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CASE REPORT

Primary Cutaneous Aspergillosis Due to *Aspergillus flavus* in an Immunocompetent Patient

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Abstract: Invasive aspergillosis is a life-threatening infection caused by *Aspergillus* species, affecting the lungs, central nervous system, nasal and orbital regions, and skin. Primary cutaneous aspergillosis (PCA) occurs through direct skin inoculation via trauma, burns, or surgical wounds, with *Aspergillus fumigatus, Aspergillus flavus*, and *Aspergillus niger* as common causative species, and is rare in immunocompetent individuals. We report a case of PCA in a 56-year-old immunocompetent patient with facial and right ankle ulcers, persisting for two years. The patient had no history of diabetes, corticosteroid use, or immunodeficiency. Fungal culture and metagenomic next-generation sequencing (mNGS) confirmed *A. flavus* infection. Voriconazole therapy, surgical debridement, and specialized wound care led to the gradual healing of the ulcers. This case highlights the importance of early diagnosis and intervention to prevent infection spread and progression to systemic aspergillosis or septic shock.

Keywords: invasive aspergillosis, primary cutaneous aspergillosis, *A. flavus*, fungal infection

Background

Invasive aspergillosis primarily affects immunosuppressed individuals, including those on corticosteroid therapy, with neutropenia, hematologic malignancies, or those receiving hematopoietic stem cell or solid organ transplants. This condition can lead to serious complications, including bronchopneumonia, orbital infections, invasive pulmonary aspergillosis, osteomyelitis, and cutaneous manifestations.[1–3] Cutaneous aspergillosis can result from direct inoculation of *Aspergillus* species at the site of skin injury, often due to intravenous catheter insertion, traumatic wounds, the use of occlusive dressings, thermal injuries, or surgical incisions. Alternatively, it may result from hematogenous dissemination from a primary internal focus or direct extension from adjacent structures or cavities.[4]

Skin trauma is a major risk factor for PCA. The clinical presentation is often nonspecific, ranging from macules, papules, and plaques to bullae, and may progress to necrotic ulcers.[5] Due to the nonspecific nature of these clinical presentations, misdiagnosis and delayed diagnosis are common. Without prompt recognition and treatment, the infection may disseminate, leading to systemic invasive aspergillosis and a significantly increased risk of mortality. Direct microscopy, culture, serological testing, and molecular diagnostics are crucial for accurately confirming the diagnosis of PCA.[6] The key element of PCA treatment is systemic antifungal therapy, with voriconazole as the first-line agent. Adjunctive interventions, such as surgical debridement and optimized wound care, are crucial for lesion healing and recovery.

This report describes a rare case of PCA caused by *A. flavus* in an immunocompetent patient. We present the diagnostic and therapeutic approach, providing insights into managing infectious lesions with nonspecific dermatologic manifestations. This case highlights the critical importance of early diagnosis and timely intervention to reduce complications and mortality.

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Case Presentation

A 56-year-old male presented with chronic facial and right ankle ulcers and erosions, accompanied by purulent discharge, persisting for two years. Two years earlier, the patient developed pruritic erythema on the face, leading to excoriation and the formation of cutaneous lesions. He self-applied traditional herbal compresses, which relieved pruritus, but the lesions progressed, leading to erosions and ulcers. The patient visited local hospitals but did not receive an accurate diagnosis and effective treatment. Eventually, similar lesions appeared on the right ankle, he continued to apply herbal medicines topically over the ulcerated areas for an extended period, and the lesion gradual worsened. When first examined at our hospital, both the facial and right ankle ulcers were covered with thick crusts formed by a mixture of herbal medicines and purulent discharge (Figure 1A–F). The patient had no history of hypertension, diabetes, or prolonged use of corticosteroid or immunosuppressant. Laboratory tests revealed elevated white blood cell count and infection-related proteins, while other hematological parameters were normal. Fresh ulcer edge secretions were collected using an aseptic swab for both bacterial and fungal cultures. No bacterial growth was observed, while fungal cultures on potato dextrose agar (PDA) showed light green velvety colonies with radial grooves, from which *A. flavus* was identified (Figure 2A). Calcofluor white (CFW) and lactophenol cotton blue (LPCB) staining revealed numerous conidial heads with radiating chains and septate hyphal structures (Figure 2B–D), consistent with a diagnosis of *A. flavus* infection. mNGS of lesional tissue identified *A. flavus*. During hospitalization, the patient received an initial loading dose of intravenous voriconazole at 400 mg every 12 hours, followed by a maintenance dose of 200 mg every 12 hours. Surgical debridement of the skin

