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RAPID REVIEW OF RECENT INDIAN PAPERS IN MYCOLOGY

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Athavale-Wad J et al. Comparative Clinical Characteristics and Outcomes of Candida (Candidozyma) auris vs. Non-C. auris Candidemia in Non-neutropenic Patients in South India. Mycopathologia. 2025; 190(5):72.

Out of a total of 372 candidemia episodes, 85 (22.8%) were caused by *C. auris*, which was the second most common species after *C. tropicalis*. *C. auris* showed 100% resistance to fluconazole and 81% resistance to amphotericin B and no resistance to echinocandins. A negative beta-D glucan (BDG) value was seen in a quarter of patients with both *C. auris* as well as with other species. *C. auris* candidemia occurred in patients with a lower SOFA score as compared to non auris candidemia ($p < 0.05$). It was seen more commonly in ECMO patients. Overall survival at 28 days was only 40%. Interestingly survival at 28 days was 53% with *C. auris* and 37% with non *C. auris* ($p= 0.012$). Outcome analysis was however limited by many patients who left the hospital against medical advice.

Comments

This retrospective analysis of non-neutropenic cases with blood culture proven candidemia provides important epidemiologic data. 22.8% of candidemia episodes were found to be due to *C. auris*, a predominantly nosocomial pathogen, which highlights the fact that infection control is vital. The observation that nearly one quarter of patients had a negative BDG test reduces the negative predictive value of the test and thus reliance on negative BDG alone for discontinuing empiric antifungal therapy becomes somewhat questionable. The lower mortality seen in the *C. auris* is in agreement with previous studies probably owing to the lower virulence of *C. auris*.

Swain S et al. Epidemiology of Triazole Resistant Aspergillus fumigatus in Asia: A Systematic Review and Meta-Analysis. Mycoses. 2025; 68(8):e70099.

Ninety seven unique studies were included, providing resistance data on 8,049 clinical and 6,949 environmental isolates of *Aspergillus fumigatus*. The pooled proportion of triazole-resistant *A. fumigatus* (TRAF) in clinical isolates (predominantly respiratory > ear > other sources) was 4%; whereas in environmental isolates, it was 14%. Among clinical isolates, higher rates were observed in Türkiye (7.5%), India (6.0%), Iran (7.5%), and Japan (7.2%). For environmental isolates, a higher proportion was reported in Iran (24.0%), Thailand (16.8%), and China (12.8%). Among all TRAF isolates, resistance to itraconazole was most common (86.3%), followed by posaconazole (66.5%) and voriconazole (65.4%). Notably, 53.5% of TRAF isolates were pan-triazole resistant. The TR34/L98H mutation was the most frequently reported, detected in 34.5% of clinical and 38.6% of environmental isolates.

Among the Asian population, triazole-resistant *Aspergillus fumigatus* (TRAF) can be seen in a small but significant proportion of patients with aspergillosis, most of which have been reported in pulmonary aspergillosis.

Comments

In contrast to earlier studies which showed a low incidence rate of triazole resistant *Aspergillus fumigatus* (TRAF) in India, the proportion is now found to be approximately 6%. Diagnosis of TRAF relies on fungal culture and species identification followed by antifungal susceptibility

Message from the Editor

Dear Friends,

A very warm welcome to the delegates of Mycocon 2026 at Chandigarh. This newsletter is a mixed bag of review of important papers and case reports. The rapid review of important papers includes both papers published from India as well as international publications. The case reports are a combination of common fungi (Tinea, Histoplasma and Aspergillus) as well as the less common ones (Basidiobolus, Hyphopichia and Medicopsis). All the cases have important messages pertaining to diagnosis, identification, anti-fungal susceptibility testing and management of fungal infections.

You are also invited to visit our website www.fisftrust.org which has many other educational resources including previous issues of the newsletters.

Wishing you an academically enriching time at the conference.

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Welcome All Delegates

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testing and molecular detection of resistance mutations. Well-equipped labs with facilities to identify the resistance are limited to select tertiary centres in India and thus pose problems in usual practice. Voriconazole has long been the first line therapy for invasive and chronic pulmonary aspergillosis. Currently, there is been a trend among clinicians to shift towards alternatives such as isavuconazole, posaconazole, itraconazole due to high frequency of drug-drug interactions and toxicity issues. However, this meta-analysis demonstrates that resistance among TRAF isolates to all azoles is similar.

Soundappan K et al. Incidence and prevalence of chronic pulmonary aspergillosis in patients with post-tuberculosis lung abnormality: Results from a community survey in North India. Mycoses. 2024; 67(3):e13711.

117 subjects with post tuberculosis lung abnormality (PTLA) were included with a median of 3 years after ATT completion. (CT) of the chest and estimated serum *A. fumigatus*-specific IgG were done. Subjects were categorized as PTLA with or without CPA using a composite of clinical, radiological, and microbiological features and resurveyed at 6 months (or earlier) for the presence of new symptoms. Eleven subjects had CPA in the initial survey, and one additional case developed CPA during the second survey. The prevalence of CPA in PTLA subjects was 10.3% (12/117). CPA incidence rate (95% confidence interval) of 4.2 (1.8-6.5) per 100-person years was found.

Thus, chronic pulmonary aspergillosis complicates 10% of PTLA subjects after successful outcomes with ATT. Four new CPA cases may develop per 100-persons years of observation after ATT completion.

Comments

In clinical practice, patients presenting with persistent or recurrent respiratory symptoms after ATT pose a significant diagnostic challenge, as clinicians must differentiate chronic pulmonary aspergillosis from TB recurrence, drug resistant TB, secondary bacterial infection and non-tuberculous mycobacterial disease. Radiological reassessment with CT chest helps in identifying progressive cavitation, nodules, or fibrotic changes, but cannot establish a microbiological diagnosis. Excluding this condition requires multiple investigations such as, sputum smear and culture, Xpert MTB/rif for drug resistance, mycobacterial culture and drug susceptibility testing. Confirming CPA requires integration of chronic symptoms, imaging finding, and microbiological or immunological evidence – like elevated BAL/serum galactomannan, serum Aspergillus specific IgG, fungal culture or histopathology, when available.

The reported 10% prevalence of CPA makes it a clinically relevant complication of post tuberculosis lung abnormality (PTLA). The median time of 1 year to CPA development after ATT completion emphasizes the continued need for vigilance even during extended follow ups.

Nawaz RS et al. Sensitivity and Specificity of Plasma and Bronchoalveolar Lavage Fluid PCR for Diagnosing Pulmonary Mucormycosis in Subjects With Diabetes Mellitus. Mycoses. 2025;68(4):e70063.

Mucorales polymerase chain reaction (PCR) is used to diagnose pulmonary mucormycosis (PM) among neutropenic individuals. The primary objective was to assess the diagnostic performance of a commercial real-time PCR assay (MucorGenius) in plasma and bronchoalveolar lavage fluid (BALF) for diagnosing PM (proven and probable cases only) in patients with suspected invasive mould disease (IMD). For the secondary objective, we evaluated the performance of the MucorGenius assay in all PM (proven, probable, and possible) cases.

Patients with suspected IMD were enrolled and assessed the performance of Mucor Genius PCR (index test) in plasma and BALF samples. 43 (41.7%) patients were confirmed to have PM. Plasma PCR showed a sensitivity of 18.6% (95% CI: 8.4-33.4) specificity of 90.7% (95% CI: 77.9-97.4), PPV of 66.7%, and NPV of 52.7%. Including possible PM/IMD cases improved the plasma PCR sensitivity to 30.0% and retained specificity at 90.7%. BALF PCR had better sensitivity (47.4%) but poorer specificity (69.6%), with a PPV of 56.3% and NPV of 61.5%.Thus, plasma and BALF MucorGenius PCR have poor diagnostic performance for diagnosing PM among individuals with diabetes mellitus.

Comments

Pulmonary mucormycosis remains a challenging diagnosis. Though, radiologic features such as – consolidation, reverse halo sign, cavitation, or pleural effusion on CT are described, these findings are non-specific and overlap with other invasive fungal infections, bacterial pneumonia, tuberculosis. Unlike invasive pulmonary aspergillosis, where biomarkers such as galactomannan and BDG support diagnosis, mucormycosis lacks any biomarkers. Earlier studies using breath tests based on volatile sesquiterpene metabolites showed promising ways for the diagnosis, but this research has not translated into clinical practice and remains experimental. Histopathological confirmation by biopsy remains a reliable way of diagnosing, however it has limitations due to its invasive nature and difficult interpretations at times.

Given these problems, molecular tools such as PCR offer a good option for early detection. A European study that was conducted predominantly in neutropenic and immunocompromised patients, observed high PCR positivity rates possibly due to higher fungal burden in such patients. By contrast, this study conducted in patients with DM, could explain the lesser sensitivity of PCR and thus its reduced utility.

RAPID REVIEW OF RECENT PAPERS IN MYCOLOGY 2025

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Breakthrough Invasive Mould Infections in Hematologic Cases: Relevance of the Host's Factors

Rodríguez-Goncer I et al. OFID. 2025 January. doi: 10.1093/ofid/ofaf025

Breakthrough invasive mould infections (bIMIs) occurring despite mould-active antifungal prophylaxis in hematologic patients were studied. In this single-centre retrospective cohort (2017–2022), 37 bIMI episodes were identified, predominantly in patients with significant immunosuppression. Most cases occurred during posaconazole or isavuconazole prophylaxis, with *A. fumigatus* remaining the predominant pathogen. Importantly, when therapeutic drug monitoring

(TDM) was available, triazole levels were therapeutic in over 90% of patients, indicating that pharmacokinetic failure alone did not explain breakthrough disease.

