

SUBCUTANEOUS PHAEOPHYPHOMYCOSIS DUE TO CLADOPHIALOPHORA SPECIES: A CASE REPORT AND SYSTEMATIC REVIEW OF CASES

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ABSTRACT

Background: One type of melanized fungus that causes brain abscesses is *Cladophialophora*. Recently, however, subcutaneous phaeohyphomycosis has been found in temperate, tropical, and subtropical regions of the world. It is necessary to review the cases because there haven't been many recorded in India and other nations thus far. **Materials and Methods:** We report a case of *Cladophialophora* species-induced cystic subcutaneous phaeohyphomycosis and evaluate all worldwide reports of culture-confirmed subcutaneous phaeohyphomycosis caused by *Cladophialophora* species. **Result:** Immunocompromised patients made up half of the 8 cases found. The infection sites were the hand (n = 5), face (n = 2), foot (n = 1), and back (n = 1). Only two patients reported experiencing pain at the lesion site. Fifty percent (n = 4) of the patients had several lesions, while fifty percent (n = 4) had isolated lesions. There was one case with coinfection like leprosy. Of the patients, 37.5% (n = 3) involved surgical intervention. The antifungal treatment consisted of itraconazole (n = 4), fluconazole (n = 2), amphotericin B deoxycholate (n = 1), potassium iodide (n = 1), and voriconazole (n = 1). Overall, 12.5% (n = 1) of people died, and while no deaths have been reported in other nations yet, they are not statistically significant. **Conclusion:** The infection caused by *Cladophialophora* species is becoming more widespread. An emerging and promising diagnostic test is next-generation sequencing. The result may be improved by using efficient antifungals and early, full excision of the lesion.

INTRODUCTION

A diverse array of phaeoid fungi can cause phaeohyphomycosis, which can result in systemic and subcutaneous infections. Instead of being a clinical entity, the disease is more histological.^[1] Chromoblastomycosis, phaeohyphomycosis, and eumycotic mycetoma are the three classes into which the main infection patterns are divided according to histological features. The word "phaeohyphomycosis" refers to a large category of primary and opportunistic mycoses caused by *Exophiala*, *Cladophialophora*, and other fungi that produce melanized filaments in their host tissues. Despite the disease's global prevalence, India has reported relatively few instances. A case of subcutaneous phaeohyphomycosis caused by *Cladophialophora* species is described here, and a systematic review of cases until the year 2025 is carried out.^[2-9]

MATERIALS AND METHODS

We describe a case of *Cladophialophora* species-induced cystic subcutaneous phaeohyphomycosis and conduct a systematic assessment of culture-confirmed subcutaneous mycosis reports until 2025. In terms of presentation, management, and results, we also contrasted Indian and non-Indian situations. After being tentatively identified at our facility, the *Cladophialophora* species was forwarded to the Advanced Molecular and Diagnostic Research Centre for Fungi (AMDRC), All India Institute of Medical Sciences, Bhubaneswar, for internal transcribed spacer (ITS) sequencing confirmation.

Literature search

We methodologically reviewed published cases and case series of subcutaneous phaeohyphomycosis due to *Cladophialophora* species. We explored the literature, including PubMed, Google Scholar, Medline, and Embase, with the following keywords: 'cystic subcutaneous phaeohyphomycosis,' 'Cladophialophora,' 'subcutaneous infection,' 'phaeoid fungi,' human infections, clinical cases, and case reports were used along with Boolean operators

like “AND,” “OR,” and “NOT.” Additionally, each article's reference list was carefully examined to confirm that all published cases had been compiled for this review. It was ensured to omit cases likely to cause duplicate reporting. Standards for a case to be included were the ensuing: Culture confirmed *Cladophialophora* caused subcutaneous phaeohyphomycosis.

Statistical analysis

The data are shown as means and standard deviation (SD) or as percentages. For categorical data, Fisher's exact test is used to statistically evaluate proportional differences. For statistical significance, a two-sided p-value of less than 0.05 was used.

