Current Fungal Infection Reports (2018) 12:44–50
https://doi.org/10.1007/s12281-018-0308-y

EPIDEMIOLOGY OF FUNGAL INFECTIONS (T CHILLER AND JW BADDLEY, SECTION EDITORS)

# *Emergomyces*: a New Genus of Dimorphic Fungal Pathogens Causing Disseminated Disease among Immunocompromised Persons Globally

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Published online: 10 February 2018


## Abstract

**Purpose of Review** The emergence of a group of previously unknown or unrecognized dimorphic fungal species causing systemic human disease resulted in taxonomic shifts and the creation of a new genus, *Emergomyces*, within Onygenales. We review the morphology, taxonomy, physiology, and ecology of *Emergomyces* spp., and the epidemiology, clinicopathology, diagnosis, and management of disease.

**Recent Findings** *Emergomyces* species have been reported as causes of human disease in Europe, Asia, Africa, and North America. *Es. pasteurianus* is most cosmopolitan, and *Es. africanus,* in southern Africa, causes the largest reported disease burden; in fact, emergomycosis is the most common endemic mycosis diagnosed in South Africa. The classic clinical picture is of disseminated disease, often with cutaneous involvement, in immunocompromised individuals.

**Summary** Members of the genus *Emergomyces* are uncommon but important agents of systemic disease in immunocompromised hosts worldwide. Knowledge gaps include the biology of the fungus, and the pathophysiology and management of disease.

**Keywords** Emergomyces · emergomycosis · emmonsia · emmonsiosis · dimorphic · fungus · mycosis · opportunistic infection · endemic mycosis

## Introduction

Recently, a new genus of thermally-dimorphic fungi within the Ajellomycetaceae was described to accommodate *Emmonsia pasteuriana* and several newly-named species of "*Emmonsia*-like" fungal pathogens [1]. *Emergomyces* was so-named because of the apparent emergence of related but previously unknown fungi causing systemic disease in immunocompromised hosts globally. Evidence of the earliest case of this mycosis (known as emergomycosis, formerly disseminated emmonsiosis) dates back to at least 1992 [2]; however, the recent recognition of these fungi and the disease they cause are attributed more to the contemporary use of molecular identification techniques in clinical and research laboratories than their sudden emergence as human pathogens [3].

This article is part of the Topical Collection on *Epidemiology of Fungal Infections*

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## Etiological Agents

Emergomycosis is caused by several fungal species within the newly-described genus, *Emergomyces* [1]. The type species, *Es. pasteurianus*, was first described as *Emmonsia pasteuriana* in 1998, based on apparent relatedness to *Ea. crescens* and *Ea. parva* [4]. Similarly, *Es. africanus* was thought to be a novel *Emmonsia* species when it was first reported [3]. The most-recently described species is *Es. orientalis* [5], reported from Asia; additional proposed species include *Es. europaeus*, currently represented by a strain isolated from the lung of a patient with rheumatoid arthritis in

Germany [6] and *Es. canadensis,* from immunocompromised patients in Canada and the USA [2, 7].

## Taxonomy

The genus *Emergomyces* is currently placed within the family Ajellomycetaceae alongside other thermally-dimorphic fungal pathogens such as *Histoplasma*, *Blastomyces*, and *Paracoccidioides* [1, 8]. Although some members of the group were initially described as novel species of *Emmonsia*, subsequent phylogenetic analyses revealed the genus *Emmonsia* to be polyphyletic [9, 10]. Consequently, a need was identified to accommodate several emerging thermally-dimorphic *Emmonsia*-like fungi distinguished in part from *Ea. parva* and *Ea. crescens,* the classic *Emmonsia* species, by small yeast-like cells rather than adiaspores as the parasitic phase [1, 11]. To date, only the anamorph (asexual form) of *Emergomyces* has been described [1]. Whole genome sequencing data show that both *Es. africanus* and *Es. pasteurianus* contain the alpha mating-type locus (MAT1–1) [1].