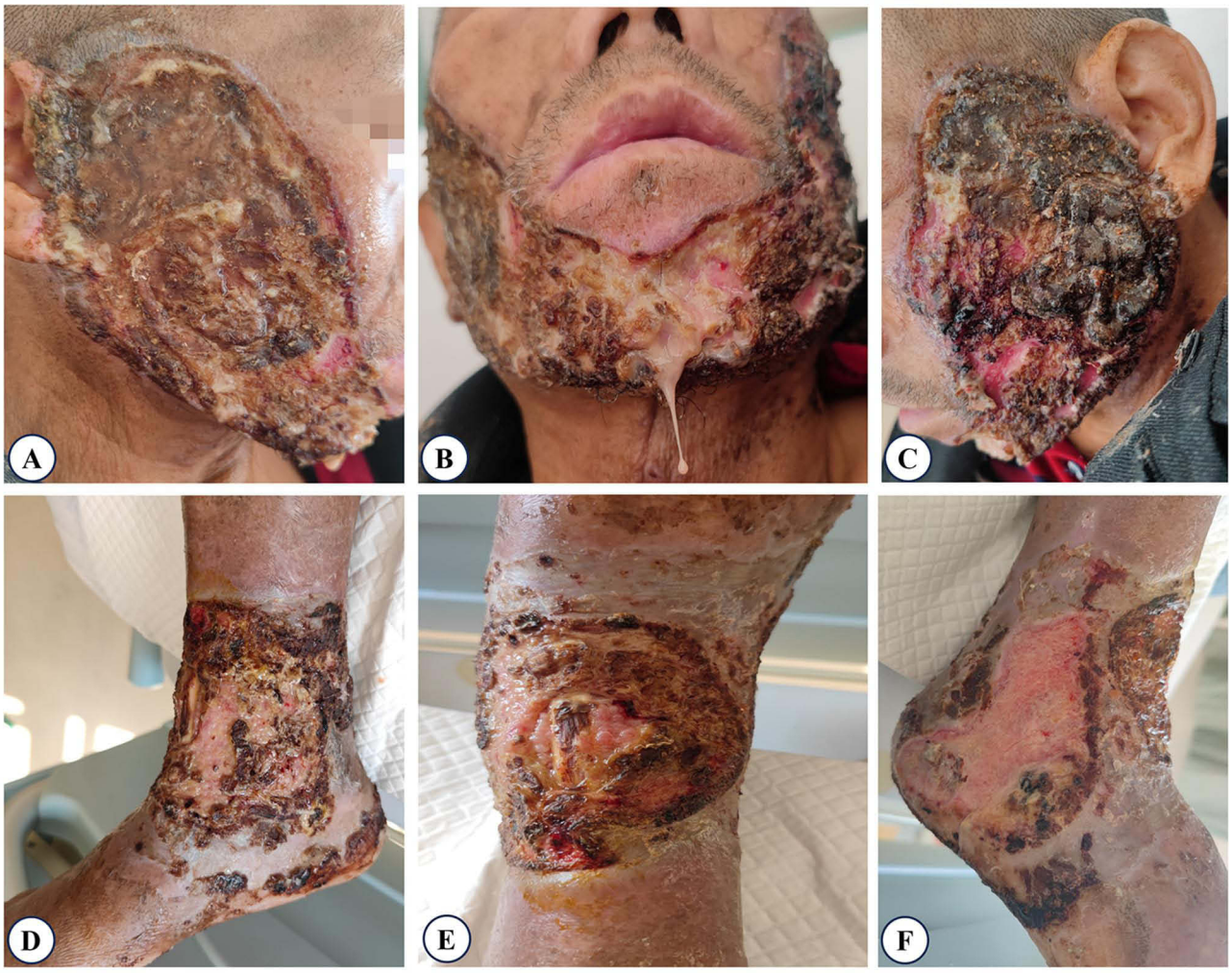

Figure 1 Clinical presentation of lesions prior to treatment. (**A–C**) Facial skin lesions. (**D–F**) Right ankle skin lesions.

