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Review Article

Emergomycosis (*Emergomyces africanus*) in Advanced HIV Disease

Nelesh P. Govender[a, b] Wayne Grayson[b, c]

[a]National Institute for Communicable Diseases (Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses), a Division of the National Health Laboratory Service, Johannesburg, South Africa; [b]School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [c]Ampath National Laboratories, Johannesburg, South Africa

Keywords
Emergomyces africanus · Emergomycosis · *Emmonsia* · Deep fungal infection · Advanced HIV

Abstract
In 2013, a novel thermally dimorphic fungal pathogen was described to cause disseminated disease among persons living with advanced HIV/AIDS in South Africa. Although the organism was initially described as an *Emmonsia*-like fungus, it is now known to belong to a new genus of thermally dimorphic fungi and was recently named *Emergomyces africanus*. There is considerable clinical and histopathological overlap between emergomycosis and histoplasmosis. This review addresses taxonomic, clinical, diagnostic, and therapeutic aspects of *Es. africanus* disease, a condition which has, to date, only been reported from southern Africa.

Introduction

In 2013, a novel thermally dimorphic fungal pathogen was described to cause disseminated disease among persons living with advanced HIV disease in South Africa [1]. This fungus belongs to the first new genus of thermally dimorphic fungi to be described since *Talaromyces marneffei* was characterised in 1956 [2] and has been recently named *Emergomyces africanus* [3]. The filamentous or mycelial form of *Es. africanus* has a reservoir in soil [4]. Analogous to histoplasmosis, human disease (known as emergomycosis) is

Prof. Nelesh P. Govender
Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses
National Institute for Communicable Diseases
Private Bag X4, Sandringham, Johannesburg 2131 (South Africa)
E-Mail neleshg@nicd.ac.za

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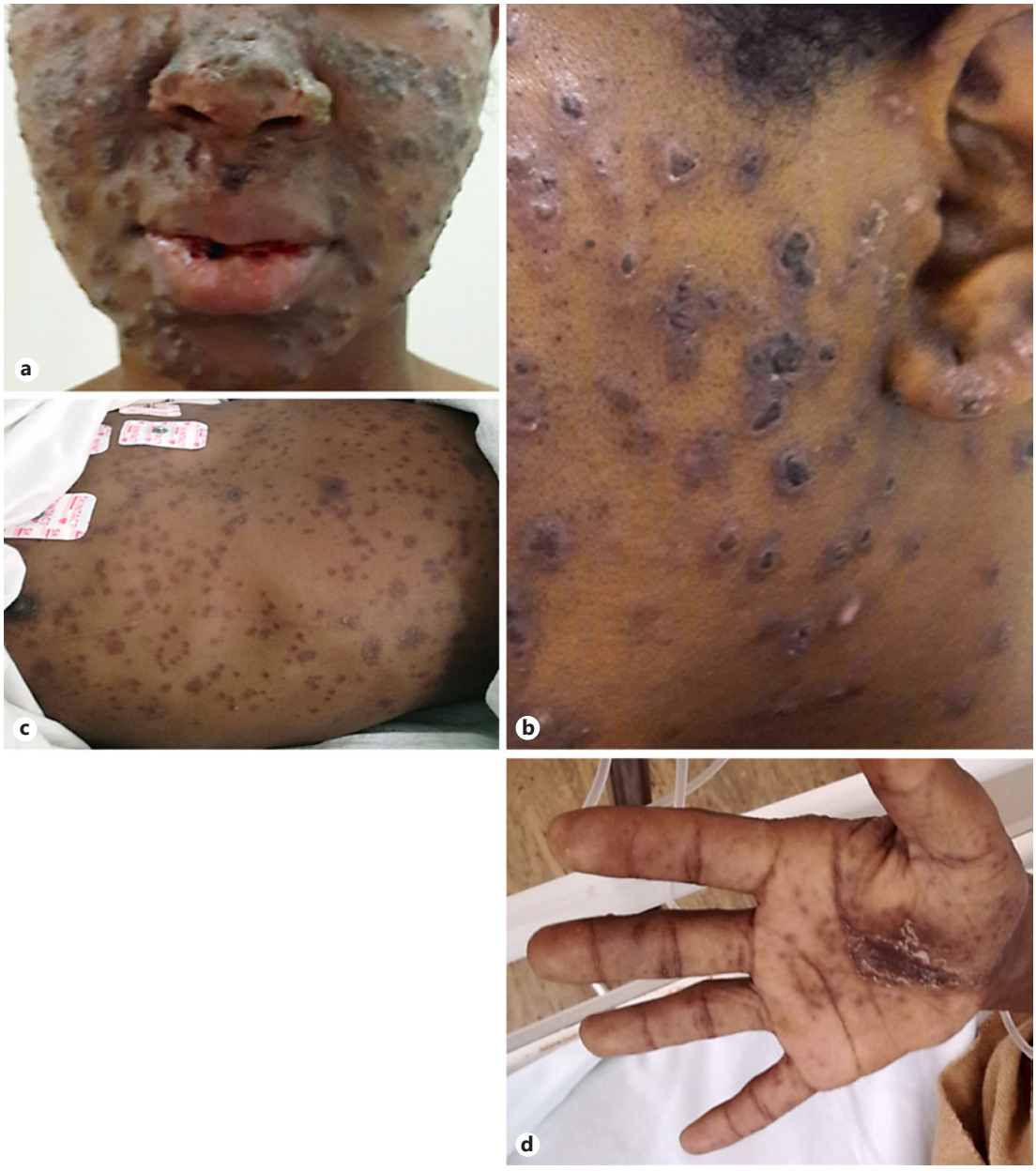