## Epidemiology

Cases of emergomycosis have been reported from four continents: Europe, Asia, Africa, and North America. The true geographic range of *Emergomyces* spp. is unknown.

The largest described burden of emergomycosis is among HIV-infected persons in South Africa, where most cases are attributed to *Es. africanus.* In fact, emergomycosis is now recognized to be the most common endemic mycosis in South Africa [8]. Cases have since been diagnosed in six of nine provinces [8, 12], which include (in decreasing frequency) Western Cape [3, 12–15], Eastern Cape [12], Gauteng [8, 12, 16], Free State [12], Mpumalanga [12], and KwaZulu-Natal provinces (authors' unpublished data). In addition, emergomycosis has been reported in a patient from Lesotho [12]. Although country-level surveillance data is lacking, a clinical and laboratory surveillance study diagnosed 17 culture-proven cases of emergomycosis over 15 months at public hospitals in Cape Town (authors' unpublished data), a city in Western Cape province with an estimated 3.7 million inhabitants [17] and an estimated HIV prevalence of 5.2% [18].

*Es. pasteurianus* appears to be the most cosmopolitan species, causing disease on three continents. Emergomycosis due to *Es. pasteurianus* has been diagnosed in patients from Italy [4], Spain [19], France [20], India [21], China [22, 23], and South Africa [8].

Disease caused by *Es. orientalis* has been diagnosed only once, from a patient in Shanxi, China whose only reported comorbidity was diabetes mellitus [5]. Emergomycosis has been recently described in North America [8]. Four cases have been diagnosed, in immunocompromised patients from Saskatchewan, Canada, and Colorado and New Mexico, USA [2, 8].

Another proposed new species has been reported to cause disease in a single case: a farmer from Germany treated with corticosteroids for rheumatoid arthritis who was diagnosed with a chronic pneumonia [6].

Nearly all cases of emergomycosis have been reported in immunocompromised patients. Most cases have been diagnosed in patients with advanced HIV-infection [3, 4, 7, 12, 14–16, 21, 24] or other defects of cell-mediated immunity, like immunosuppression for organ transplantation [2, 13, 24].

## Ecology

Knowledge of the environmental reservoir of *Emergomyces* spp. is important for understanding the organism's biology, and may be useful in predicting the geographic range; for other described thermally-dimorphic fungi, the environmental reservoir harboring the mold-phase is soil or other organic material [25]. When the mold is disturbed, conidia are aerosolized, and may become inhaled by mammals and, in some cases, cause disease [25].

Environmental sampling studies have only been reported for *Es. africanus*. Molecular detection of *Es. africanus* was demonstrated in 30% of soils sampled from South Africa (mostly from Western Cape), including from a wide range of soil habitats [26]. Soil samples were also evaluated for culturable fungus using direct culture methods as well as indirect culture, including via mice inoculation; despite the finding that the latter technique could detect as few as $10^2$ conidia in 10 g of soil (similar to PCR), attempts to culture *Es. africanus* from soil have thus far been unsuccessful [26].

Schwartz et al. also used molecular techniques to detect *Es. africanus* propagules trapped in air samples collected in an industrial area of Cape Town [27]. The presence of airborne *Es. africanus* propagules was observed on 10% of all days, suggesting that exposure to the conidia may be common even in urban areas.

To date, animal infection with *Emergomyces* has not been demonstrated. Cronjé et al. did not find evidence of *Es. africanus* in the lungs of 1402 animals (comprising 23 species) from South Africa screened with PCR [28]. To our knowledge, no cases of veterinary disease have been reported.

Although exposure to *Es. africanus* conidia is likely common in some heavily-populated endemic areas [29], only a small portion of patients with severely impaired cell-mediated immunity develop emergomycosis [15]. The reasons why only some exposed immunocompromised persons develop the disease are not clear, and further investigation is warranted.