Clinical outcomes were guarded but better than those reported in earlier papers, with a 30-day attributable mortality of 24%. Mortality correlated more strongly with host factors, poor ECOG performance status, higher Charlson comorbidity index, older age, and persistently elevated CRP rather than with the choice of prophylactic antifungal agent. Diagnostic yield of serum and BAL galactomannan was low as compared to lung biopsy, which when feasible, was frequently diagnostic. Most patients were treated empirically with combination therapy, typically liposomal amphotericin B plus a triazole.

Comments

This study demonstrates that breakthrough mould infections are often driven by host factors rather than antifungal failure. The finding that most bIMIs occurred despite therapeutic azole levels should caution physicians against reflexely attributing breakthrough disease to poor compliance or absorption issues alone. Instead, an approach that prioritizes early suspicion, aggressive diagnostics (including tissue biopsy where possible), and prompt escalation of therapy should be adapted. However in the Indian setting, with less frequent TDM monitoring and less attention to drug interactions, low levels of the prophylactic drug may play an important role in bIMI.

Antifungal Resistance in Non-fumigatus Aspergillus Species

Djenontin E et al. Mycoses. 2025 April. doi: 10.1111/myc.70051.

This comprehensive review examines the emerging problem of acquired antifungal resistance in non-fumigatus Aspergillus species such as *A. flavus, A. terreus, A. niger and A. nidulans*. The review synthesizes data on resistance prevalence, laboratory detection methods, and geographic trends, underscoring that azole resistance is now documented across continents.

Molecular mechanisms of resistance, such as CYP51 gene alterations and others are described. Importantly, resistance patterns and mechanisms differ substantially from *A. fumigatus*, limiting the extrapolation of diagnostic assays and clinical breakpoints. The review concludes by discussing the clinical implications of in vitro resistance and strategies such as combination therapy and newer antifungals.

Comments

This review is relevant for India, where non-fumigatus Aspergillus species—especially *A. flavus* are major causes of invasive aspergillosis, fungal rhinosinusitis, and post-tubercular or viral associated pulmonary aspergillosis. *A. flavus* is known to have variable azole and amphotericin B susceptibility, making resistance a concern. Indian data showing azole-resistant *A. flavus* and *A.niger* isolates, reinforce the need for species-level identification and antifungal susceptibility testing whenever feasible. One of the causes of azole resistance could be the indiscriminate spraying of crops with azoles in India. In resource-limited Indian laboratories where routine MIC testing or molecular assays are not universally available, awareness of species-specific intrinsic resistance patterns (e.g.itraconazole and isavuconazole resistance in *A. niger,* amphotericin B resistance in *A. terreus*, higher azole MICs in *A. tubingensis*) becomes critical for empiric therapy.

Diagnostic Value of Microscopy, Galactomannan, and PCR in Aspergillus Culture- Positive BALF Samples

Govrins et al., Mycoses. 2025 August doi: 10.1111/myc.70103

This laboratory-based pilot study evaluated the diagnostic reliability of direct microscopy (calcofluor white), galactomannan (GM; cut-off 0.5), and Aspergillus PCR (Ct <38) in 92 bronchoalveolar lavage fluid (BALF) samples that were culture-positive for Aspergillus fumigatus. Positivity rates were 12.0% for microscopy, 27.2% for GM, and 28.3% for PCR. Concordant positivity across all three assays was observed in six samples. Among microscopy-positive cases, 10/11 were supported by GM and/or PCR, while GM and PCR detected additional isolated positives. Notably, 58.7% of culture-positive samples lacked corroboration by other mycological tests. A composite diagnostic score incorporating mycological findings and clinical suspicion was applied. Scores ≥3, suggestive of invasive fungal disease, were observed in 28.3% of cases, while 16.3% reached scores ≥4, consistent with probable IA. High composite scores showed a very strong association with microscopy positivity, whereas GM and PCR demonstrated only moderate individual associations.

Comments

It can be concluded from the study that direct microscopy can be a good "rule in" test. Calcofluor or KOH microscopy is cheap, rapid, and widely available. Although sensitivity is low, a positive result supports early antifungal initiation, in-line with ESCMID and IDSA recommendations. In addition to this, positive GM was also associated with active hyphal supports a diagnostic strategy well suited to India: prioritising microscopy for rapid rule-in, GM for fungal burden assessment, PCR as a sensitive adjunctive tool, and culture as supportive but non-decisive evidence. Such stratification is essential to balance early diagnosis with the risks of overtreatment.

Immune Phenotypes in Patients with Invasive Mould Infection Support the Use of PD-1 Inhibition as Potential Treatment Option

Mellinghoff et al. Mycoses. 2025 March doi: 10.1111/myc.70044.

IMI, particularly invasive aspergillosis (IA) and mucormycosis (IM), continue to carry high mortality despite advances in antifungal therapy, highlighting the need for novel adjunctive treatment strategies. This observational study aimed to characterise immune phenotypes in patients with IMI, with a particular focus on immune checkpoint expression, to explore the rationale for immune checkpoint inhibition as a therapeutic option. The study included 25 patients with IA and 7 patients with IM, alongside two control groups: healthy controls (n=5) and haematological patients without IMI (n=10). Peripheral blood mononuclear cells (PBMCs) were analysed using multicolour flow cytometry to assess lymphocyte subsets and the expression of immune regulatory molecules. The consistent upregulation of co-inhibitory markers such as PD-1 and CTLA-4 in both IA & IM supports their potential role in disease pathogenesis and highlights immune

exhaustion as a relevant therapeutic target. However, several challenges limit immediate clinical translation. Immune exhaustion is a dynamic, time-dependent process, and immune profiling was performed only a few days after IMI diagnosis, potentially capturing an early phase of checkpoint induction rather than its full evolution.

Comments

The occurrence of IMI in even non neutropenic patients and demonstration of T-cell exhaustion with increased T regulatory cell counts supports the occurrence of functional immune paralysis in the patients. This immune paralysis occurs due to higher expression of costimulatory inhibitor molecules like PD-1 and PD-1 inhibitors could be used to counter act the same. However, use of PD-1 Inhibitors in still being researched and poses significant challenges as may exacerbate autoimmune phenomena and are costly and not easily accessible in low middle income countries (LMIC).

CT Findings for Differentiating Pulmonary Mucormycosis from Invasive Pulmonary Aspergillosis, Prior to Invasive Procedure Such as a Biopsy or Surgery: A 22-Year Single-Center Experience

Jang HM et al. Mycoses. 2025 September. doi: 10.1111/myc.70115.

This 22-year single-center study compared biopsy-proven pulmonary mucormycosis (PM) and invasive pulmonary aspergillosis (IPA) to identify CT imaging features that could help differentiate the two prior to invasive diagnostic procedures. The authors analysed 94 proven cases (60 IPA, 34 PM) and systematically evaluated the corresponding thoracic CT findings. On analysis, three imaging features emerged as independent predictors of pulmonary mucormycosis: a representative lesion size ≥ 4 cm, the presence of a reverse halo sign (RHS), and the absence of airway-invasive lesions .

Using these factors, the authors developed a simple point-based CT scoring system (≥ 4 cm lesion = 11 points; RHS = 17 points; airway invasion = −12 points). A total score > 8 predicted pulmonary mucormycosis with 70.6% sensitivity and 78.3% specificity. The study highlights that while angio-invasion is common to both IPA and PM, large consolidations, necrotising lesions, and RHS strongly favour mucormycosis, whereas airway-invasive disease favours IPA.

Comments

Due to high burden of mucormycosis in India, this study is particularly relevant. Early differentiation between IPA and PM is crucial because voriconazole, often used empirically for suspected IPA is ineffective as well as likely to worsen invasive mucormycosis, and diagnostic delays can be catastrophic. However, the reported sensitivity and specificity may not inspire confidence. Nevertheless, the imaging-based scoring system proposed here offers a practical tool in settings where tissue diagnosis may be delayed or not feasible.

The need for ID physicians to interpret CT images themselves cannot be emphasized enough. While this scoring system should not replace histopathology, it provides valuable guidance for early empiric antifungal selection, particularly in high-risk patients with negative galactomannan assays and non-diagnostic cultures.

Performance of Quantitative PCR to Distinguish *Pneumocystis jirovecii* Pneumonia From Colonisation in Immunocompromised Patients

Cederwall et al. Mycoses. 2025 October doi: 10.1111/myc.70120.

Diagnosis of PCP remains challenging because there is no gold standard for diagnosis, clinical and radiological findings are non-specific, and asymptomatic *P.jirovecii* colonisation is common, particularly in immunocompromised hosts. This retrospective study evaluated 520 adult patients with PCR- or microscopy-positive respiratory samples (BAL, sputum, or oral wash). Patients were classified as proven PCP, probable PCP, possible PCP, or colonisation using modified EORTC criteria; proven and probable cases were considered PCP, while possible cases were excluded. Routine duplex qPCR targeted the mitochondrial large subunit rRNA (mtLSU) and beta-tubulin genes. When both targets were detected, results were reported as "*P. jirovecii* DNA detected" without further interpretation. Detection of mtLSU alone was reported as "weak positive", with a comment noting the difficulty in distinguishing colonisation from active PCP. Nearly half of patients (47.5%) had true PCP, while the remainder represented colonisation, highlighting the diagnostic challenge in clinical practice. qPCR fungal burden, expressed as Cq values, showed clear discriminatory value in BAL and sputum samples, with significantly lower Cq values in PCP disease than in colonisation. In contrast, oral wash samples showed no meaningful difference and were unreliable for clinical decision making. From a clinical perspective, two Cq thresholds were most relevant. A Cq <31 in BAL or sputum was highly specific for PCP (>95%) and was associated with a positive predictive value >85%, supporting initiation of PCP-directed therapy. A Cq ≥38 had a high negative predictive value (BAL 89%, sputum 73%), indicating a low likelihood of PCP and supporting consideration of alternative diagnoses and avoidance of unnecessary toxic therapy.