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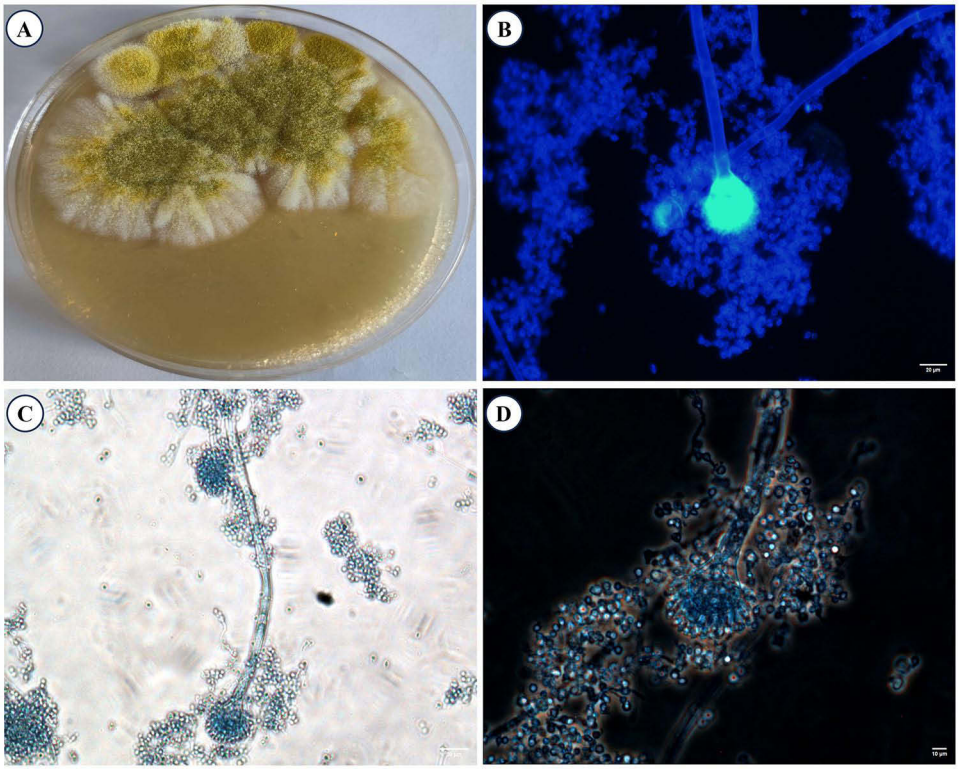

Figure 2 Culture and staining of lesional tissue specimens. (**A**) PDA culture. (**B**) Calcofluor white staining. (**C** and **D**) Lactophenol cotton blue staining.

lesions was also performed (Figure 3A–F). Upon discharge, the patient was instructed to continue taking voriconazole tablets at a dose of 200 mg twice daily for 2 months. Additionally, a specialized wound care team managed regular wound dressing replacements. After 46 days of antifungal therapy and surgery, the facial and right ankle erosions and ulcers showed gradual healing (Figure 4A–F).

Discussion

Invasive aspergillosis is a fungal infection caused by various *Aspergillus* species, commonly found in soil, water, and decaying organic matter. This infection can affect the lungs, central nervous system, and skin, among other organs. However, cutaneous involvement is rare, with reported incidence rates ranging from 1% to 5%.[7]

The predominant species causing PCA varies across studies. In a retrospective analysis, *A. fumigatus, A. flavus*, and *A. niger* accounted for 43.3%, 35.1%, and 10.8% of infections, respectively.[8] In contrast, another study identified *A. flavus* as the pathogen in 70% of PCA cases, accounting for 7 out of 10 cases.[9] PCA predominantly affects immunocompromised individuals and is rarely seen in immunocompetent hosts. A review of 130 cases (1967–2015) by Tatara et al identified key risk factors: hematologic malignancies (28.5%), HIV/AIDS (15.4%), infancy (12.3%), solid organ transplantation (9.2%), burns (6.2%), corticosteroid use (4.6%), stem cell transplantation (3.8%), diabetes (2.3%), and trauma (2.3%). Notably, 11.2% of cases occurred in patients without identifiable risk factors, highlighting PCA's rare occurrence in healthy individuals.[8] In this case, the patient had a history of facial trauma but no history of diabetes, corticosteroid use, or immunodeficiency, as confirmed by diagnostic evaluations.