## Clinical Manifestations

Emergomycosis is typically a disseminated disease of immunocompromised hosts. The most common clinical manifestation—best described for disease caused by *Es. africanus* [12])—is the appearance of widespread cutaneous lesions, which can include papules, plaques, or ulcerations [3, 4, 7, 12, 22, 23] (Fig. 1).

Pulmonary disease is also common, and three-quarters of patients have abnormal chest radiographs [12]. Radiographic changes may include diffuse interstitial infiltrates, focal airspace disease, and/or hilar lymphadenopathy. In a minority of cases, upper airway involvement is reported, with symptoms such as epistaxis, rhinorrhea, or nasal congestion [12]. Although inhalation is presumed to be the route of infection [10], disease limited to the lungs is uncommon [6]. Extrapulmonary disease involving organs other than skin has been reported, including of liver [30], lymph node [7, 12], and cervix [7].

In at least half of HIV-infected patients, the diagnosis of emergomycosis only becomes apparent after the appearance or worsening of widespread cutaneous lesions after initiation of antiretroviral therapy (ART), suggesting an unmasking immune reconstitution inflammatory syndrome (IRIS) [12, 15].

## Pathogenesis

Knowledge of the pathogenesis is inferred from clinical observations and extrapolation from related dimorphic fungi. Emergomycosis is presumed to occur following the inhalation of conidia released from environmental, saprobic mycelia [10]. In the lungs, a temperature-dependent transformation of the conidia to yeast-like cells occurs. A molecular switch, analogous to *DRK1* (dimorphism-regulating kinase-1) in *B. dermatiditis* and *H. capsulatum* [31], has not yet been identified. In the absence of a competent host immune response, the yeast-like cells are capable of causing pulmonary and, upon hematogenous dissemination, extrapulmonary disease [3].

Among HIV-infected individiuals, the host response appears to be a function of CD4+ T-lymphocyte count, mediated by ART status. The histopathological picture in patients with low CD4 counts, who are not yet on ART, is of many yeast-like cells, with little or no inflammatory response; patients on ART demonstrate a more robust immune response, with few yeast-like cells [3]. This finding, combined with the clinical observation that many patients develop new or worsening cutaneous lesions upon ART initiation [12], suggests that the phenomenon of unmasking IRIS is common. In contrast, paradoxical IRIS (apparent clinical worsening of previously controlled disease upon ART initiation) appears to be uncommon [32].

## Diagnosis

Diagnosis of emergomycosis is currently made by detection of the yeast phase from affected tissue during histopathology examination or by isolation of the fungus from appropriate specimens such as skin tissue, blood, bone marrow, respiratory tissue, liver tissue, and lymph node tissue [10]. Non-culture-based methods to detect fungal antigens or DNA directly from clinical specimens could potentially improve the speed of diagnosis but are not yet commercially available.

### Histopathology

Histopathological examination of affected tissue is, in most cases, the fastest way to establish the diagnosis of deep fungal infections [33]; however, specificity is limited because the yeast-like cells of *Emergomyces* morphologically resemble those of *H. capsulatum* and, to a lesser extent, *Sporothrix schenckii* sensu stricto (Fig. 2) [15]. Small (2 to 5 μm), intracellular and extracellular oval to round narrow-budding yeast-like cells may be observed in tissue sections stained with hematoxylin and eosin, Periodic acid-Schiff, Gomori's methenamine silver, or Wright-Giemsa. The yeast-like cells of *Emergomyces* (Fig. 2a, b) are similar in size and morphology to those of *H. capsulatum* (2 to 5 μm) (Fig. 2c) [15] but smaller than those of *B. dermatitidis* (10 to 15 μm) which