Comments

The study provides thresholds of quantitative PCR which help in distinguishing between infection & colonization. The grey zone of Cq values between 31 and 38 is the part where it is difficult to interpret the test results. BDG may be used as another adjunct to the diagnosis. The actual technique of BAL sampling, use of various different targets for PCR, methods of extraction, reporting as Ct values or copy numbers adds to the complexity of interpreting the results. In conclusion, diagnosis of PCP is a challenging task. However, use of qPCR in addition to the use of clinical, radiological and other serological tests increases the diagnostic accuracy and helps in prevention of overtreatment. However, clinicians who have made a diagnosis of colonization will have to remain vigilant about progression to invasive disease. It is important to note that availability of qPCR in a LMIC like India is an area of concern wherein the test may not be easily available and lack of standardisation may be seen.

EMERGING CHALLENGE OF RECALCITRANT TINEA CRURIS DUE TO *TRICHOPHYTON INDOTINEAE* MANAGED SUCCESSFULLY WITH POSACONAZOLE

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Background

Chronic and recalcitrant dermatophytosis has become a major public health and therapeutic challenge in India over the past decade. The emergence of *Trichophyton indotineae*, a dermatophyte increasingly associated with high-level resistance to terbinafine and azoles, has complicated management of a common condition.[1-3] Patients frequently experience recurrences, partial responses, and significant impairment in quality of life, despite prolonged guideline-based therapy.[1]

Conventional antifungal regimens, once reliable, are increasingly failing, prompting clinicians to reconsider empirical strategies and emphasize susceptibility-guided therapy.[1,3] This case illustrates the management of long-standing, multidrug-resistant tinea cruris due to *T. indotineae*, which responded favourably to posaconazole, highlighting evolving therapeutic approaches for difficult-to-treat dermatophytosis.[1,2]

Case Report

A 22-year-old male from Hyderabad, with no known comorbidities, presented with recurrent pruritic groin lesions for eight years. He experienced frequent exacerbations of severe itching and burning, particularly during hot and humid conditions, leading to sleep disturbance, psychosocial distress, and a significant reduction in quality of life. There was no history of diabetes mellitus, immunosuppression, chronic illnesses, or systemic steroid use. Family history was non-contributory.

The patient had received multiple courses of topical and systemic antifungals over the years, including itraconazole and luliconazole, each for 6–8 weeks. Despite initial partial responses, he experienced frequent relapses, with diminishing efficacy over time.

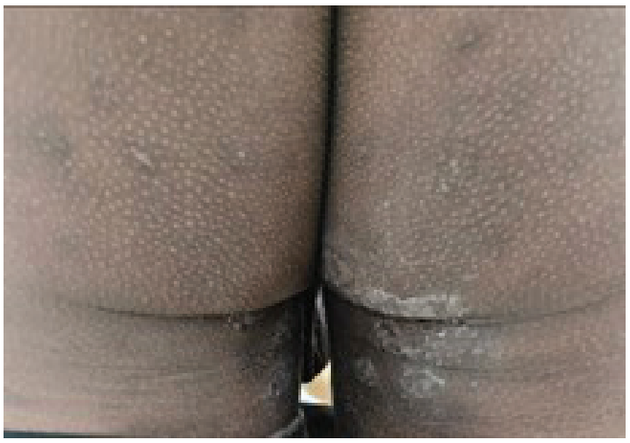
On examination, there were large, well-defined, erythematous and hyper pigmented scaly plaques over bilateral groin folds with prominent raised borders and central clearing (Figure 1, 2). Excoriation marks were consistent with pruritus. Nail and scalp involvement was absent, and no signs of secondary bacterial infection were noted. Systemic examination was unremarkable. Baseline laboratory evaluation revealed normal blood counts, liver and renal function tests, negative HIV serology, and normal HbA1c.

Due to the chronicity and repeated treatment failures, mycological confirmation and antifungal susceptibility testing (AFST) were pursued. Skin scrapings from the active border were sent for direct microscopy by KOH/Calcofluor white mount, fungal culture, species identification, and susceptibility testing to the ICMR-Advanced Mycology Diagnostic & Research Centre, Dept. of Microbiology, Nizam's Institute of Medical Sciences, Hyderabad. The KOH mount was positive for septate hyphae. The fungus grew on SDA and mount showed narrow, branching, septate, hyaline hyphae (Figure 3and 4). Fungus was identified by DNA sequencing of the ITS region as *Trichophyton indotineae*. AFST was done by CLSI Broth Microdilution method (Table 1).[4]

CLSI has not yet established Clinical Breakpoints (CBPs) for *Trichophyton indotineae*. Interpretation is based on published Epidemiological Cutoff Values (ECVs) where available, which categorize the isolate as Wild Type/ Non-Wild Type. Elevated MICs were seen for Terbinafine, Griseofulvin, Fluconazole and Voriconazole.[1-3] Itraconazole MIC was 0.5 µg/ml approaching the upper limit of wild type (UL-WT) MIC value of $\geq$1 µg/ ml).

Management and Outcome

Given recalcitrance and clinical failure with itraconazole therapy and the results of AFST, salvage therapy with posaconazole was initiated because of its favourable pharmacokinetics and emerging evidence in resistant dermatophytosis along with topical luliconazole. Posaconazole



Figures 1 & 2: Hyperpigmented plaques with peripheral scaling over the groin, genital, and gluteal regions.

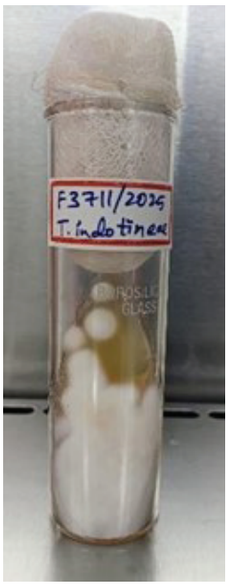


Figure 3: Colony on Sabouraud's Dextrose Agar incubated at 30C

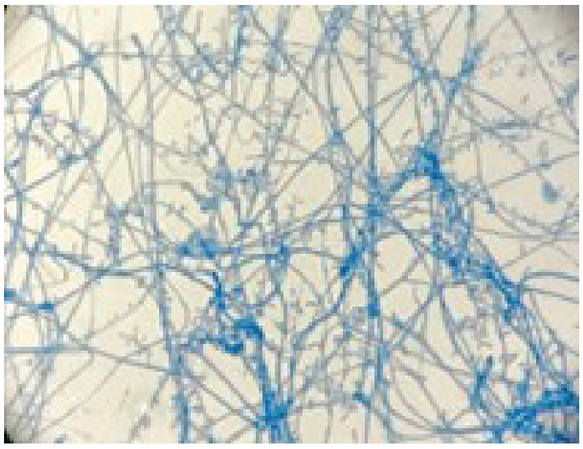


Figure 4: Mount showing hyaline, septate, branching hyphae with microconidia.

was administered at a dose of 300 mg per day. Baseline and periodic liver function monitoring was performed during therapy. Therapeutic drug monitoring (TDM) was not undertaken due to financial constraints and the patient's satisfactory clinical response. Adjunct measures included strict hygiene, keeping the groin dry, avoiding tight clothing, and discontinuation of topical steroid–antifungal combinations. The patient exhibited rapid symptomatic improvement, with marked reduction in erythema, scaling, and pruritus within weeks. Lesions nearly resolved by the end of 8 weeks when treatment was stopped, leaving only post-inflammatory hyperpigmentation. Follow-up demonstrated sustained remission.

Discussion

India is currently experiencing an epidemic of chronic, recurrent dermatophytosis, driven by misuse of topical steroid-antifungal combinations, subtherapeutic dosing, poor adherence, and rising antifungal resistance. *Trichophyton indotineae* has emerged as the dominant species (50–80%), overtaking *T. rubrum* (10–30%) and other members of the *T. mentagrophytes/ interdigitale* complex (10–25%).[1,3,5] DNA sequencing is required to separate *T. indotineae* from other members of the *T. mentagrophytes/ T. interdigitale complex*. Clinically, *T. indotineae*

Table 1: AFST results

S. No.	Antifungal	MIC(µg/ml)
1	Terbinafine	8
2	Griseofulvin	32
3	Fluconazole	32
4	Itraconazole	0.5
5	Voriconazole	1
6	Posaconazole	0.06

infections are extensive, inflammatory, recurrent, and often involve family clusters. In contrast, Trichophyton rubrum is usually associated with a chronic, less inflammatory course, with predominant involvement of the feet and nails. Diagnosis should combine direct microscopy using KOH-CFW mount, fungal cultures followed by identification of the species by DNA sequencing and AFST.[1,3,5] Resistance mechanisms include SQLE mutations (F397L, A448T, L393S) for terbinafine and CYP51 mutations, efflux pumps, or overexpression for azoles.[1-3] MIC-guided therapy ensures optimal outcomes: posaconazole ≤0.5 µg/mL (caution 1 µg/mL), voriconazole ≤1 µg/mL (caution 2 µg/mL). Emerging therapeutic options include pipeline agents such as fosravuconazole.[3]

Current treatment strategies in India can be summarized as

- Itraconazole 200 mg/day (100 mg twice daily) for 4–6 weeks (extend 1–2 weeks beyond clinical cure), with attention to interactions, LFT monitoring, and TDM if needed. SUBA-itraconazole offers improved bioavailability.
- Topical adjuncts: luliconazole or sertaconazole, continued 1–2 weeks post-cure.
- Salvage therapy: voriconazole or posaconazole for refractory infections, guided by MIC's.