CASE REPORT

A 53-year-old male labourer by occupation presented with swelling over the left great toe (Figure 1) in the past 3 months. He was known to be diabetic and hypertensive for five years. He was provisionally diagnosed as a case of subcutaneous mycosis and sent for the fine needle aspiration cytology (FNAC) section. Pus aspirate sample was collected and processed for both fungal culture and histopathological analysis. On potassium hydroxide (KOH) mount of pus aspirate, narrow, septate fungal hyphae were seen (Figure 2), which were confirmed on histopathological examination (Figure 3). Sabouraud's Dextrose Agar (SDA) grew dark pigmented fungus after 3 days of incubation (Figures 4, 5).

On lactophenol cotton blue mount (LPCB), phaeoid fungus showed septate hyphae with long chains of conidia (Figure 6) and was provisionally identified as *Cladophialophora* species. The isolate was submitted to the Advanced Molecular and Diagnostic Research Centre for Fungi (AMDRC), All India Institute of Medical Sciences, Bhubaneswar. The swelling was surgically excised after three days, followed by the patient being prescribed oral fluconazole, leading to complete resolution of the lesions.

REVIEW OF LITERATURE

A total of 11 cases were retrieved, of which three could not be added for further analysis because complete case details could not be retrieved. Finally, 8 cases were assessed for eligibility and included for review (Figure 7).

Clinical characteristics of Indian patients against non-Indian patients

Out of the eight cases, three cases were reported from India, two from Brazil, one from Italy, one from the United Kingdom, and one from the United States. The age range of the patients reported during the study period was 23 to 55 years. The majority of the cases (n=5) occurred in males. The majority of the patients (n=4) from countries other than India were immunocompromised. Patients from non-Indian countries had a past history of steroid intake (n=3),

systemic lupus erythematosus (n=1), malignancy (n=1), and transplantation (n=1). Patients who developed subcutaneous phaeohyphomycosis from non-Indian countries were on treatment for Type 2 Diabetes Mellitus (n=2), Chronic Obstructive Pulmonary Disease (n=2), and Systemic Hypertension (n=2). Based on the site of infection, the majority of the cases (n=5) where the lesions were present were in the hand, followed by the face (n=2), foot (n=1), and back (n=1), respectively. But there is not much predominance found when it comes to the number of lesions. Only two cases reported pain at the site of the lesion, along with a history of trauma. The majority of the cases (n=6) reported were solely diagnosed based on the clinical picture and conventional culture methods (phenotypic). Only two cases reported were confirmed by molecular-level identification. But only three cases need surgical intervention. Out of 8 cases, 4 cases were prescribed itraconazole, 2 cases were prescribed fluconazole, and drugs like voriconazole and amphotericin B were also used in the treatment. But the only good thing after reviving all cases reported was that only one case succumbed to death due to treatment failure and poor immune status. Even though the p-value was not showing significance in all analytical variables, clinical significance was noted in some cases (Table 1).



