Emergomycosis, caused by the genus Emergo myces, represents a significant and evolving challenge in fungal infections, particularly among immune compromised individuals. With its varied clinical presentations spanning multiple organ systems and the potential for systemic dissemination, emergomycosis underscores the importance of heightened awareness among clinicians.

Based on the above conclusion, the following recommendations were forwarded:

- Clinicians should maintain a high level of suspicion for emerge mycosis, particularly in immune compromised patients with unusual skin lesions or pulmonary symptoms, due to the disease's difficulty in diagnosis and frequent misunderstanding.
- Patient management would be greatly improved by the development of uniform diagnostic criteria and treatment guidelines through thorough clinical studies.
- Promoting early detection and effective treatment of emergomycosis requires raising the knowledge of healthcare professionals about the disease, particularly its epidemiology and clinical symptoms.
- Collaboration among physicians, microbiologists, and public health officials can improve surveillance, increase diagnostic capacity, and create effective treatment and prevention plans.
- An attempt should be made to investigate the efficacy of Pal sunflower seed medium for the isolation of Emergomyces from the clinical specimens of the patients.

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Author's Contribution

All authors worked for the manuscript.

Conflict of Interest

There was no conflict of interest among the authors.

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