Conclusion

This case highlights the rising challenge of multidrug-resistant *Trichophyton indotineae* dermatophytosis in India. Recurrent or refractory disease requires laboratory confirmation and susceptibility-guided therapy. Clinical–laboratory correlation is essential, as failure may occur despite borderline MICs. Posaconazole may be an effective salvage option in selected cases. Strengthening mycological diagnostics, antifungal stewardship, and public health measures is critical to curb resistance and improve outcomes.

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"THINK FUNGUS": AN APPROACH AIDING DIAGNOSIS IN A PATIENT WITH RHEUMATOID ARTHRITIS PRESENTING WITH HOARSENESS OF VOICE

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Introduction

In general, invasive fungal infections are rising globally. But awareness is still limited. Therefore, keeping a fungal infection as one of the differentials or "Think Fungus" is a good strategy for making early diagnosis of invasive fungal infections. Histoplasmosis cases are increasingly diagnosed in India even from non-endemic regions.[1] Availability of Histoplasma antigen tests have facilitated diagnosis apart from the conventional microbiological tests and histopathology. Serum galactomannan (GM) cross reacts with Histoplasma antigen and can be used as a surrogate marker in absence of availability of Histoplasma antigen. We are describing here a case of disseminated histoplasmosis from a non-endemic area in a patient with rheumatoid arthritis with no clinical suggestive symptoms where the "Think fungus" strategy enabled the diagnosis

Case Report

A 49 years old male residing in Jodhpur presented in October 2025 with chief complaints of hoarseness of voice, soreness in mouth and occasional chest pain since the past 6 weeks. He also complained about worsening pain and swelling of small and large joints with morning stiffness over the past 4 weeks. He was a diagnosed case of seropositive rheumatoid arthritis for the last four years and had received hydroxychloroquine, oral prednisolone, methotrexate and tofacitinib for a variable periods. He had stopped this treatment for more than a month. He had also received two courses of antibiotics and anti-allergic medications for current complaints from an otolaryngologist without benefit. He came to us for evaluation and treatment. His personal history was remarkable; he was a farmer residing in a small village near Jodhpur, Rajasthan. He was a bidi smoker and consuming alcohol for the last 20 years. In the last 4 years he started the consumption of 'Afim' (opium), soon after his diagnosis of rheumatoid arthritis. He denied any other past medical illnesses.

He had no fever, normal appetite with stable weight. Otolaryngologist documented a small nodular lesion over the vocal cord, examination showed two superficial palatal ulcers with sharp margin. The patient complained of pain when eating spicy food. His systemic examination was unremarkable with pulse rate of 80/min and blood pressure of 150/80 mm of Hg.

After this history and examination, a RA flare was considered more likely than an infection since he had discontinued his treatment. His routine work up, including CBC, LFT and creatinine were within normal limits. HIV, HBsAg, X-ray chest and ultrasound abdomen, neck and axillae were suggested, with a note to get a biopsy from the vocal cord nodule. His X- ray showed bilateral nodular infiltrates while the ultrasound findings were unremarkable. His HIV and HBsAg results were non-reactive. His CT scan thorax showed bilateral reticulo-nodular lesions situated in the periphery, as seen in Fig 1, there was no lymphadenopathy and both adrenal glands were unremarkable.

Given the combination of oral mucosal lesions and pulmonary nodules in an immunosuppressed host, differential diagnoses included pulmonary tuberculosis, histoplasmosis, cryptococcosis, and malignancy. Bronchoscopy with Bronchoalveolar Lavage (BAL) and Transbronchial Lung Biopsy was performed. Microbiologic testing of BAL fluid revealed elevated histoplasma antigen (3.09 ng/mL; reference <0.20) and BAL galactomannan index of 1.82. BAL cryptococcal antigen and GeneXpert MTB/RIF were negative. Transbronchial lung biopsy showed ill-formed necrotizing granulomas composed of polygonal histiocytes. ZN stain was negative for acid fast bacilli. Gomori Methanamine Silver (GMS) stains showed small monomorphic 2 – 4-micron size predominantly extracellular yeast forms of histoplasma (Fig 2). These findings supported the diagnosis of disseminated histoplasmosis involving the pulmonary parenchyma, oral mucosa and vocal cord nodule. Absence of constitutional clinical features like fever, fatigue, and weight loss was striking.

Given the patient's relatively mild systemic symptoms and stable clinical status, oral itraconazole (200mg three times a day for three days followed by 200mg twice a day) was initiated on an outpatient basis. Therapeutic drug monitoring on day 10 showed combined itraconazole and hydroxyitraconazole levels of 1.62 mg/L. Pleuritic chest pain resolved while hoarseness of voice and palatal ulcer showed marked improvement within 3 weeks. Because of persistent RA activity, a multidisciplinary discussion between infectious diseases and rheumatology teams led to cautious reintroduction of prednisolone 10 mg daily, hydroxychloroquine, and four weeks after starting antifungal therapy, weekly methotrexate. At two-month follow-up, the patient demonstrated clinical improvement of pulmonary and mucosal disease and adequate control of RA symptoms. Oral prednisolone was gradually tapered.

Discussion

This case illustrates several important clinical principles. First, Histoplasmosis cases are increasingly diagnosed from non-endemic areas especially from Rajasthan and Gujarat.[1] Second, disseminated histoplasmosis can present with limited or atypical symptoms, including localized mucosal lesions, chest pain and hoarseness of voice, without

classic systemic manifestations such as high-grade fever or weight loss. Disseminated histoplasmosis term is used for patients in which histoplasma species spreads hematogenously from the lungs to involve multiple extrapulmonary sites, most notably the reticuloendothelial system (liver, spleen, bone marrow, lymph nodes), gastrointestinal tract, adrenal glands, and, less commonly, the skin and central nervous system. Our patient has oral mucosal lesions (GI tract) and pulmonary lesions along with vocal cord nodule. This form of disease though seen generally in immunocompromised hosts, but is also described in immunocompetent individuals, particularly older adults or those with subtle defects in cellular immunity.[2] Common presenting features includes fever, weight loss, hepatosplenomegaly, and thrombocytopenia along with organ specific symptoms e.g. oral mucosal ulcerations, gastrointestinal ulcerations, adrenal insufficiency and CNS symptoms in case of meningitis.

The patient presented here had no features generally seen in disseminated histoplasmosis. It was suspected from the presence of mucosal lesions and from the CT scan that showed multiple reticulonodular lesions. "Think Fungus" strategy should be used to keep high index of suspicion especially in immunocompromised host. Immunosuppression from DMARDs, corticosteroids, and small-molecule inhibitors (e.g., tofacitinib), together with comorbid exposures (alcohol, opioids), likely contributed to susceptibility and dissemination. Both opium and alcohol impair host defense mechanisms, especially opioids, which can reduce the activity of immune cells such as Natural Killer (NK) cells and T lymphocytes. Our patient's worsening joint pain and swelling is likely to be due to RA flare but inflammatory response to acute histoplasmosis can have rheumatologic symptoms like arthralgia or arthritis. So always "Think Fungus" as a differential diagnosis. The clinical presentation of histoplasmosis in India differ significantly from the rest of the world, with a higher frequency of disseminated disease in immunocompetent individuals, more frequent adrenal involvement (often bilateral), and atypical cutaneous/oropharyngeal involvement. It is sometimes mistaken as tuberculosis, although in other areas, it is largely a disease of immunocompromised hosts with more typical pulmonary and systemic symptoms. [3]

Third, a combined diagnostic approach using imaging, histopathology, and antigen detection expedited diagnosis: BAL Histoplasma antigen was markedly elevated and correlated with histopathologic demonstration of yeast forms on GMS stain. Finally, cross-reactivity of Aspergillus GM with Histoplasma antigen may be diagnostically useful when specific assays are unavailable; a positive GM (with compatible clinical features) should prompt evaluation for histoplasmosis.[5]

The treatment consists of amphotericin B (liposomal preferable) for two weeks followed by prolonged course of itraconazole for patients with disseminated histoplasmosis. Our patient had mild symptoms with histoplasmosis, hence we opted for OPD based oral itraconazole treatment for his disseminated histoplasmosis. TDM for itraconazole is essential since the bioavailability can vary.

