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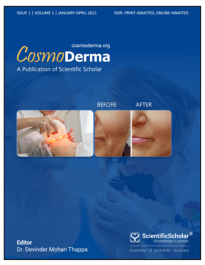

Perspective

The simmering rise in incidence, severity, and atypical clinical presentations of subcutaneous and deep fungal infections in India: Will complacence cost us this battle of David versus Goliath?

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Received: 03 December 2024
Accepted: 13 February 2025
Published: 15 March 2025

DOI
10.25259/CSDM_204_2024

Quick Response Code:

ABSTRACT

Fungal infections have often been overlooked as a public health issue by us by labeling them as rare or easily treatable. In contrast, bacterial infections have been extensively researched, with multiple strategies for detection, management, and prevention in place. While fungal infections were once considered less prevalent than other forms of infections, the landscape has changed significantly in recent years. A global dermatophytosis epidemic is well-documented, but equally concerning is the subtle yet definite increase in subcutaneous and deep/systemic fungal infections such as sporotrichosis, chromoblastomycosis, eumycetoma, pheohyphomycosis, invasive candidiasis, histoplasmosis, zygomycosis, and cryptococcosis. It is imperative that we recognize and address this potential public health threat, giving subcutaneous/deep fungal infections the attention they deserve, and work toward implementing measures for improved diagnosis, management, and control.

Keywords: Deep/systemic fungal infections, Public health issue, Rising trend, Subcutaneous fungal infections

The legend of tiny David triumphing over mighty Goliath may have inspired many of us in our childhood. But as we matured, we realized that at times, we might unwittingly become the Goliaths of this fabled tale, succumbing to complacency. Unfortunately, in the context of the ongoing war between fungal infections versus medical science, we risk being the Goliath and ending on the losing side.

Fungal infections have often been overlooked as a public health issue by us by labeling them as rare or easily treatable. In contrast, bacterial infections have been extensively researched, with multiple strategies for detection, management, and prevention in place. Similarly, extensive funding and research efforts have led to the availability of vaccines for many viral infections and treatment for chronic and deadly viral infections such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C. However, funding and support for fungal disease public health programs and research significantly lag behind other disease groups with comparable mortality or morbidity.

While fungal infections were once considered less prevalent than other forms of infections, the landscape has changed significantly in recent years. According to assessments by the Global

Action Fund for Fungal Infections,[1] the burden of fungal infections is huge with alarming statistics: Fungal keratitis causes blindness in over 1 million eyes annually, nearly 1 billion individuals suffer from cutaneous fungal infections, and approximately 300 million people experience serious fungal infections, resulting in around 1.5 million fatalities each year. In 2019, according to data from Global Burden of Disease (GBD),[2] the incidence of fungal infections affecting the skin and subcutaneous tissue was 1,646,596,956 worldwide and 278,295,577 (16.9%) in India with 0.37% resulted in years lived with disability globally and 0.33% in India.[2]

The global dermatophytosis epidemic is well-documented, but equally concerning is the subtle yet definite increase in subcutaneous and deep/systemic fungal infections such as sporotrichosis, chromoblastomycosis, eumycetoma, pheohyphomycosis, invasive candidiasis, histoplasmosis, zygomycosis, and cryptococcosis. The precise epidemiological data of these fungal infections are not available due to the lack of public health programs to monitor these trends, scarcity of epidemiological studies and difficulty in diagnosis due to limited access to diagnostic laboratory investigations, and lack of awareness among clinicians and atypical presentations of these infections. While mycetoma, chromoblastomycoses, and other deep fungal infections have been included in the list of neglected tropical diseases by the World Health Organization recently,[3] specific strategies to restrain these infections have not yet been formulated and their research funding has been negligible.

The rise in incidence as well as the surge in severe, prolonged, and atypical clinical presentations of these fungal infections can be easily appreciated in tertiary referral centers and can be attributed to host-related factors like an increase in the number of immunosuppressed patients due to the rise in number of patients with HIV, post-organ transplants, malignancy, diabetes, kidney disease, and other chronic illness, immunosuppressive drugs, genetic and congenital disorders, etc., or pathogen-related factors like shift in the genetic constitution of fungus, leading to changed virulence and resistance to antifungals. Unwarranted use of corticosteroids causing local or systemic immunosuppression and antibiotics disrupting the symbiotic bacterial flora are also contributing significantly [Figure 1].