Fig. 1. Clinical images depicting the diverse dermatological spectrum of *Emergomyces africanus* infection, including ulcerated and crusted facial plaques and nodules (**a**, **b**), vasculitis-like lesions (**c**), and even palmar involvement (**d**).

presumed to occur following inhalation of tiny airborne conidia that lodge in the terminal airspaces of the lung and convert, at human body temperature, to the budding yeast phase [4, 5]. Although *Es. africanus* was initially described as an *Emmonsia*-like fungus, its conversion to a budding yeast state in vivo is clearly distinct from *Emmonsia crescens*, which produces larger non-budding structures known as adiaspores in tissue and causes a very rare human disease called adiaspiromycosis [3]. There are several other species within the genus *Emergomyces*, all of which cause disseminated disease in severely immunocompromised hosts [3, 6, 7]. Based on a phylogenetic analysis of five genes, fungi within

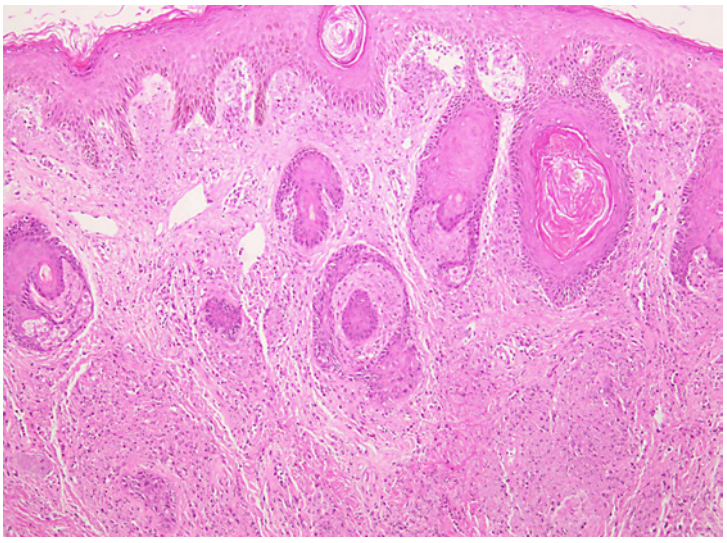

Fig. 2. Low-power photomicrograph showing dermal expansion by vast numbers of intracellular and extracellular fungal yeasts (haematoxylin and eosin, original magnification ×100).

Emergomyces are genetically related to, but distinct from other pathogens in the family *Ajellomycetaceae* such as *Blastomyces*, *Histoplasma*, *Paracoccioides*, and *Emmonsia* [8]. To date, cases of disease caused by *Es. africanus* have only been reported from southern Africa.

