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Systematic Review

Cutaneous manifestations of deep mycoses in Nigeria: a systematic review

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Abstract

Background: Deep mycoses are serious fungal diseases commonly associated with the immunocompromised but can also present in the immunocompetent following severe exposure to fungal pathogens. Included in this group are subcutaneous and systemic fungal infections.

Objectives: Reviews highlighting skin involvement in patients with deep mycosis in the Nigerian setting are sparse in the literature. This systematic review summarized the clinical presentation, risk factors, and diagnosis of deep mycosis presenting with cutaneous manifestations in Nigerians.

Design: This was a systematic review conducted following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

Data sources and methods: PubMed, Google Scholar, and the African Journal Online database were searched from inception to February 2024 to identify published articles from Nigeria on deep mycoses with cutaneous manifestations. We included single case reports and case series on cutaneous involvement in deep fungal infections in Nigeria. Review articles, guidelines, meta-analyses, animal studies, and fungal studies not relating to the Nigerian setting were excluded.

Results: We identified 16 well-documented articles on deep cutaneous mycoses published in Nigeria over the past six decades which amounted to 137 cases; 102 (74.5%) cases were reported before the year 2000, while the remainder were published within the past two decades. The 137 cases were majorly histoplasmosis ($n = 87$, 63.5%) and eumycetoma ($n = 19$, 13.9%) and predominant risk factors, farming ($n = 13$, 9.5%) and diabetes mellitus ($n = 3$, 2.2%), The diagnosis of cases was predominantly via histopathology ($n = 131$, 95.6%) with a few cases diagnosed by fungal culture ($n = 15$, 10.9%), and antigen assay ($n = 1$, 0.7%) respectively. Twenty-one (15.3%) were clinically diagnosed as cancers including a case of carcinoma of the skin, and one each (0.7%) as skin tuberculosis or neurofibromatosis but all histologically confirmed as deep cutaneous mycoses.

Conclusion: The decline of reports on deep cutaneous mycoses in recent times suggests neglect or a low index of suspicion from attending clinicians. This is further buttressed in the misdiagnosis of cases as other clinical entities. Ensuring a histological diagnosis of skin lesions, especially in at-risk patients will mitigate these gaps.

Keywords: cutaneous mycoses, deep mycoses, HIV/AIDS, invasive fungal infections, Nigeria

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Introduction

According to the Global Burden of Disease project, skin diseases remain the 4th leading cause of nonfatal disease burden with skin fungal diseases ranked among the top 10 most prevalent diseases worldwide.[1] Compared with other common

diseases such as HIV, tuberculosis, or malaria, skin fungal diseases are often ignored or perhaps not prioritized.[2] Although commonly associated with superficial and cutaneous mycoses, especially dermatophytosis, skin involvement in fungal diseases can also be a clinical manifestation of deep mycoses. For instance, opportunistic fungi like *Cryptococcus* species, *Aspergillus* species and *Histoplasma* species which cause invasive disease can also present with cutaneous manifestations.[3–6] Invasive fungal diseases presenting with cutaneous manifestations may result from direct inoculation of fungal pathogens following trauma or as an initial sign of disseminated disease. Infection usually occurs following the exposure of an individual to the spores of these fungal pathogens. In the immunocompetent, it is usually contained in the lungs and often presents as an asymptomatic disease. However, in the immunocompromised, hematogenous dissemination occurs to involve multiple organ systems including the skin.[3–6]

Data on skin manifestations of fungal infections from Nigeria is abundant in the literature but is largely limited to dermatophytosis including onychomycosis, tinea corporis, tinea capitis, and tinea pedis.[7–10] Of the several studies on invasive mycoses including histoplasmosis, aspergillosis, and cryptococcosis conducted in Nigeria, none documented cutaneous manifestations.[11–14] Studies reporting cutaneous manifestations of deep mycoses in Nigeria are rather fragmented in the literature as case reports or series and currently, no large-scale reviews describing the occurrence are available in the literature and as such could be deemed to be uncommon leading to misdiagnosis or underdiagnosis of such cases. This is quite concerning as Nigeria has a significant proportion of its population at risk of invasive mycoses such as people living with comorbidities such as diabetes mellitus and HIV infection. This is evidenced in findings from recent estimates which revealed a national HIV prevalence of 2.1% corresponding to approximately 2 million people living with HIV and a type 2 diabetes mellitus prevalence rate of 5.7% accounting for 4.7 million cases.[15,16] We aimed to highlight a comprehensive review of cutaneous manifestations of deep fungal infections reported in Nigeria and drive awareness of this seemingly rare clinical entity in our setting.