Climate and geographical factors play a key role in the prevalence and distribution of *Aspergillus* species. *A. flavus*, prevalent in higher temperatures, is more common in tropical regions such as India, Mexico, Pakistan, Sudan, and Saudi Arabia.[10–12] Additionally, humidity significantly affects the prevalence of *A. flavus*, as increased water availability fosters fungal growth and conidiation.[4] Human infection primarily occurs through respiratory exposure to conidia, but transmission can also occur via direct contact with skin or wounds, intravenous infusion, and infected wound dressings.[13,14]

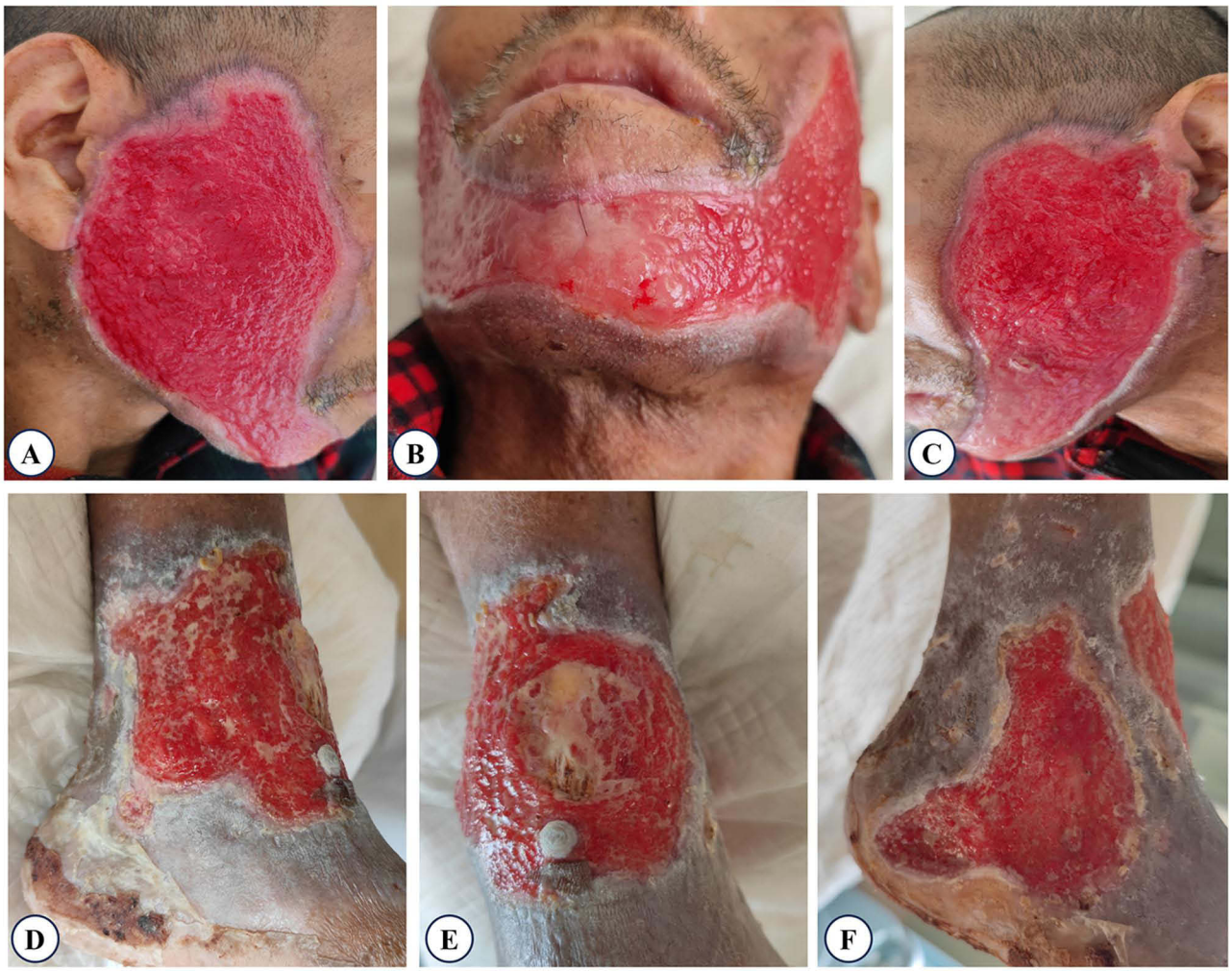

Figure 3 Post debridement skin manifestations. (**A–C**) Facial skin lesions. (**D–F**) Right ankle skin lesions.

The World Health Organization (WHO) defines a medicinal plant as "any plant containing substances in one or more of its parts that can be used for therapeutic purposes or as precursors for semi-synthetic drugs".[15] Herbal plants can be contaminated with various pathogenic fungi during cultivation, harvesting, preparation, storage, and transport.[16] In China, Zheng et al identified 126 fungal strains from traditional Chinese medicinal herbs, with *Aspergillus* and *Penicillium* as the most common general.[17] A study assessed the mycobiota and mycotoxin profiles of 48 herbal medicine samples, demonstrating that over 70% were contaminated with mycotoxins, including aflatoxins, ochratoxin A, and citrinin[18]. This highlights the risk of *A. flavus* contamination in herbal preparations.

This case report describes a rare instance of PCA due to *A. flavus* in an immunocompetent patient residing in a hot, humid region endemic for this species, increasing the risk of infection. The patient initially presented with facial erythema and pruritus, leading to scratching that compromised the skin barrier and facilitating fungal invasion. The likely source of infection was the application of herbal poultices, potentially contaminated with *A. flavus*, directly to the wound site. Persistent scratching and friction likely facilitated the spread of the fungus from the facial lesions to the right ankle, resulting in similar lesions at a distant site. This aligns with the findings of Alquraish et al who reported *Aspergillus* infections linked to the use of herbal poultices on surgical wounds.[19] Such cases underscore the heightened risk of fungal infections when unverified herbal remedies are applied to compromised skin, highlighting the need for caution in their use.