Management of immunosuppressives in newly diagnosed histoplasmosis is challenging and tricky. Minimizing immunosuppressive therapy is a general principle for patients taking immunosuppressive therapy at the time of histoplasmosis diagnosis, especially stopping biologics- TNF-

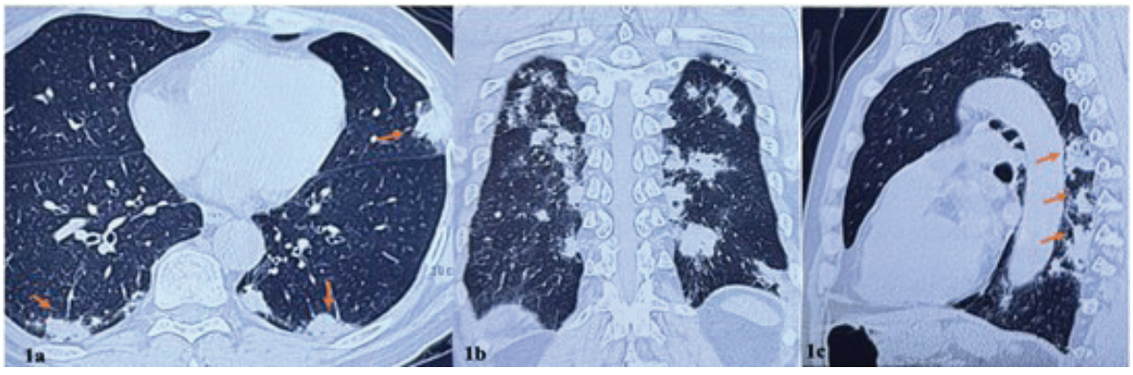

Figure 1: CT Thorax- plain study: 1a Axial view, 1b Coronal view, 1c Sagittal view showing multiple parenchymal reticulonodular infiltrate

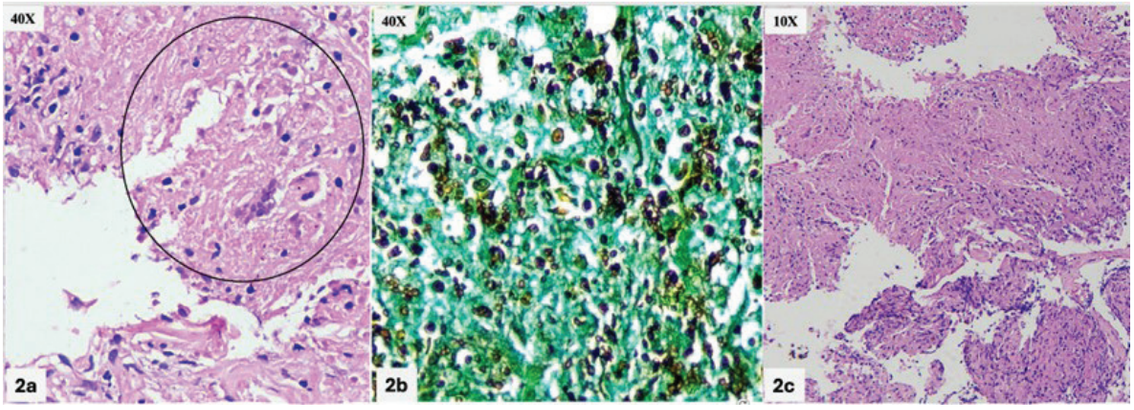

Figure 2: Transbronchial lung biopsy: Figure 2 a: H & E stain showing multiple intracellular and extracellular yeasts 2b: GMS stain showing multiple yeast 2c: H & E stain showing ill formed granulomas

alpha inhibitors until the patient responds to the antifungal drugs. For transplant recipients for whom immunosuppression cannot be stopped totally, a delicate balance needs to be maintained by reducing the immunosuppression to maintain graft function while also controlling the infection. This requires multidisciplinary co-ordination. One more challenge would be monitoring drug-drug interactions between itraconazole and immunosuppressives, especially tacrolimus.

Similarly, the decision to restart immunosuppressives depends upon the need of immunosuppression to control diseases and the patient's response to the antifungal agent. Patients should be monitored closely with frequent visits, TDM and laboratory studies to confirm continued response to antifungal drugs. Our patient had RA flare with severe painful arthritis, requiring immunosuppressives apart from NSAIDs and Disease-Modifying Antirheumatic Drugs (DMARD). The rheumatologist, after discussion with the ID team, started 10mg of prednisolone, along with HCQS and NSAIDS. Once the patient had completed 4 weeks of antifungal with clinical response, steroids were tapered and additional immunosuppressives (weekly methotrexate) were added to control RA.

How long we should treat histoplasmosis is again a challenge for the ID team. In general, the treatment lasts for several months upto a year, but the duration depends upon host characteristics. In transplant recipients long term therapy is needed to prevent relapse. Another approach is to stop therapy in these patients and monitor urine histoplasma antigen test to detect a relapse. [6,7]

Conclusions

Clinicians should maintain a high index of suspicion for invasive fungal infections and use fungal biomarkers to make early and appropriate diagnosis. Early integration of antigen testing, BAL/biopsy, and histopathology enables prompt diagnosis and treatment. Multidisciplinary collaboration is essential to balance antifungal therapy with immunosuppressives for control of the underlying inflammatory disease.

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WE MET A RARE YEAST! *HYPHOPICHIA BURTONII* FUNGEMIA WITH SEPTIC SHOCK

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Introduction

Hyphopichia burtonii is a rare, ascomycetous yeast belonging to the Saccharomycetes class, historically recognized in stored bakery products, fermented feed and marine environments with minimal human disease literature. First reported in humans in 2021 in a peritoneal dialysis patient with fungal peritonitis, it remains an uncommon pathogen. We present probably the first case of fungemia caused by this organism in an elderly patient with sepsis and renal failure.

Case report

An 85-year-old female with diabetes, hypertension, chronic kidney disease not on hemodialysis, atrial fibrillation on apixaban and newly diagnosed hypothyroidism presented with a 5-day history of generalized weakness, poor oral intake, drowsiness and headache. She had no recent hospitalization. She was taking nutraceuticals (omega-3 supplements) and had a pet African grey parrot.

Initial labs showed Hb 10.6gm%, TLC 13,000/cumm, serum creatinine 2.4mg%, urea 74mg%, NT-pro-BNP 1800pg/ml. The patient was started on piperacillin-tazobactam and a urinary catheter was inserted. Blood culture sent at admission was negative.

By day 3 of admission, the patient deteriorated with worsening encephalopathy, generalized tonic-clonic seizure, and septic shock (lactate 6.6mmol/L, pH 7.21, on dual vasopressors). She was intubated and antibiotics were escalated empirically to meropenem, linezolid, ceftazidime-avibactam and aztreonam. Central and arterial lines were inserted for hemodynamic monitoring. Septic workup showed neutrophil predominant leukocytosis (WBC=54,000/cumm), rising creatinine, and mild thrombocytopenia. Ultrasonography of the abdomen showed small right kidney with bright echotexture of both kidneys and no other abnormality. CT brain revealed acute-on-chronic right subdural hematoma with mass effect and midline shift.

On day 4 of ICU admission, blood culture two sets taken from two different peripheral sites in 3 out of four bottles grew yeast, forming

Figure 1: Creamy-white colonies of yeast *Hyphopichia burtonii* on blood agar

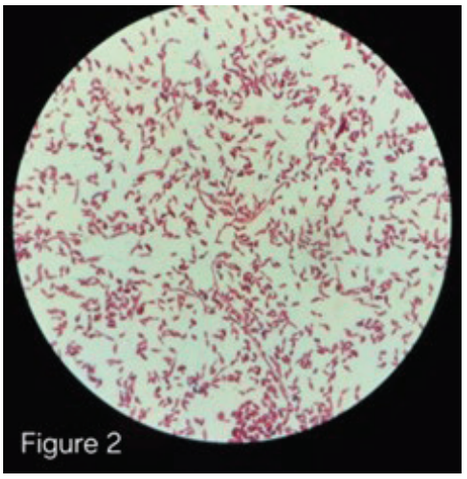

Figure 2: Gram stain showing budding yeast with pseudohyphae

creamy white colonies on subculture blood agar at 37°C (Figure1). The colonies on gram stain showed budding yeast with elongated hyphae (Figure 2). MALDI-TOF MS (Bruker Biotype Sirius) failed to identify it on repeated attempts hence ID was performed using BD Phoenix Yeast ID panel which identified *Hypopichia burtonii* with 99% confidence. Antifungal susceptibility by broth microdilution was done using commercial AFST kits (Sensititre Yeast One, ThermoFisher Scientific) and susceptibility was reported as IE (Insufficient Evidence) due to lack of established clinical breakpoints (Figure 3).

Micafungin was initiated before the yeast antifungal susceptibility was available. The patient's shock had improved. Repeat blood cultures showed clearance of fungemia hence micafungin was continued despite high MIC's to micafungin. The patient underwent right frontal and parietal burr-hole evacuation of subdural hematoma. No significant neurological recovery was found and the patient succumbed on day 14 of hospitalization.

Figure 3: Antifungal susceptibility by BMD (Broth Microdilution)

Specimen: Blood culture, Organism: *Hyphopichia burtonii*

Antifungal agent	MIC (ug/ml)	Interpretation
Anidulafungin	0.5	IE
Micafungin	2	IE
Caspofungin	0.5	IE
Amphotericin B	0.12	IE
5-Flucytosine	<0.06	IE
Posaconazole	0.12	IE
Voriconazole	0.06	IE
Itraconazole	0.12	IE
Fluconazole	8	IE

Figure 3: Antifungal susceptibility profile on sensititre-Yeast One

Discussion

Hyphopichia burtonii, formerly *Pichia burtonii*, is a slow-growing, food-spoilage yeast[1] with environmental reservoirs in zebra dove droppings[2], soil and fermented substrates. Human infections are extraordinarily rare—only three prior reported cases of fungal peritonitis have been documented [3,4,5] To our knowledge this may be the first reported case of fungemia due to this yeast.