Methods

Study design

We conducted a systematic review of literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] and adhered to the PRISMA checklist (Supplemental Document S1).

Search strategy and databases

We conducted a comprehensive literature search using PubMed, Google Scholar, and African Journal Online from inception to February 2024 to identify articles from Nigeria reporting cutaneous manifestations of deep fungal infections (BEE). The following search terms were used: ((Nigeria) AND (histoplasmosis OR cryptococcosis OR aspergillosis OR invasive candidiasis OR mucormycosis OR emergomycosis OR talaromycosis OR blastomycosis OR sporotrichosis OR coccidioidomycosis OR paracoccidioidomycosis OR mycetoma OR basidiobolomycosis OR conidobolomycosis)) OR ((Nigeria) AND (invasive mycoses)).

Eligibility criteria

Case reports, case series, and original articles reporting primary data on deep fungal infections with cutaneous involvement in Nigeria were eligible for inclusion. The inclusion of cases was based on the European Organization for Research and Treatment of Cancer and the Mycoses Study Group consensus definitions for proven invasive fungal diseases.[18] Studies or case reports that did not meet this criterion were excluded from the review.

Study selection process and data extraction

Four authors (IO, WOE, PO, and DEE) independently assessed the search outcomes by screening titles and abstracts to establish eligibility. Duplicates and articles not relevant to this review were excluded. Retrieval of pertinent full-text articles was undertaken. References in all papers that met the inclusion criteria were further reviewed for additional publications on studies documenting skin manifestations of deep fungal diseases in Nigeria that may not have been captured in the searched databases. Any indifferences were resolved by a consensus. Data extraction was performed by two authors (BEE and TEB) and included study authors, location of study, year of publication, type

of study, age, sex, clinical presentation, underlying comorbidities, and method of diagnosis.

Statistical analysis. Descriptive analyses were used to summarize the demographic and clinical characteristics of included cases. No meta-analysis was conducted, given that data pooling was not warranted.

Risk of bias

We performed a risk of bias assessment using the Joanna Briggs Institute's checklist for case series and checklist for case reports, respectively. The risk of bias was categorized as follows: low risk of bias (⩾7 stars) or high risk of bias (<7 stars).[19]

Results

Search results

We identified a total of 604 articles from our initial search. After screening their titles and abstracts, 570 were excluded as not relevant to the subject of this review for several reasons, including guidelines on the management of fungal diseases, reviews on fungal infections, articles on fungal diseases not related to Nigerian settings, and studies done in animals among others. In addition, nine articles were excluded as duplicates. Of the 25 studies sought for retrieval, 9 articles were not accessible in full text. A total of 16 articles were assessed for eligibility and eventually included in the review, Figure 1.