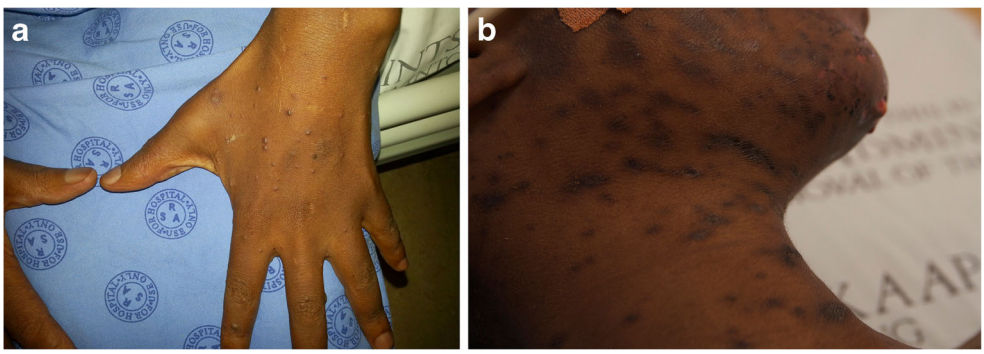


**Fig. 1** Cutaneous lesions in two patients caused by *Emergomyces africanus*. **a** Widespread papules. **b** Widespread plaques and ulcers. (Photographs courtesy of Dr. Che Daniels and Dr. Rosie Burton, respectively, Khayelitsha District Hospital, Cape Town, South Africa). Reproduced with permission from [39]