The source of infection in this patient is unknown, possibly being the pet African grey parrot droppings or nutraceutical omega-3 supplements which were being consumed by the patient or an unknown environmental source. Rare non-candida yeasts can pose diagnostic and therapeutic challenges due to their atypical morphological features, failure to identify even using technologies like MALDI-TOF MS, absence of clinical breakpoints for correct susceptibility interpretation and lack of reported clinical data.

Antifungal susceptibility testing gave valuable insights. The *H burtonii* isolate demonstrated low MIC's to amphotericin B and most azoles except fluconazole, aligning with reported in vitro and limited clinical data. The isolate's MIC to micafungin (2.0 µg/mL) was on the higher side, yet response was favorable with fungemia clearance. The two previously reported *Hyphopichia burtonii* peritonitis cases were treated with source control (Peritoneal dialysis catheter removal) combined with fluconazole. We speculate that *Hyphopichia burtonii* should be producing (1,3)-β-d-glucan (BDG). However, production of BDG cannot be equated to therapeutic response to echinocandins for reasons including reduced FKS gene target susceptibility to echinocandins, chitin overproduction and alternative pathways of cell wall production in such rare yeasts. Guideline for rare yeast infections therefore recommends lipid formulation amphotericin B (L-AmB) as first-line empiric therapy for most rare yeasts pending susceptibility data, given the limited clinical evidence[6].

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THE SHOULDER SWELLING THAT DIDN'T READ THE TEXTBOOK

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Background

Basidiobolomycosis is a rare subcutaneous zygomycosis caused by *Basidiobolus ranarum*, typically affecting immunocompetent individuals in tropical regions. The disease often mimics other granulomatous infections such as tuberculosis or bacterial abscesses, leading to diagnostic delays. Recognition of characteristic histopathological features, especially eosinophil-rich granulomas and the Splendore–Hoeppli phenomenon, is crucial for early diagnosis and appropriate management.

Case Report

A 3-year-7-month-old girl from rural Telangana presented with a slowly progressive swelling over the right shoulder of 7 months' duration. The lesion was initially painless but later became associated with purulent discharge and intermittent low-grade fever. She had received multiple courses of antibiotics (cefuroxime, levofloxacin, clindamycin) for several weeks and approximately four months of empirical antitubercular therapy without clinical response. There was no history suggestive of immunodeficiency; the mother had tested negative for HIV during pregnancy, and the child was fully immunised for age.

The child's weight was 14 kg (25th–30th percentile). She did not appear toxic. Physical examination revealed a large, tense, dome-shaped swelling over the deltoid region. The overlying skin was erythematous to violaceous, stretched, and shiny (Figure 1). Multiple discrete ulcerative and pustular lesions were present on the surface, several with central necrotic or purulent bases and surrounding induration. Mild warmth and tenderness were noted. A few lesions appeared to be draining. Perilesional skin showed scaling. No obvious bleeding was noted. The surrounding area appeared oedematous.

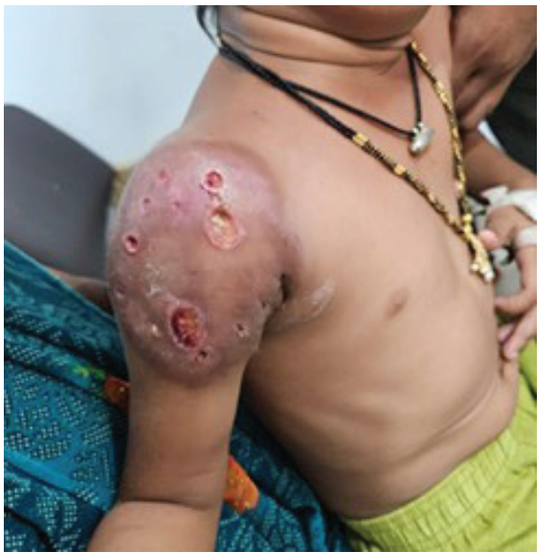

Figure 1 Clinical photograph showing a swollen right shoulder with multiple ulcerated nodular lesions and areas of discharge.

Ultrasonography revealed a 22 × 13 mm hypoechoic lesion in the subcutaneous plane with well-defined hypoechoic areas containing tiny internal echoes, along with an enlarged 7-mm axillary lymph node.

Biopsies performed elsewhere showed granulomatous inflammation with suppuration and giant cell reaction; Ziehl–Nelsen staining was negative. A second biopsy demonstrated acute suppurative inflammation with abscess formation and foci of palisading, ill-defined epithelioid granulomas with multinucleate giant cells (Langhans-type giant cells). Pus samples tested by Xpert® MTB/RIF Ultra, Gomori methenamine silver staining, Ziehl–Neelsen staining, and routine bacterial cultures were all negative.

A repeat biopsy at our centre revealed eosinophil-rich granulomatous inflammation with Splendore–Hoeppli material, findings highly suggestive of entomophthoromycosis (Figure 2, 3). Ziehl–Neelsen, bacterial stains were negative. GMS stain showed broad ribbon shaped hyphae.

The patient was treated with oral itraconazole at 5 mg per kilogram every 12 hours (75 mg twice daily) and trimethoprim–sulfamethoxazole, providing 120 mg per day of trimethoprim (8.57 mg per kilogram per day). She was treated for a total of 11 weeks. Within two weeks of initiating therapy, she showed marked clinical improvement, with a reduction in lesion size, healing of ulcers, and regression of axillary lymphadenopathy (Figure 4). Fungal culture later demonstrated thin-walled, aseptate hyphal growth; further species identification was not pursued because of cost constraints. She completed the full 11-week course with good clinical resolution (Figure 5).

Discussion

Basidiobolomycosis poses significant diagnostic challenges in endemic regions due to its clinical and histopathological overlap with tuberculosis and bacterial infections. Repeated negative Ziehl–Neelsen, bacterial,

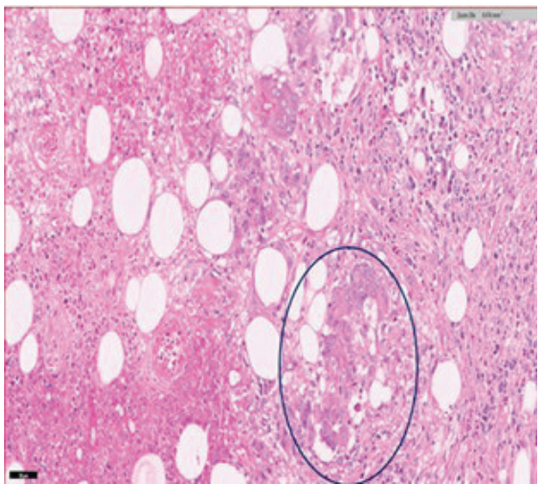

Figure 2: 20x magnification: Ill-defined epithelioid granulomas; giant cell containing a structure with Splendore-Hoeppli phenomenon around it

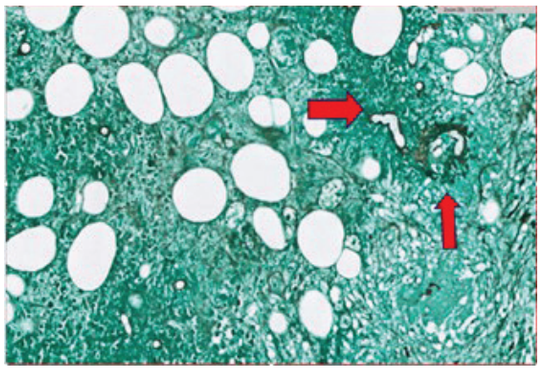

Figure 3: 20x magnification: GMS staining showing broad, aseptate ribbon-shaped hyphal forms

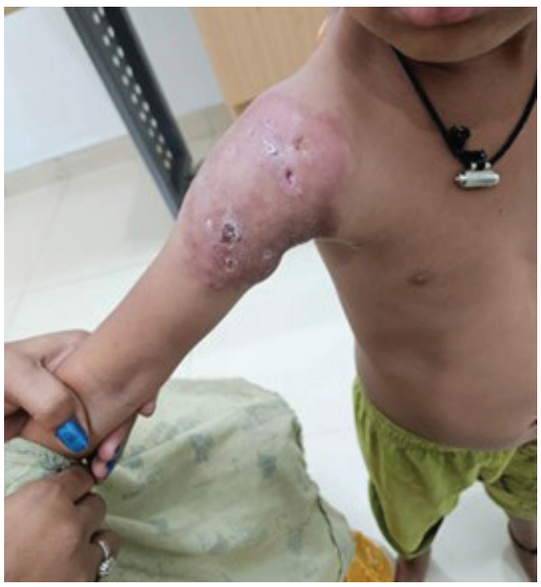

Figure 4: Clinical photograph after 3 weeks of antifungal therapy showing marked reduction in swelling, healing of ulcers, and residual hyperpigmentation.

and fungal stains may lead to misdiagnosis and prolonged inappropriate therapy. The presence of eosinophil-rich granulomatous inflammation and Splendore–Hoeppli material on histopathology is highly suggestive of entomophthoromycosis and should prompt early antifungal therapy.