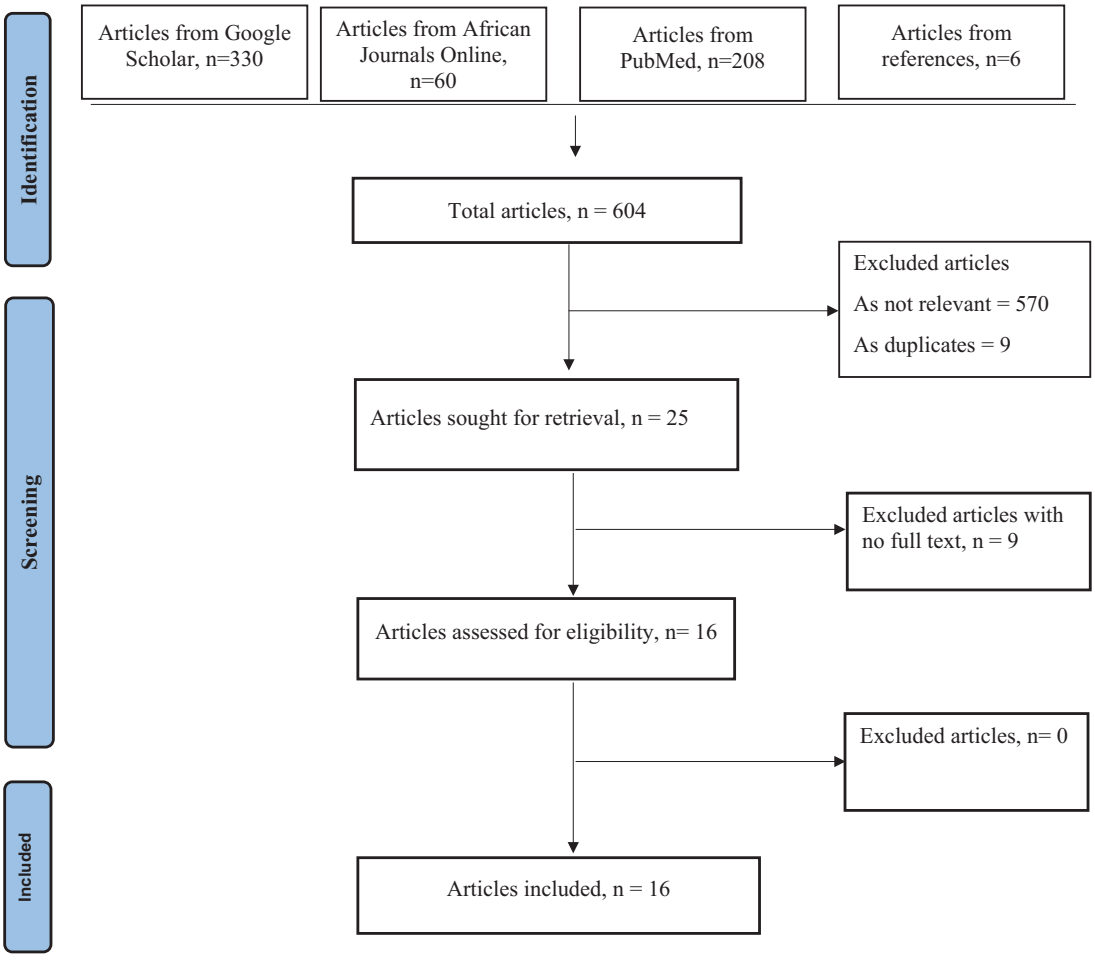

Figure 1. PRISMA flow diagram.

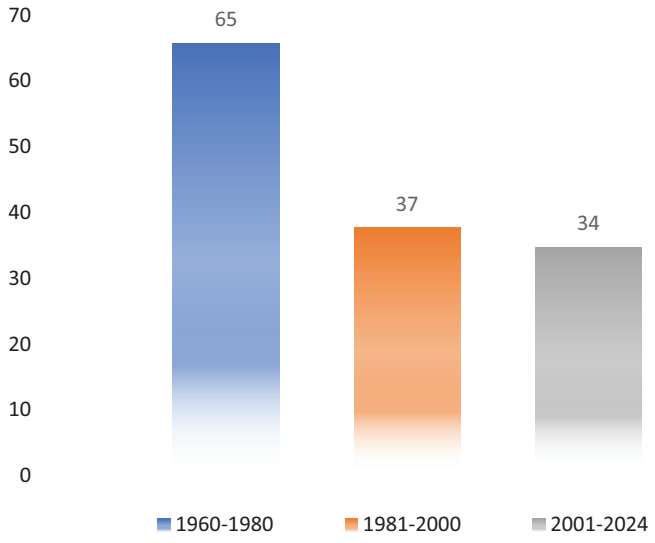

Figure 2. Trends in the report of deep cutaneous mycoses in Nigeria.

Summary of studies

A total of sixteen articles comprising eight case series and eight individual case reports amounting to one hundred and thirty-seven cases were published between 1964 and 2022. Of the 137 cases, 102 (74.5%) were reported before the year 2000, while the remainder were published within the past two decades. Figure 2 gives a representation of the distribution of cases with regard to timelines. The 137 cases comprised histoplasmosis ($n=87$, 63.5%), eumycetoma ($n=19$, 13.9%), chromoblastomycosis ($n=2$, 1.5%), sporotrichosis ($n=2$, 1.5%), aspergillosis ($n=3$, 2.2%), coccidioidomycosis ($n=1$, 0.7%), paracoccidioidomycosis ($n=1$, 0.7%), mucormycosis ($n=4$, 2.9%), phaeohyphomycosis ($n=2$, 1.5%), and phycomycosis ($n=16$, 11.7%), Tables 1 and 2.

Regarding the risk of bias assessment, a total of 15 studies were classified as low risk of bias and one study as having a high risk of bias (Supplemental Document S2).