Figure 1: Swelling in the patient's left great toe

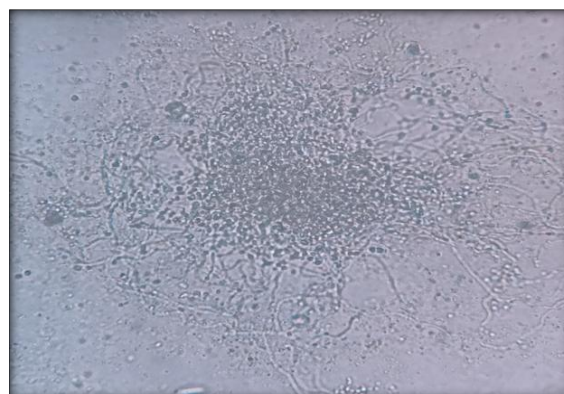


Figure 2: Potassium hydroxide (KOH) mount of pus aspirate 40X

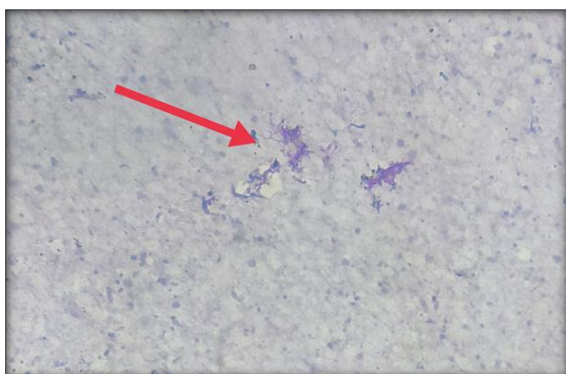


Figure 3: Periodic acid-Schiff (PAS) stain 40X



Figure 4: Sabouraud dextrose agar (obverse)



Figure 5: Sabouraud dextrose agar (reverse)

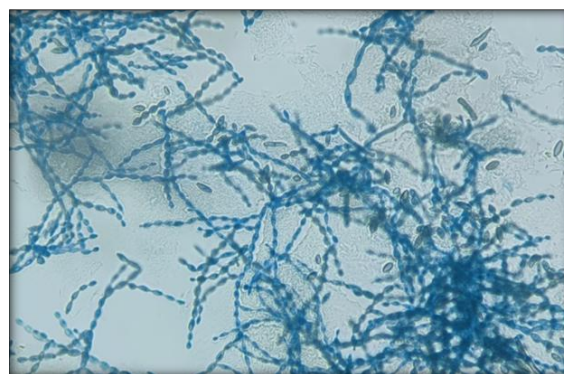


Figure 6: Lactophenol cotton blue (LPCB) mount 40X

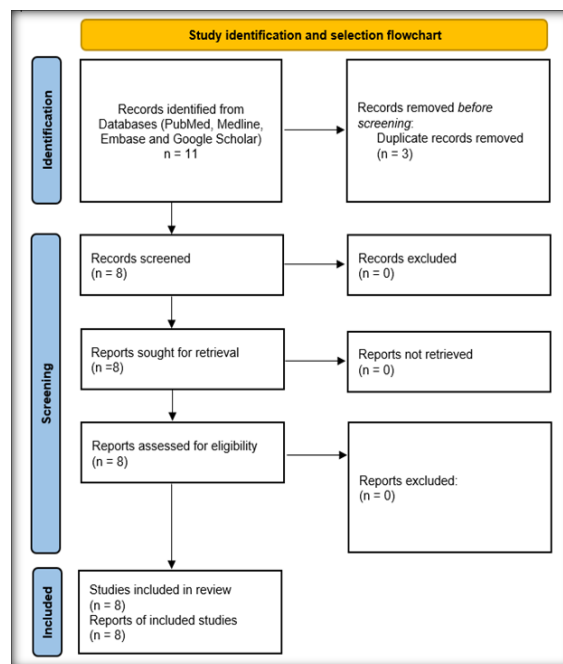


Figure 7: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Table 1: Clinical characteristics between Indian versus non-Indian patients

Clinical characteristics	Indian patients	Non-Indian patients	p value
Gender			
Male (n = 5)	20% (n = 1)	80% (n = 4)	0.464
Female (n = 3)	66.6% (n = 2)	33.3% (n = 1)	
Age category			
≥50 years (n = 4)	25% (n = 1)	75% (n = 3)	>0.999
≤49 years (n = 4)	50% (n = 2)	50% (n = 2)	
Site of infection			
Face (n = 2)	100% (n = 2)	0% (n = 0)	0.246
Hand (n = 5)	40% (n = 2)	60% (n = 3)	