Review/Discussion

Clinical Manifestations

Emergomycosis has been described to occur almost exclusively among persons with advanced HIV disease (in adults, this is defined as clinical stage III or IV and/or CD4+ T-lymphocyte count <200 cells/μL) and only multi-system disease has been reported [9]. This probably reflects a diagnostic and reporting bias because clinicians consider emergomycosis when the fungal disease has progressed to an advanced stage with fungaemia, involvement of the lungs, liver, spleen, and bone marrow, and widespread cutaneous lesions [1]. The spectrum of mucosal and cutaneous disease is very wide with macules, papules, nodules, plaques, and ulcers being reported (Fig. 1). Skin lesions with varying morphologies have been observed in individual patients. An unmasking immune reconstitution inflammatory syndrome (IRIS)-like picture has been described among patients whose cutaneous lesions worsen clinically after initiation of antiretroviral treatment [10].

Histopathology

There is considerable overlap between the histomorphological spectrum of *Es. africanus* disease and that of histoplasmosis; in fact, these infections are virtually indistinguishable from one another in skin biopsy material alone, and a definitive diagnosis, therefore, requires detailed clinico-pathological correlation and the use of fungal culture and ancillary PCR studies [11]. Although there is usually a granulomatous and/or suppurative dermal inflammatory infiltrate, some examples may show vast numbers of extracellular and intracellular organisms, the latter contained within macrophages (Fig. 2). The small globose or oval fungal yeasts measure 2–7 μm in diameter and usually exhibit single narrow-based budding in tissue (Fig. 3); less commonly, however, multiple, polar budding

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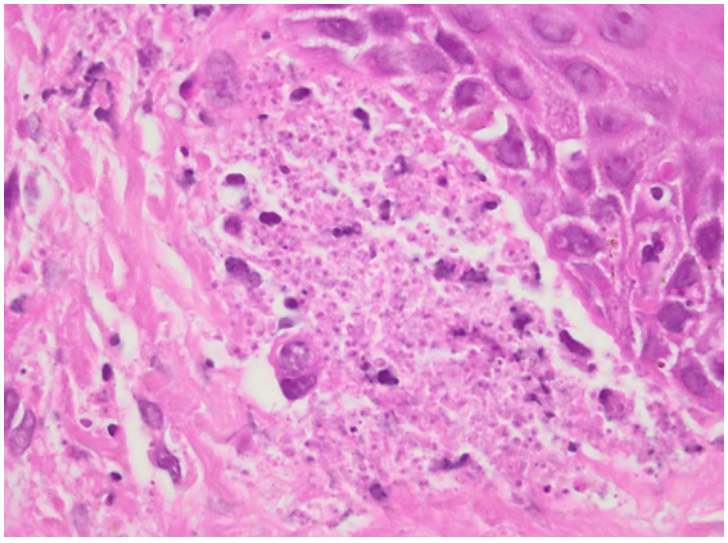

Fig. 3. *Es. africanus* organisms occupying the papillary dermis, as seen under oil emersion (haematoxylin and eosin, original magnification ×1,000).

yeasts formed from a narrow base attachment may be encountered in cultured isolates [1, 11, 12]. The organisms are highlighted with PAS and methenamine silver histochemical stains (Fig. 4). Pronounced pseudo-epitheliomatous hyperplasia is sometimes seen and is usually accompanied by transepidermal and/or transfollicular elimination of the fungal organisms. Invasion of dermal nerves may also be encountered (Fig. 5). An associated host inflammatory response may be minimal to virtually absent in profoundly immunosuppressed hosts; in such cases, the skin biopsy may appear near-normal on cursory inspection (Fig. 6a). Careful examination of the routinely stained sections should nevertheless declare the intradermal yeasts, which may be easily overlooked when present in relatively sparse numbers (Fig. 6b). Cases occurring as a manifestation of IRIS are said to exhibit a more pronounced mixed dermal inflammatory infiltrate and even micro-abscess formation [1, 12].