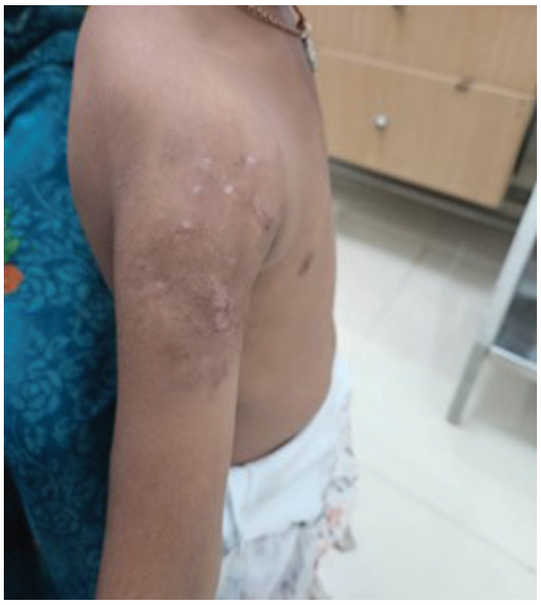

Figure 5: Clinical photograph after completion of antifungal therapy showing marked resolution of swelling with healed lesions and residual scarring.

Although itraconazole remains the mainstay of treatment, trimethoprim–sulfamethoxazole has demonstrated clinical efficacy and is frequently used as adjunctive or alternative therapy. The exact mechanism is not fully understood; however, *Basidiobolus ranarum* appears to be susceptible to sulfonamides, possibly by inhibiting folate synthesis pathways. In addition, trimethoprim–sulfamethoxazole may exert anti-inflammatory effects and provide coverage against secondary bacterial infection, which can complicate subcutaneous lesions. Combination therapy has been associated with faster clinical resolution and improved outcomes, particularly in resource-limited settings.

Conclusions

Not all granulomatous lesions are tubercular. In patients with chronic subcutaneous swellings that are unresponsive to standard antibacterial or antitubercular therapy, especially in tropical regions, alternative diagnoses such as basidiobolomycosis should be actively considered. Histopathological clues, such as eosinophil-rich granulomas and the Splendore–Hoeppli phenomenon, should guide the correct diagnosis and early antifungal therapy.

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ATYPICAL PNEUMONIA, TYPICAL MOULD

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Introduction

Invasive mould infections (IMI) like Invasive Pulmonary Aspergillosis (IPA) & Invasive Pulmonary Mucormycosis (IPM) are now being reported in critically ill patients without the classical host factors as mentioned in the EORTC/MSGERC document.[1]

Case

A 39-year-old female with no known comorbidities presented with dry cough, myalgia, low-grade fever, and progressive breathlessness. She was intubated & mechanically ventilated. She was diagnosed as right sided pneumonia due to *Mycoplasma pneumoniae* based on endotracheal tube secretion multiplex PCR result. This was being treated with doxycycline which was planned for 14 days.

Patient had a prolonged ICU stay with persistent oxygen requirement with HFNC which prompted a repeat CT chest. This revealed multiple nodules in the left lung, including one with a reverse halo sign (RHS) (Figure 1). Therefore, a suspicion of IPA and/or IPM was raised.Bronchoalveolar lavage (BAL) revealed a strongly positive galactomannan assay (8.2), and serum galactomannan was also elevated (3.04). BAL aspergillus PCR was positive, while BAL Mucorales PCR was negative. Other bacterial PCR were negative, thus ruling out secondary bacterial infections.

The patient was started on isavuconazole which would cover both IPA and IPM. She gradually recovered completely.

Discussion

This patient's clinical features had raised a suspicion of IPA and/or IPM.

As regards IPA, host factor in this patient was prolonged ICU stay. IPA after *Mycoplasma pneumoniae* has been documented in only a single case report by Ordronneau et al[2] and therefore it may not be a host factor in this patient. Radiological findings such as nodules in lungs and mycological tests including galactomannan (GM) and PCR are other features needed for diagnosis.

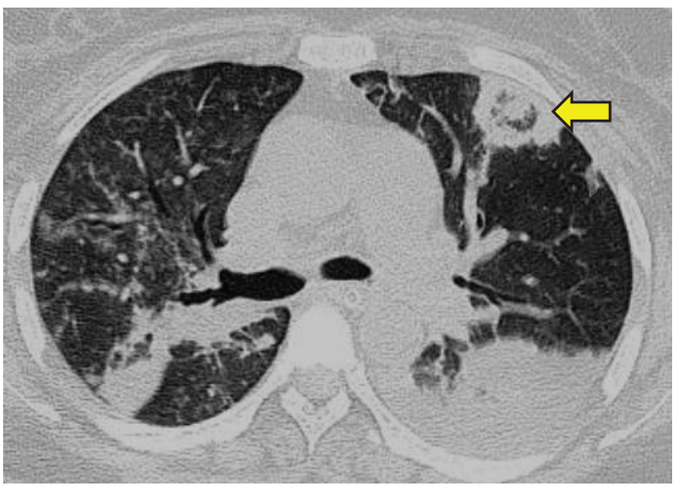

Figure 1: CT Chest showing Nodule with RHS

As far as IPM is concerned, risk factors include mainly diabetes mellitus & use of steroids, which were absent in this patient. Radiological feature like the reverse halo sign (RHS) often alert to the possibility of IPM but is not specific and can occur in other conditions as well. No firm diagnostic mycological tests are available for IPM/IM. PCR is one of the options but lacks sensitivity especially in non-neutropenic patients as shown in a recent paper[3].

Conclusion

Host factors for both IPA and IPM are evolving. Radiological features are often overlapping. Mycological tests have problem with sensitivity & specificity. Therefore, clinical judgement along with all these factors is needed for devising the treatment. However, the choice of newer triazoles like isavuconazole & posaconazole circumvent this problem as they have efficacy against both invasive aspergillosis (IA) & invasive mucormycosis (IM).

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TRUST, BUT VERIFY: CLINICO MICROBIOLOGIC CORRELATION TO PREVENT DIAGNOSTIC ANCHORING IN TRANSPLANT-ASSOCIATED MYCOSES

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Background

Phaeohyphomycosis comprises infections caused by melanized fungi seen histologically as pigmented, septate hyphae. These molds are environmental and primarily affect immunocompromised patients,

particularly solid organ transplant (SOT) recipients and those receiving prolonged immunosuppression. Among them, *Medicopsis romeroi* (formerly *Pyrenochaeta romeroi)* is an uncommon but increasingly recognized pathogen. Diagnosis is difficult because clinical findings are nonspecific, isolates frequently fail to sporulate, and confirmation often depends on molecular techniques. Optimal therapy remains undefined. Reported management combines surgical excision or debridement with prolonged azole therapy, yet relapse and treatment failure are common, especially in immunocompromised hosts.

We present a renal transplant recipient with progressive infection due to *M. romeroi*, underscoring the need for clinico microbiologic correlation when an initial identification as Malassezia conflicted with the clinical course.

Case Report

A 39-year-old grocery shop owner, five months after renal transplantation and receiving tacrolimus, prednisolone, and mycophenolate, initially presented to an outside hospital with a six week history of a painless enlarging nodule on the ulnar aspect of the right little finger (Figure 1). He denied fever, weight loss, trauma, joint pain, or other systemic symptoms.

Excision biopsy demonstrated dense inflammatory infiltrates, and fungal culture yielded *Malassezia furfur*. Itraconazole was started. Despite therapy, the lesion progressed, developing ulceration, local invasion, and satellite nodules, raising concern for an alternative diagnosis (Figure 2).

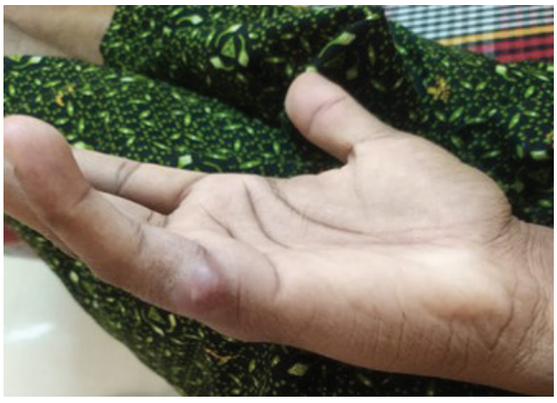

Figure 1: A single nodular lesion over the ulnar aspect of the right little finger.

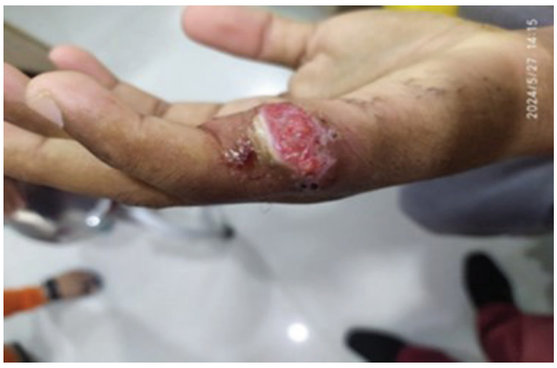

Figure 2: Worsening nodular lesion with tissue invasion

When he presented to our center, the continued deterioration prompted renewed consideration of invasive fungal and bacterial etiologies in the setting of significant immunosuppression, including sporotrichosis, atypical mycobacterial infection, cutaneous nocardiosis, entomophthoromycosis, hyalohyphomycosis, phaeohyphomycosis, and molds such as aspergillosis and mucormycosis. Empiric therapy was transitioned to posaconazole given its broader activity against dematiaceous fungi.

The patient received detailed counseling regarding the need for repeat surgical debridement with adequate tissue acquisition. Following an interval of approximately four weeks, he proceeded for surgery, and specimens were obtained.

Histopathology revealed multinucleated giant cells and septate, brown-pigmented hyphae within a granulomatous inflammatory background, findings highly suggestive of infection with dematiaceous fungi (Figure 3, 4).