Patient demographics

Deep cutaneous mycoses were reported from only eight locations in Nigeria including Ibadan ($n=54$, 39.4%), Zaria ($n=40$, 29.2%), Enugu ($n=16$, 11.7%), Calabar ($n=19$, 13.9%), Maiduguri ($n=5$, 3.6%), Makurdi ($n=1$, 0.7%), Benin City ($n=1$, 0.7%), and Ilisa-Remo ($n=1$, 0.7%). The distribution of cases across Nigeria's geopolitical zones is summarized in Figure 3. The gender of participants was identified in only 68 cases and unclear in the remainder. Of the 68 cases, 50 were males. The male-to-female ratio was 2.8:1. Age was also highlighted in 68 cases with a mean (±standard deviation) of 28.5 ± 15.1. The overall range for all case patients was 2 years to 80 years, Tables 1 and 2.

Underlying comorbidities and clinical presentation

The underlying comorbidities and or risk factors identified were malnutrition,[23] diabetes mellitus,[29–31] HIV infection,[32,33] farming,[23,26,27] trauma,[27,28] herding,[23] contaminated sources[34] and indigenous treatment,[22] Table 3. Clinical presentation was varied with manifestations including cutaneous granulomas,[21] ulcers,[24–26,34] fungating skin lesions,[22,23,32,33] papules,[22–24] nodules,[22,23,25,26,28,32,33] warty lesions,[23] lymphatic lesions,[23] and skin swellings,[22–26,28–30,33,35] Tables 1 and 2. In one case series, the initial (clinical) diagnosis in fifteen cases were cancers ($n=14$) and skin tuberculosis ($n=1$) but were histologically diagnosed with deep mycoses.[28] Similarly in another series, cancers were suspected in four cases which were confirmed by histology as deep mycoses.[26] In yet another series, three cases of African histoplasmosis were initially considered as a carcinoma of the skin, osteosarcoma, or neurofibromatosis, respectively.[25] The clinical mimicry with malignancies was also seen in a single case report clinically suspected to

Table 1. Cutaneous manifestations of deep mycosis reported in Nigeria (1964–2000).

Type of study	Number of cases	Age	Sex	Essential investigations	Diagnosis	Skin features	Reference number
Case series	1	6	Male	Histopathology	Subcutaneous phycomycosis	Infiltrations into the skin	*20
Case series	50	Not stated	Not stated	Histopathology	African histoplasmosis	Superficial cutaneous granuloma, subcutaneous granuloma and abscess, and osteolytic lesions with secondary involvement of the skin	21
Case series	14	2–50 years	Males ($n=11$), females ($n=3$)	Histopathology	African histoplasmosis ($n=6$), phycomycosis ($n=5$), Eumycetoma ($n=3$)	Fungating skin lesions, papules, lymphadenopathy, nasal swelling, orbital swelling, suppurative nodules, and discharging sinuses	22
Case series	13	12–60 years	Males ($n=11$), females ($n=2$)	Culture ($n=12$), histopathology ($n=7$)	Eumycetoma ($n=3$), chromoblastomycosis ($n=2$), phycomycosis ($n=3$), African histoplasmosis ($n=2$), sporotrichosis ($n=2$), paracoccidioidomycosis ($n=1$)	Skin lesions, nodulo-papular skin eruptions, madura foot, warty lesions, cutaneous-lymphatic lesions, swelling of the tissues of the nose, cheek, and upper lip	23
Case series	2	6- and 11-year-old	Males ($n=2$)	Histopathology ($n=2$), culture ($n=1$)	African histoplasmosis	Ulcers, cutaneous swellings, papules and lymphadenopathy	24
Case series	3	9–38 year old	Males ($n=2$), females ($n=1$)	Histopathology	African histoplasmosis	Ulcerated swelling and subcutaneous nodules	25
Case series	19	8–80 years	Not stated	Histopathology	African histoplasmosis ($n=12$), eumycetoma ($n=4$), paranasal aspergilloma ($n=2$), and phycomycosis ($n=1$)	Ulcerating skin swelling and subcutaneous nodules with discharging sinuses	26

*A series of two postmortem reports: subcutaneous phycomycosis and intestinal mucormycosis.

be cancer, which was confirmed as African histoplasmosis.[35]

Diagnosis

Histopathology was the predominant evidence for deep mycosis among the 137 cases included in this review with 130 cases ($n=94.9\%$) diagnosed via this method. Fungal culture was deployed in 15 cases (10.9%), antigen assay was utilized in only one case (0.7%) and one case was diagnosed postmortem. Molecular methods were not used to further identification in any of the cases.