Foot (n = 1)	0% (n = 0)	100% (n = 1)	
Back (n = 1)	0% (n = 0)	100% (n = 1)	
Pain at site of the lesion			
Yes (n = 2)	50% (n = 1)	50% (n = 1)	>0.999
No (n = 6)	33.3% (n = 2)	66.7% (n = 4)	
Lesions			
Single (n = 4)	0% (n = 0)	100% (n = 4)	0.143
Multiple (n = 4)	75% (n = 3)	25% (n = 1)	
History of trauma			
Yes (n = 2)	0% (n = 0)	100% (n = 2)	0.465
No (n = 6)	50% (n = 3)	50% (n = 3)	
Immune status			
Immunocompromised (n = 4)	0% (n = 0)	100% (n = 4)	0.051
Steroid Treatment (n = 3)	0% (n = 0)	100% (n = 3)	
Leprosy (n = 1)	100% (n = 1)	0% (n = 0)	
Systemic Lupus Erythematosus (n = 1)	0% (n = 0)	100% (n = 1)	
Malignancy (n = 1)	0% (n = 0)	100% (n = 1)	
Renal transplantation (n = 1)	0% (n = 0)	100% (n = 1)	
Comorbidities			
Type 2 Diabetes Mellitus (n = 3)	33.3% (n = 1)	66.7% (n = 2)	0.548
COPD (n = 1)	0% (n = 0)	100% (n = 1)	
Systemic Hypertension (n = 2)	0% (n = 0)	100% (n = 2)	
Molecular Identification			
Yes (n = 2)	0% (n = 0)	100% (n = 2)	0.465
No (n = 6)	50% (n = 3)	50% (n = 3)	
Surgical Management			
Yes (n = 3)	33.3% (n = 1)	66.7% (n = 2)	>0.999
No (n = 5)	40% (n = 2)	60% (n = 3)	
Medical Management			
Fluconazole (n = 2)	50% (n = 1)	50% (n = 1)	0.415
Itraconazole (n = 4)	25% (n = 1)	75% (n = 3)	
Voriconazole (n = 1)	0% (n = 0)	100% (n = 1)	
Amphotericin B (n = 1)	100% (n = 1)	0% (n = 0)	
Potassium Iodide (n = 1)	100% (n = 1)	0% (n = 0)	
Mortality			
Yes (n = 1)	100% (n = 1)	0% (n = 0)	0.375
No (n = 7)	28.6% (n = 2)	71.4% (n = 5)	

DISCUSSION

Even though there is the availability of case reports/series, the importance of this study focusing on *Cladophialophora* species, an uncommon fungal infection causing subcutaneous phaeohyphomycosis, cannot be undervalued. Regardless of the variety of clinical scenarios, follow-up, and prognosis, it provides a detailed analysis with insights into the treatment and outcome, especially given the recent increases in the number of cases.

There is no preponderance observed in either age or sex in the review of 8 cases reported. Notably, two cases were reported in Italy due to *Exophiala jeanselmei* and *Cladophialophora carrionii*, respectively, in immunocompetent patients.^[4] Itraconazole was used in both cases but was later instituted with complete disappearance of the lesions. But in the case reported due to *Exophiala jeanselmei*, the nodules persisted even after itraconazole treatment, and the patient was treated surgically. But in a case reported in Dallas due to *Cladophialophora bantiana* presented with recurrence of lesions even after surgical excision.^[8]

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis, diseases caused by black fungi, published in 2014, recommend adding a single or combination of antifungals that might improve survival.^[10] But there is no clarity on the medical treatment for subcutaneous cases; different combinations of antifungal drugs have been used in different cases.

Limitations and strength

The only limitation of this article is not including subcutaneous phaeohyphomycosis caused by other phaeoid fungi in this review. However, to the best of our knowledge, this is the finest study to review the cases reported as subcutaneous phaeohyphomycosis caused by *Cladophialophora*.

CONCLUSION

Cladophialophora is a global emergency infection. Almost always, the condition can only be identified via time-consuming, traditional methods like biopsy and culture. A new and promising diagnostic tool that

could speed up the start of treatment and possibly enhance patient outcomes is next-generation sequencing with a quick turnaround time. These instances may have better results if the lesion is removed completely and early using an antifungal medication.

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