Diagnosis and Treatment

HIV-seropositive patients with a suspected disseminated mycosis should be carefully investigated. Blood, skin tissue, bone marrow aspirate and/or trephine biopsy, induced sputum, or bronchoalveolar lavage specimens are appropriate for mycological investigation (i.e., direct microscopy and fungal culture), depending on the clinical manifestations. Intracellular budding yeasts may be observed on peripheral blood smears in cases of emergomycosis. In fungal culture, *Es. africanus* can be converted from the mycelial to the yeast phase using specialised media and incubation at 35 °C. The mycelial form of *Es. africanus* grows much faster than *Histoplasma capsulatum* and, by light microscopy, morphologically resembles *Sporothrix schenckii*. Molecular confirmation of cultured isolates is ideal for this reason. Serological and direct molecular assays have not been validated for diagnosis of emergomycosis, though a commercially available *Histoplasma* galactomannan urine antigen assay may cross-react in some cases [12]. Biopsy specimens should be submitted in parallel for histopathological examination. The recommended antifungal treatment of emergomycosis is similar to that of disseminated histoplasmosis in AIDS, with amphotericin B and mould-active triazole agents having the most potent activity [13].

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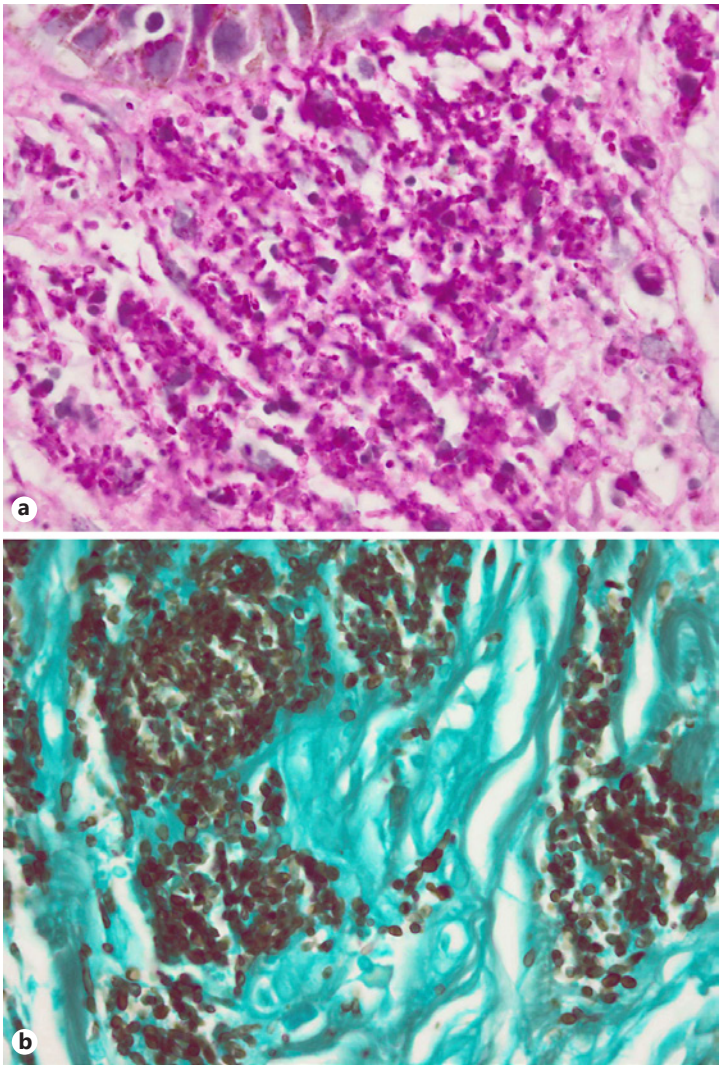

Fig. 4. *Es. africanus* organisms observed under oil emersion. **a** Periodic acid-Schiff stain. **b** Grocott stain.