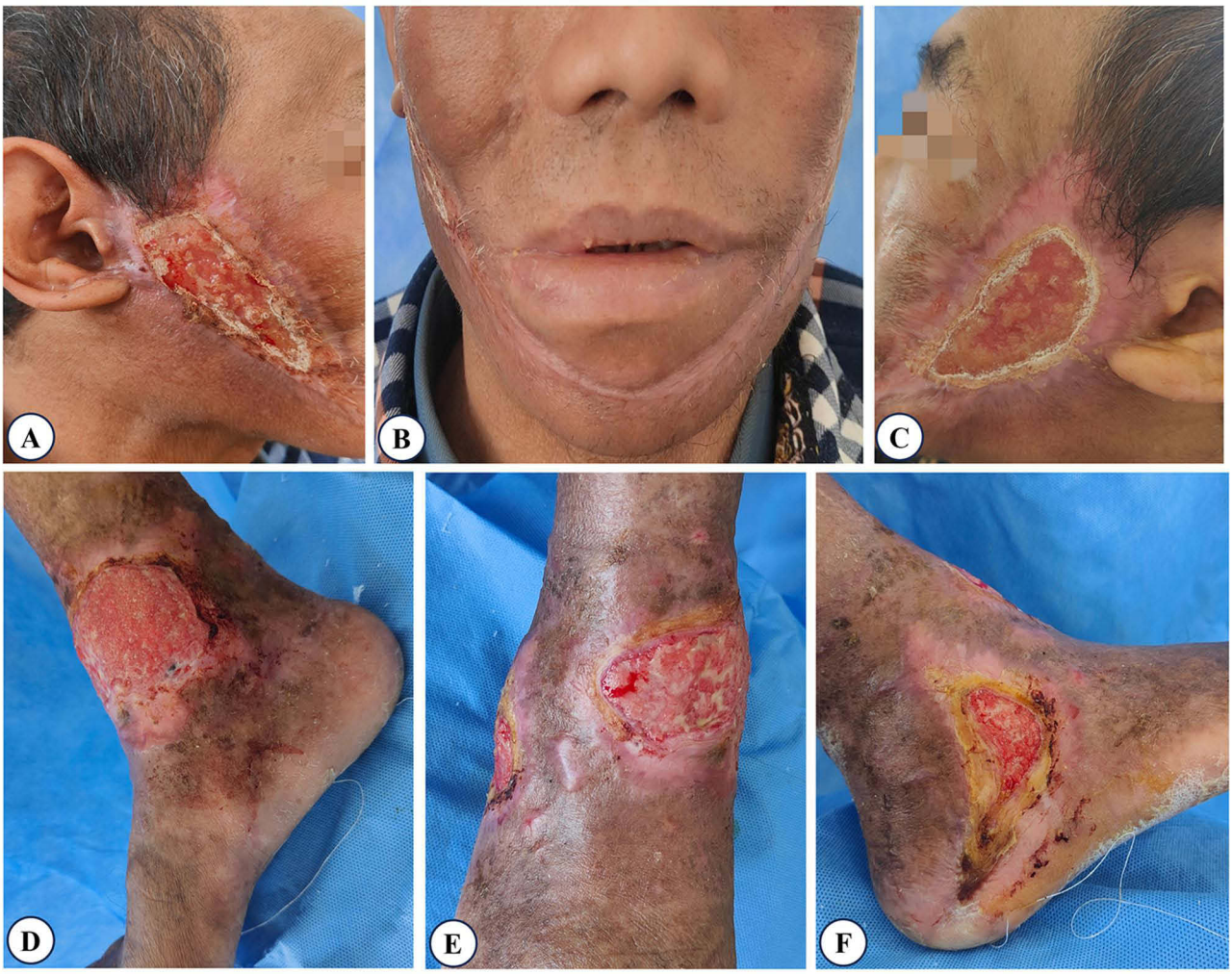

Figure 4 The skin lesions gradually healed after systemic antifungal therapy and enhanced wound care. (**A–C**) Facial skin lesions. (**D–F**) Right ankle skin lesions.

Direct microscopy, culture, serological tests, and molecular diagnostics are critical for diagnosing *Aspergillus* infections. With advancements in sequencing technologies, mNGS has become a key tool in pathogen detection. In this case, the patient's lesions, featuring erosions and ulcers with purulent discharge, presented as nonspecific signs of infection. While bacterial cultures were negative, fungal culture and staining confirmed *Aspergillus* infection. Additionally, mNGS of the lesion tissue identified an infection with *A. flavus*. The limitation of this case report is that it is based on a single patient and the lack of antifungal susceptibility testing. Additionally, the specific herbal medicines that might have been contaminated by *A. flavus* could not be identified. Based on the patient's environment, medical history, physical examination, fungal culture, staining, mNGS results, and positive therapeutic response, a diagnosis of PCA caused by *A. flavus* was confirmed. The patient was treated with voriconazole, combined with surgical debridement and enhanced wound care, resulting in the gradual reduction of ulcers in the affected area.

Conclusion

This case reports a rare instance of PCA caused by *A. flavus* in an immunocompetent patient. Delayed recognition and inappropriate treatment resulted in progressive deep ulcerations with purulent discharge on the face and right ankle. Diagnosis was confirmed by fungal culture, staining, and mNGS. Treatment with voriconazole, surgical debridement, and specialized wound care resulted in gradual healing. The case highlights that PCA, though typically seen in

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immunocompromised patients, can also occur in immunocompetent individuals presenting with nonspecific infections. Early diagnosis and timely, targeted therapy are critical to prevent disease progression and complications.

Abbreviations

PCA, Primary Cutaneous Aspergillosis; mNGS, Metagenomic Next-Generation Sequencing; PDA, Potato Dextrose Agar; CFW, Calcofluor White; LPCB, Lactophenol Cotton Blue; WHO, World Health Organization.

Data Sharing Statement

The data of mNGS is available with the following link: https://www.ncbi.nlm.nih.gov/sra/PRJNA1370181.

Ethical Approval and Informed Consent

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (No. 2022-L-190), and no institutional approval is needed to publish the details of this case.

Consent for Publication

The patient provided written informed consent for publication of these case reports and accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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