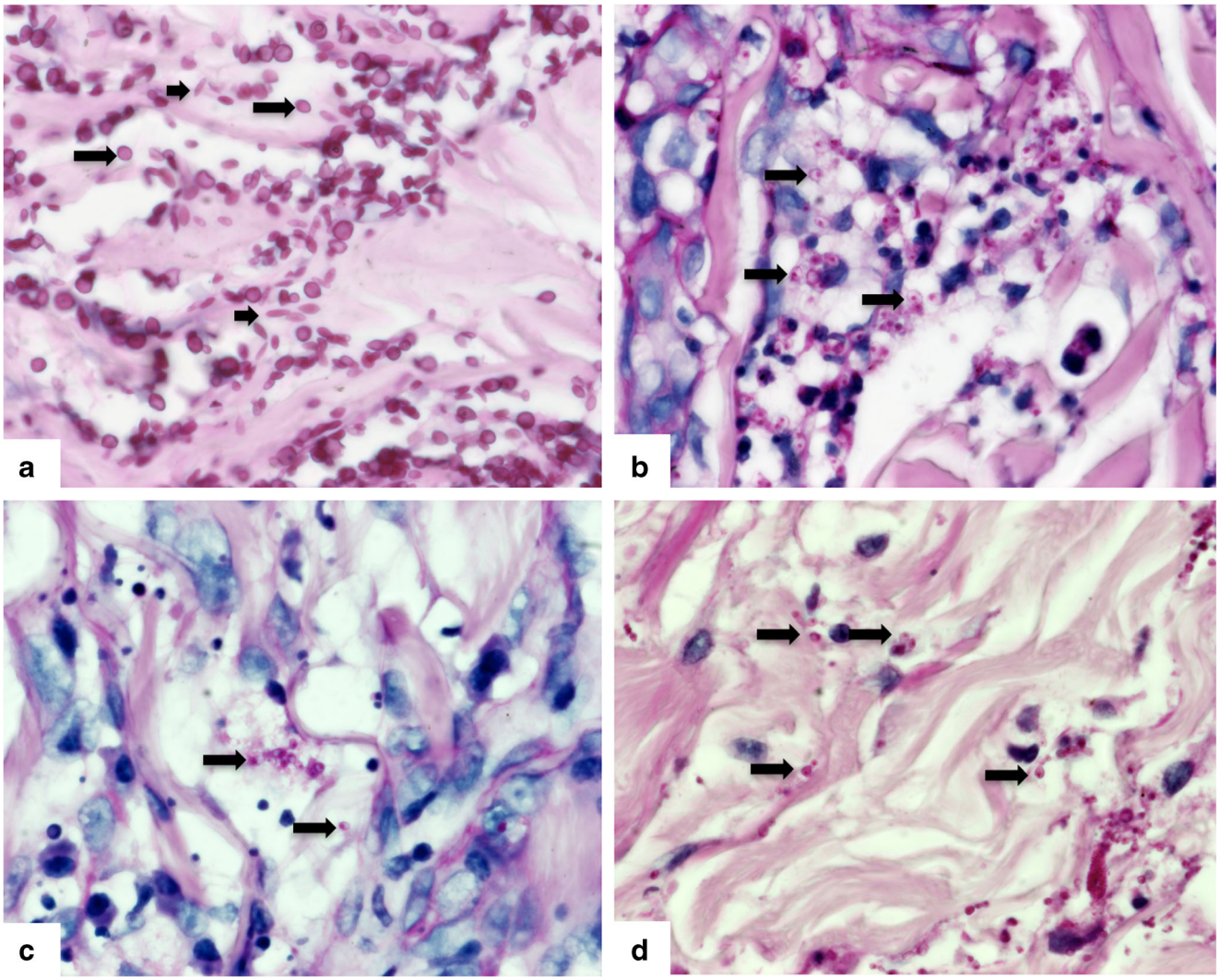


**Fig. 2** Histopathology of skin biopsies from South African patients with HIV-associated systemic mycoses. **a** *Sporothrix schenckii* sensu stricto. Ovoid yeast-like forms that measure 2–8 μm in size (long arrows), as well as elongated "cigar bodies" that vary in diameter from 2 to 4 and in length from 4 to 10 μm (short arrows). The larger size of the yeast-like forms and the presence of elongated forms are helpful to distinguish *S. schenkii* from *Histoplasma capsulatum* and *Emergomyces africanus.* (Periodic Acid Schiff [PAS], ×1000). **b** *H. capsulatum*. Round to ovoid yeasts that vary in size from 2 to 3 to 3–5 μm with single budding nuclei and thin walls. Intra- and extracelluar organisms are present (arrows). (PAS, ×1000). **c**, **d** *Es. africanus*. Morphological features of fungal elements in tissue sections simulate the yeasts of *H. capsulatum* in particular (arrows). (PAS, ×1000). Reproduced with permission from [15]

may demonstrate budding with broad-bases [33]; while the yeast-like cells of *S. schenckii* are similar in size, they may also assume a more elongated morphology (Fig. 2 d) [15]. Affected tissue should be submitted in saline for fungal culture to make an etiological diagnosis.

## Culture

Appropriate biosafety precautions should be implemented when culturing these agents. There are currently no risk assessments published by national or international bodies, but given that disease has only been reported in immunocompromised individuals, we recommend that mycelial cultures should be handled under biosafety level 2 conditions (i.e., in class II biosafety cabinets with additional personal protective equipment such as N95 respiratory masks).

*Emergomyces* spp. can be isolated using standard fungal media, such as Sabouraud agar, malt extract agar, or potato dextrose agar [1, 3]. Growth is observed after 7 to 30 days of incubation at 24 to 30 °C. Morphologically, colonies appear beige and are slow-growing and filamentous at room temperature (Fig. 3). Conidiophores are short, unbranched, arising at right angles from thin-walled hyaline hyphae, slightly swollen at the top, sometimes with short, secondary conidiophores bearing 'florets' of conidia [1, 3]. Mold to yeast conversion can be helpful for confirming the identification and is achieved by transferring a piece of the mold colony into enriched media such as brain heart infusion (BHI, with or without 5% blood) or

**Fig. 3** Mycelial-phase culture of *Emergomyces africanus* on Sabouraud agar (20-day-old colonies). Note the white to pale brown colonies, which were glabrous at first, and have become powdery and wrinkled or cerebriform with age. Reproduced with permission from [39]

malt extract agar and incubating at 35 °C for 7 to 21 days [1, 3]. Yeast-phase colonies appear small, cream to smooth gray-brown, and heaped [1]. Small round to oval yeast-like cells with narrow buds are formed [1, 3].