Direct KOH microscopy demonstrated septate melanized hyphae, and culture on Sabouraud dextrose agar at 30 °C grew a grey-black dematiaceous mold; however, no sporulation was observed on lactophenol cotton blue mount. Together, these findings established subcutaneous phaeohyphomycosis (Figure 5).

Since the isolate could not be identified phenotypically, it was referred to the ICMR-Advanced Mycology Diagnostic & Research Centre, Dept. of Microbiology, Nizam's Institute of Medical Sciences, Hyderabad for further workup. Sanger sequencing of the internal transcribed spacer

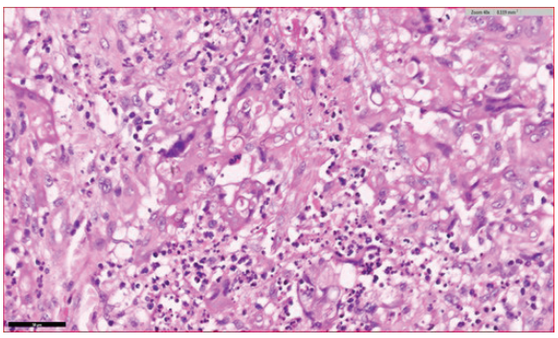

Figure 3: Histopathological examination revealed a dense inflammatory infiltrate with numerous multinucleated giant cells and scattered epithelioid histiocytes

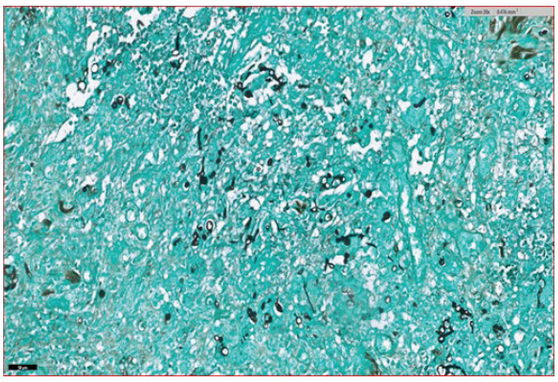

Figure 4: Methanamine silver stain highlighting the fungal hyphae with beaded appearance

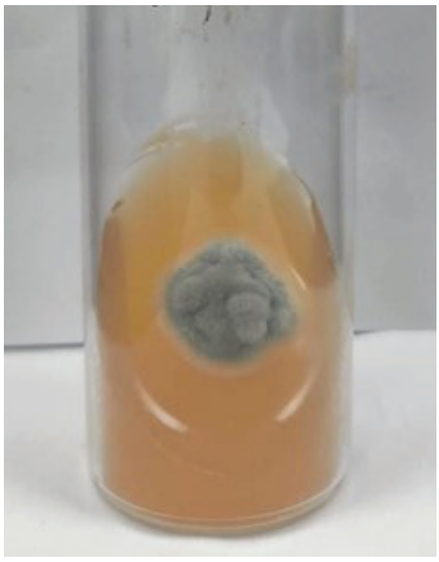

Figure 5: Fungal culture on Sabouraud dextrose agar at 30 °C grew a grey-black dematiaceous mold

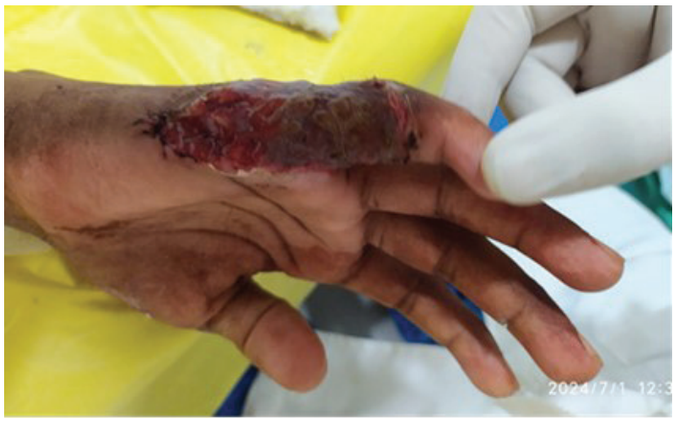

Figure 6a: New lesions with graft loss and ulceration.

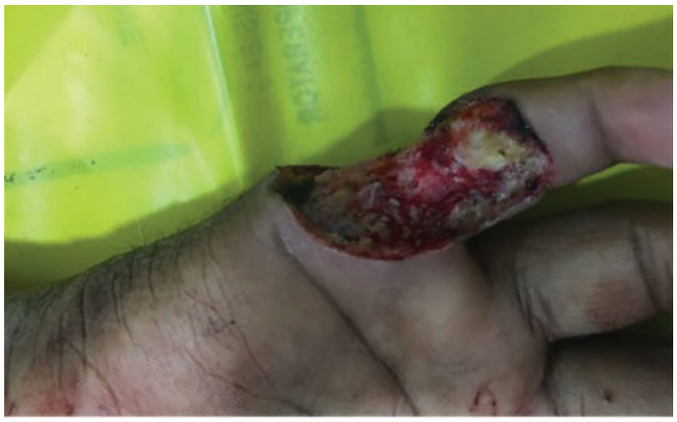

Figure 6b: Progressive disease involving underlying tissue and bone.

(ITS) region identified *Medicopsis romeroi*. Owing to non-sporulation, antifungal susceptibility testing was not feasible.

With mucormycosis excluded, therapy was changed to voriconazole. The patient initially improved, with healthy granulation tissue formation, and underwent skin grafting. However, three weeks later, new lesions appeared with graft loss, ulceration, and progression to involve deeper tissue and bone (Figure 6a, b).

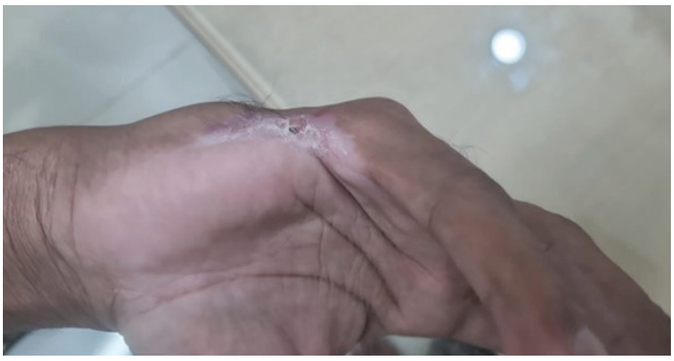

Figure 7: Healed wound with no further recurrence

In view of continued progression despite appropriately dosed antifungal therapy with therapeutic drug levels, amputation was undertaken. Postoperatively, voriconazole was continued for six weeks.

Given that voriconazole is a strong CYP3A4 inhibitor and can markedly increase tacrolimus exposure, tacrolimus doses were reduced and titrated using serial therapeutic drug monitoring to maintain target trough concentrations and prevent toxicity. Because both agents may prolong QTc, electrocardiography was performed at baseline and periodically during treatment. Liver function tests were also followed due to the hepatotoxic potential of voriconazole.

At three months after completion of therapy, the patient remained well without recurrence (Figure 7).

Discussion

Clinically, infection due to *Medicopsis romeroi* usually presents as a painless, slowly enlarging subcutaneous nodule or cyst, often on the distal extremities. Systemic symptoms are uncommon and may delay recognition. Misidentification, as occurred in this case with initial isolation of *Malassezia furfur*, can further postpone diagnosis when laboratory results fail to match the clinical picture. Malassezia species commonly cause seborrheic dermatitis, pityriasis versicolor, and folliculitis, and can produce fungemia in immunocompromised hosts. A solitary painless nodule is unusual and should prompt reassessment of the diagnosis.

Misidentification in original culture may occur when colonizing organisms outgrow the true pathogen or when the causative mold fails to sporulate, limiting phenotypic recognition. In such situations, culture results must be interpreted alongside histopathology and the clinical course, particularly when therapeutic response is discordant.

Histopathology is central to recognizing dematiaceous infection. Granulomatous inflammation with pigmented septate hyphae and multinucleated giant cells is typical, while Medlar bodies are absent, distinguishing phaeohyphomycosis from chromoblastomycosis. Culture findings are frequently nonspecific, and non-sporulation often prevents phenotypic identification, making molecular techniques such as ITS sequencing essential and increasingly regarded as the diagnostic standard.

No standardized antifungal regimen exists. Triazoles, particularly posaconazole and voriconazole, generally demonstrate the lowest MICs, yet outcomes may not parallel in-vitro susceptibility. Progression or

recurrence despite prolonged azole therapy is well described, especially in transplant recipients who remain immunosuppressed.

Our patient initially improved on voriconazole but soon deteriorated, with extension into deeper tissue and bone despite therapeutic levels. Similar patterns of partial response followed by relapse and progression have been described in SOT recipients with ongoing immunosuppression, emphasizing the limited effectiveness of medical therapy alone in such cohorts.

Surgery remains fundamental. Early, complete excision is associated with better outcomes in localized disease, whereas delay, incomplete source control, or inability to modify immunosuppression may predispose to failure. In this instance, postponement of definitive intervention and evolution to osteomyelitis ultimately required amputation, after which disease control was achieved.

Conclusions

Chronic subcutaneous lesions in immunosuppressed hosts should prompt suspicion of dematiaceous fungi. Discordance between the clinical picture and microbiologic identification should prompt re-evaluation and repeat sampling with careful clinicopathologic correlation. Early combined surgical and antifungal therapy offers the best chance of cure. *M. romeroi* infection can be aggressive and limb-threatening despite appropriate antifungal therapy, demanding vigilance and timely action.

References

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