Table 2. Cutaneous manifestations of deep mycoses in Nigeria (2001–2024).

Type of study	Number of cases	Age	Sex	Essential investigations	Diagnosis	Skin features	Reference number
Case report	1	13	Female	Culture	Subcutaneous mucormycosis	Generalized skin lesions (blisters)	27
Case series	27	2–70 years	Males ($n=20$), Females ($n=7$)	Histopathology	Histoplasmosis ($n=10$), eumycetoma ($n=9$), subcutaneous phycomycosis ($n=6$), and phaeohyphomycosis ($n=2$)	Facial swellings, nodules, subcutaneous frontal skull swelling, proptosis, nasal blockage, epistaxis, discharging leg sinuses, flank mas	28
Case report	1	40	Female	Histopathology	Rhinocerebral mucormycosis	Facial swelling with rash and ulceration of mid-face	29
Case report	1	44	Male	Histopathology	Rhino-orbito-cerebral mucormycosis	Left periocular swelling	30
Case report	1	12	Male	Histopathology	Rhinocerebral mucormycosis	Papular rashes over the dorsum of the nose	31
Case report	1	28	Female	Histopathology	Primary cutaneous coccidioidomycosis	Widespread hyperpigmented nodular skin lesions	32
Case report	1	46	Male	Histopathology, antigen assay	Disseminated histoplasmosis	Soft tissue swelling within the right nostril associated with watery discharge and congestion. Multiple nodular lesions on all limbs and ulcerated plaques on both cheeks	33
Case report	1	30	Female	Histopathology, culture	Primary cutaneous aspergillosis	Multiple axillary and perineal ulcers and sinuses	34
Case report	1	23	Female	Histopathology	African histoplasmosis	Skin swellings	35

Discussion

Our review attempts to highlight the burden of deep mycoses presenting with skin involvement in Nigeria, over the past six decades which is seemingly the tip of the iceberg when compared with the preponderance of risk factors in our setting. Moreover, the sharp decline in the report of cases over the past two decades suggests a possible neglect or a low index of suspicion in considering skin diseases as a clinical manifestation of deep mycoses. In addition, over 90% of the cases included in this review were from large case series reported before the year 2000, which suggests more studies are needed to identify invasive mycoses presenting with skin involvement.[21,22,23,26] Furthermore, the paucity of sites reporting deep mycosis with skin manifestations suggests a likelihood of a lack of expertise in making a diagnosis. This is besides the general lack of diagnostics impeding the diagnosis of invasive mycoses in our setting.[36] Caution should therefore be taken in applying the findings from this review as the low number of cases and the few locations involved contrasts with the endemicity of invasive mycoses