### Antibody and Antigen Detection

There are no commercially available serological assays developed specifically for emergomycosis. However, some assays developed for other dimorphic fungi partially cross-react with *Emergomyces*. For example, three of the ten urine samples from patients with culture-proven emergomycosis are caused by *Es. africanus* tested positive with the second-generation IMMY *H. capsulatum* (galactomannan) antigen enzyme immunoassay (EIA) (*ImmunoMycologics*, Norman, OK), which uses monoclonal *Histoplasma* antibodies [15]. Moreover, antigen derived from *Es. africanus* yeast-phase culture filtrates cross-reacts with the same *Histoplasma* EIA (authors' unpublished data).

### Molecular Detection and Genotyping

Molecular tools have been helpful in the detection of *Es. africanus* in clinical and environmental samples [27, 29], and for the identification of clinical isolates to species level [1, 3]. Identification is usually achieved by amplification and sequencing of the internal transcribed spacer (ITS) region of the ribosomal gene using ITS 1 and ITS4 primers, ITS1 and ITS2 primers or 28S rDNA (large subunit or D1/D2) primers [1, 3, 5, 12], followed by sequence alignment with those deposited in the GenBank-NCBI (National Center for Biotechnology Information) database.

Multilocus sequence typing has proven to be useful for delineating the taxonomy of *Emergomyces* [1]. In addition, whole genome sequencing of three *Emergomyces* strains (*Es. africanus* (CBS136260), *Es. pasteurianus* (CBS 101426), and *Es. orientalis* (CBS 124587 = CGMCC2.4011) has been completed [1, 34].

## Prevention and Treatment

Although it is now recognized to be the most common endemic mycosis diagnosed in South Africa [8], emergomycosis remains a relatively rare HIV-associated opportunistic infection. Apart from program-level interventions to diagnose HIV infection earlier and to early initiation of ART, there are no specific strategies currently recommended to prevent emergomycosis. Clinical detection might be improved by educating clinicians caring for HIV-infected patients in areas of higher endemicity (i.e., South Africa) on early recognition of the clinical syndrome of fever, widespread skin lesions, and systemic signs that should prompt the inclusion of systemic mycoses on differential diagnoses. Skin biopsies are imperative for early diagnosis [15].

There are no randomized-controlled trials available to guide the management of HIV-associated emergomycosis. Consequently, we recommend that clinicians caring for patients with emergomycosis follow the Infectious Diseases Society of America guidelines for the management of other endemic mycoses in immunocompromised persons [35, 36]. Generally, this should include amphotericin B (deoxycholate at a dose of 0.7–1 mg/kg daily or a lipid formulation at a dose of 3 mg/kg daily) for 7–14 days followed by a triazole antifungal agent for at least 12 months. Longer courses of treatment may be required in patients who do not achieve immune reconstitution. Although fluconazole is cheaper and easier to obtain than other triazoles, limited in vitro susceptibility data suggest that itraconazole (or voriconazole or posaconazole) may be preferred for the oral step-down phase following amphotericin B therapy [7, 8, 37].

The optimal timing of ART initiation following diagnosis of emergomycosis, among those who are ART-naïve, has not been established. Several potential interactions may occur between antifungals and ART and, where applicable, anti-tuberculosis therapy, and dosages may need to be adjusted [38].

## Conclusion

While relatively rare, fungi within the novel genus *Emergomyces* cause a potentially-fatal disseminated mycosis among immunocompromised persons in endemic areas. Much work remains to be done to understand the geographic range, ecology, epidemiology, and immunopathogenesis of this fungal disease, to understand the full clinical spectrum of disease and to optimize clinical diagnostic and treatment pathways in areas of endemicity.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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