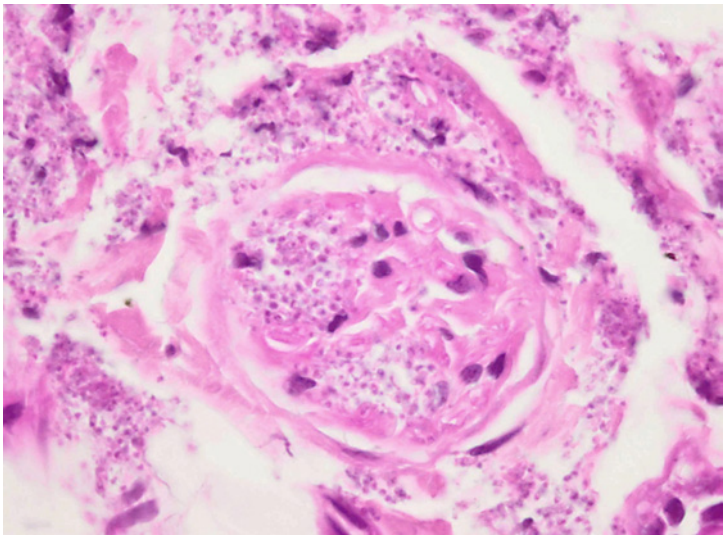

Fig. 5. Subtle dermal nerve invasion by extracellular fungi (haematoxylin and eosin, original magnification ×1,000).

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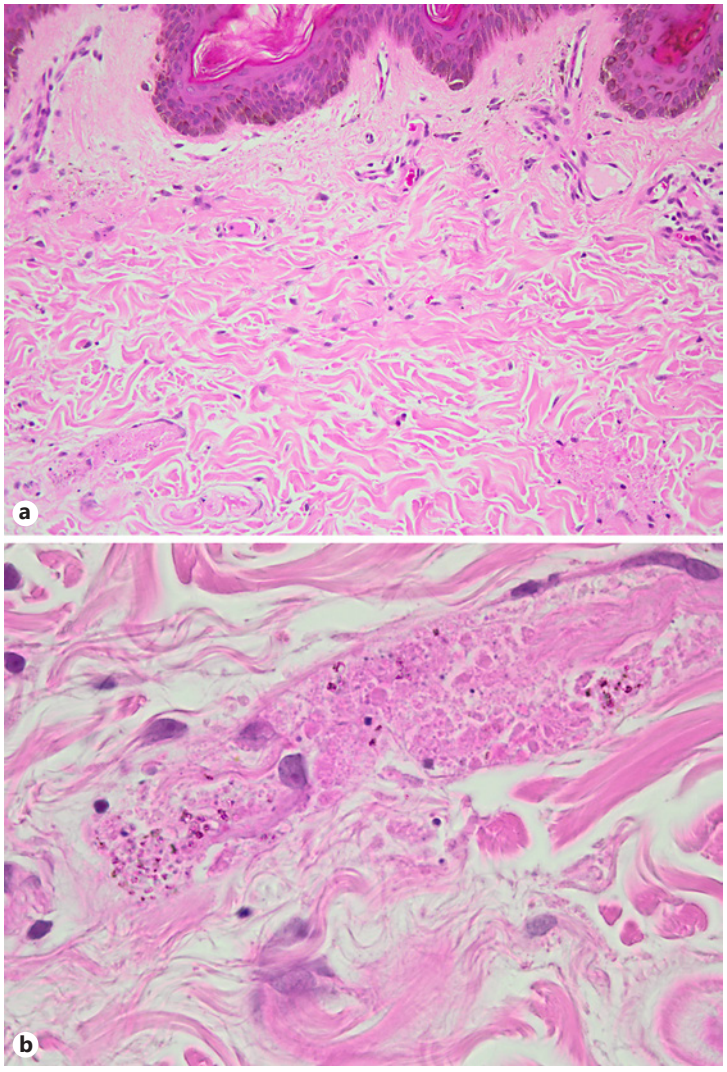

Fig. 6. *Es. africanus* infection in a profoundly immunosuppressed host with advanced HIV (AIDS). The biopsy appears near-normal on cursory examination (**a**), but closer inspection reveals sparse numbers of extracellular yeasts and a largely absent host response (**b**) (haematoxylin and eosin).

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Nelesh P. Govender wrote the introduction, clinical manifestations, diagnosis, and treatment sections. Wayne Grayson compiled the abstract and histopathology sections and was also responsible for the photomicrographs and general formatting of the manuscript.

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