The persistence of neglected tropical diseases was attributed by Morel[4] to science failures (inadequate knowledge about pathophysiology and management), market failures (medicines or vaccines are available but at prohibitive cost), and public health failures (low cost/free medicines/ prophylactic agents are available but with limited access due to logistics issues/inadequate public health support). The current scenario of subcutaneous/deep fungal infections in India can be attributed to all the above types of failures [Figure 2].

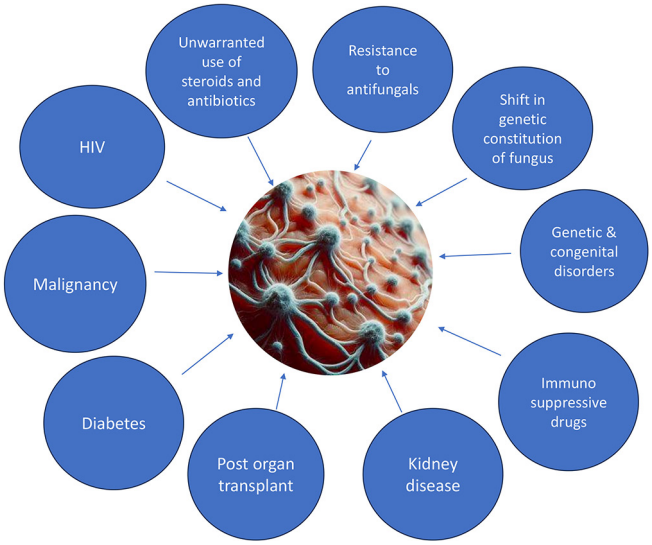

Figure 1: Factors contributing to the increasing incidence, severity, and atypical presentations of subcutaneous and deep fungal infections in India.

Figure 2: Disseminated phaeohyphomycosis presenting as well-to-ill-defined subcutaneous nodules on the dorsal aspect of the left foot and left index finger.

The ominous rise in incidence and severity of these fungal infections is further complicated by challenges in the management of these infections due to antifungal resistance, compromised quality of antifungal medicines, immunosuppressed hosts, poor compliance due to expensive treatment, long-term toxicity of antifungal therapies due to the evolutionary similarity of fungi and humans, and limited treatment options. Most of the subcutaneous fungal infections usually need long-term oral antifungal therapy; however, the response rate of these infections is mostly poor. According to the literature, the cure rate of eumycetoma is around 30%[5] and chromoblastomycosis ranges from 15% to

80%.[6] The epidemic of rhino-orbital cerebral mucormycosis during the Coronavirus disease was a wake-up call regarding the deviousness of deep fungal infections.

Several types of fungal vaccines are in the pipeline, which includes live-attenuated vaccines (e.g., a mutant strain of *Cryptococcus neoformans* devoid of sterylglucosidase enzyme), killed vaccine (e.g., formalin-killed coccidioidomycosis spherule), fungal extracts vaccine (glucan particle consisting of cryptococcal extracts), nucleic acid vaccines (DNA vaccine targeting cell wall antigen of *Penicillin marneffei*), etc. However, due to several challenges like immunosuppressed status of hosts with fungal infections, interspecies and intraspecies antigenic variation in fungi, genomic similarities in humans and fungi, challenges in translation from animal models to humans, and diversity in infection sites, there are no approved vaccines for fungus till now.[7] Although immunotherapy using recombinant cytokines and colony-stimulating factors (granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor) have been successfully used in fungal infections, their commercial use is limited.[8]

The practical challenges of treatment of subcutaneous/deep fungal infections in a country like India warrants several measures like implementation of robust public health measures for prevention, early detection and improving awareness, regional dedicated facilities for diagnosis, isolation of species, management, socioeconomic support of patients, and antifungal resistance testing and funding to promote research for these fungal infections. There is also a need for a centralized national registry, where these fungal infections can be reported by clinicians to keep data and track of the prognosis of the patients.

As the majority of these infections are consulted by dermatologists, awareness among ourselves about the clinical presentations, diagnosis, and management is vital. In a country with limited healthcare access, misdiagnosis or mismanagement may push the patient several years behind in terms of prognosis.

It is imperative that we recognize and address this potential public health threat, giving subcutaneous/deep fungal infections the attention they deserve, and work toward implementing measures for improved diagnosis, management, and control.

Ethical approval: The Institutional Review Board approval is not required.
Declaration of patient consent: Patient's consent was not required, as there are no patients in this study.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Kumar S, Meena A, Narang T. The simmering rise in incidence, severity, and atypical clinical presentations of subcutaneous and deep fungal infections in India: Will complacence cost us this battle of David versus Goliath? CosmoDerma. 2025;5:31. doi: 10.25259/CSDM_204_2024