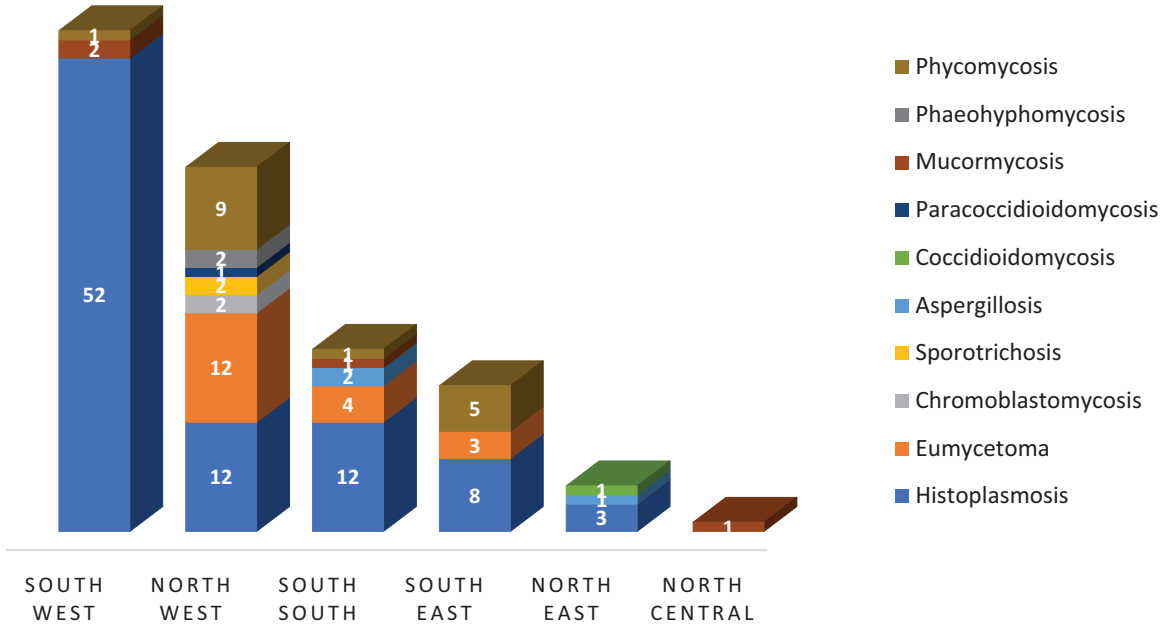

Figure 3. Distribution of deep cutaneous mycosis across Nigeria geopolitical zones.

Table 3. Frequency of comorbidities/risk factors.

Comorbidities/risk factors	*n*	(*n*/*N*) %	Deep mycoses	Reference number
Farming	13	9.5	Mucormycosis (*n* = 1), phycomycosis (*n* = 2), chromoblastomycosis (*n* = 2), eumycetoma (*n* = 6), sporotrichosis (*n* = 1), African histoplasmosis (*n* = 1)	23, 26, 27
Diabetes mellitus	3	2.2	Mucormycosis	29–31
Trauma	2	1.5	Mucormycosis, African histoplasmosis	27, 28
Indigenous treatment	2	1.5	African histoplasmosis	22
HIV infection	2	1.5	Disseminated histoplasmosis, primary cutaneous coccidioidomycosis	32, 33
Contaminated source	1	0.7	Primary cutaneous aspergillosis	34
Malnutrition	1	0.7	African histoplasmosis	24
Herding	1	0.7	Sporotrichosis	23

n, number of cases with a specific risk factor, *N*, total number of cases.

in Nigeria evidenced in several studies performed in recent times.[11–14,37]

Although skin diseases are commonly linked with an immunocompromised state, particularly HIV infection, the major predisposing factor observed in this index review was farming.[23,26,27] As fungal pathogens causing invasive fungal diseases are commonly found in the soil, activities like excavation may cause aerosolization with severe

inhalation of spores or conidia of fungal agents resulting in a localized infection at the onset and then eventually disseminated to involve other organs including the skin.[23,26,29] In some cases, it may be a result of traumatic inoculation initiating a portal for skin fungal infection and may spread to involve the underlying tissues causing osteomyelitis, fractures, lymphangitis, ulcerations, and or disseminated disease regardless of the individual's immune status.[22,27,28]

The non-specific clinical presentation of deep cutaneous mycoses is of importance to the attendant clinician and should be brought to the fore as a misdiagnosis can lead to delayed therapy, socioeconomic problems, and perhaps fatal outcomes. In addition, relying on clinical diagnosis could be misleading as seen in this review.[25,26,28,35] This is particularly concerning for centers where biopsy is not routinely done for skin lesions and or where a trained dermatologist or a histopathologist is lacking. Histoplasmosis was predominant among the invasive mycoses which is in keeping with the high prevalence of disseminated forms of this serious fungal disease in Nigeria as reported in a couple of studies: a prevalence of 7.7% among the advanced HIV disease population and 12.7% among presumptive tuberculosis patients, and case series have also documented same.[13,14,37] Howbeit, when compared with the series earlier documented,[21] and the fact that the *Histoplasma capsulatum* var *duboisii* variant is prevalent in Nigeria,[38] the total number of deep cutaneous mycoses due to histoplasmosis as reported in this review suggests we could be missing cases. Moreover, one review of histoplasmosis cases in Africa spanning six decades documented highest number of cases were reported from Nigeria,[39] and thus seemingly paradoxical to have few cases of skin involvement.

The distribution of cases across the geopolitical zones of Nigeria showed histoplasmosis was predominantly reported with 59.8% of the cases from South West Nigeria followed by South South (13.8%) and North West (13.8%). The Southwest region of Nigeria has been shown to have a high prevalence of fungal infections in several studies, especially for histoplasmosis.[13,40] This has been alluded to the high density of bats in this region, which invariably contaminates the soil with their feces thus providing a favorable ecological niche for the growth of fungal pathogens. Contrastingly, some of the rare deep mycoses such as coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and phaeohyphomycosis reported from other regions of Nigeria were not documented in the Southwest which may be linked with the differences in climatic conditions across these regions as well as the varied distribution of the causative fungal pathogens.

Relating to reports describing cutaneous manifestation of deep mycoses from other regions including sub-Saharan Africa, data is sparse in the literature, thus further buttressing the need to arouse the attention of clinicians on this subject. Howbeit, one retrospective study from Korea identified forty-one cases of deep cutaneous mycosis of which most of the cases ($n=32$) had comorbidities associated with immunosuppression including hematological or solid organ malignancy with chemotherapy (15/32) or organ transplant recipients (10/32). Besides the comorbidities, seven patients had undergone long periods of systemic corticosteroid therapy for various underlying diseases which contrasts with the risk factors in this index review which were mainly farming, diabetes mellitus, and HIV infection. Also, the predominant pathogens were contrastingly *Candida* (16/41), followed by molds including *Aspergillus*, *Alternaria*, and *Fusarium* (4/41 each). The morphology of lesions was varied with nodular skin lesions as the predominant presentation.[41] In a French study with 46 solid organ transplant recipients, receiving immunosuppressives, polymorphic lesions were reported, and were predominantly nodules and/or papules ($n=26$, 56%). Others were abscesses ($n=7$, 15%), cellulitis/ panniculitis or inflammatory plaques ($n=6$, 13%), ulcerated or necrotic lesions ($n=4$, 9%), blisters ($n=1$, 2%), proliferative lesions ($n=1$, 2%), not specified ($n=1$, 2%). Predominant fungal pathogens/infections reported were Alternarioses [(*Alternaria* species, *A. infectoria*, *A. alternata*), 16/46], Cryptococcosis (6/46), Scytalidioses (4/46), Aspergilloses [(*A. fumigatus*, *A. flavus*, *A.* species) 4/46], *Exophiala* species [(*Exophiala janselmei*, *E. lecanii-corni*), 2/46], *Scedosporium apiospermum* (2/46), histoplasmosis (2/46) and mycetoma (2/46).[42] A common finding among these studies including the present review is the predominance of skin nodules as a presenting complaint in patients with deep cutaneous mycoses. In contrast, a variance

in the spectrum of associated pathogens was observed with *Histoplasma* species as the major fungal pathogen implicated in Nigeria, and *Candida* species and *Alternaria* from Korea and France respectively. This difference may be linked with the underlying comorbidities and or predisposing factors, respectively.

Strengths and limitations

We could not present and discuss findings as per treatment and clinical outcomes as most of the series included in this review did not provide that information except for a few case reports. In addition, only three databases were used to search for cases, which may have limited the number of cases included in this review. Howbeit, this review has highlighted significant gaps in the management of deep cutaneous mycoses particularly in our setting and to some extent on a global scale, ranging from the paucity of data which may likely be due to underdiagnosis and or under-reporting, and the challenge of misdiagnosis as documented in some of the reports.

Conclusion

The sparse data on skin manifestations of deep mycoses in Nigeria suggests it is being underreported as available data shows a decline in cases documented over the past six decades. The factors underpinning these gaps may not be different from the known challenges impeding the diagnosis of fungal infections including a low index of suspicion from the attending clinician, lack of diagnostics, and the paucity of clinical experts with interest in fungal diseases, especially in dermatology and or pathology. This is a call to improve the diagnosis of this neglected clinical entity, locally and globally. Paying attention to risk factors and or underlying comorbidities in a patient presenting with dermatoses can lead to a possible diagnosis of deep cutaneous mycoses. In addition, while making a presumptive or clinical diagnosis of skin diseases, considering or ruling out invasive mycosis, especially in a patient at risk will improve diagnosis as well. This is pertinent to emphasize as a significant number of cases in this review were clinically diagnosed as malignancies and tuberculosis but contrastingly confirmed as deep cutaneous mycosis. A heightened index of suspicion and performing routine biopsies of clinical specimens for suspected cases will improve the identification of cases and outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Thelma E. Bassey: Data curation; Methodology; Resources; Visualization; Writing – review & editing.

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Geraldine L. Edim: Formal analysis; Investigation; Project administration; Resources; Visualization; Writing – review & editing.

Asukwo Onukak: Formal analysis; Methodology; Resources; Visualization; Writing – review & editing.

Bassey E. Ekeng: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All underlying data have been included in the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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