

Disseminated cutaneous fusariosis in human immunodeficiency virus-infected patient and dramatic response with oral itraconazole

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Abstract

Fusarium species are known to cause disseminated cutaneous lesions in immunocompromised patients. Some cases of fusariosis are reported in patients infected with the human immunodeficiency virus. There are two reports in such patients with systemic comorbidities like lymphoma, neutropenia and infective port-a-catheter. Another reported patient had systemic fusariosis, without skin involvement. Diagnosis and treatment of cutaneous fusariosis is difficult and resistance to antifungals is a problem. Our patient was at an advanced human immunodeficiency virus infection stage with disseminated cutaneous fusariosis, without any systemic involvement, who responded completely to oral itraconazole.

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Introduction

Fungal infections cause cutaneous lesions either directly or are metastatic in immunocompromised patients. *Fusarium* species are common plant pathogens that cause localized and disseminated infection (in immunocompromised and neutropenic patients). Majority of patients (72%–91%) have cutaneous lesions (primary or metastatic).¹ Diagnosis of disseminated cutaneous infection is difficult. The treatment is quite unsatisfactory due to the variable susceptibility of the pathogen to antifungals and the lack of supporting evidence. We herein report a rare case of disseminated cutaneous fusariosis, without systemic involvement, in a patient infected with the human immunodeficiency virus, who responded successfully to itraconazole.

Case Report

A 40-year-old farmer presented with multiple, painless, raised skin lesions with pus discharge, which were of one-and-a-half months' duration. Lesions began to appear on the face and progressed to both his arms and thighs over a period of 1 week. He was earlier diagnosed to be infected with the human immunodeficiency virus, with CD4 T-lymphocyte count of 38 cells/ μ L, and was on highly

active antiretroviral therapy from an antiretroviral therapy center for the past 6 months.

The patient was afebrile with no other systemic complaints. On examination, his body mass index was 18.88 kg/m². Multiple erythematous and tender papules and nodules with central crusting and necrosis were present on the face, neck, and bilaterally on arms and on thighs extending to the knees [Figure 1]. Trunk, distal extremities, palms, soles and mucosae were spared. There was no history of trauma and no clinically apparent onychomycosis or any breach in the skin other than the lesions present. Clinically, the possibility of cryptococcosis (common opportunistic infections in human immunodeficiency virus patients) and ecthyma gangrenosum were considered. Lymph nodes examination revealed no significant enlargement.

On hematological investigation, no significant abnormality was found. Blood culture was negative for any bacterium or fungus. All other possible systemic involvements were ruled out by appropriate

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Figure 1a: Multiple erythematous papules and nodules with central crusting present on face

tests, mainly computed tomography of the chest, x-rays of the paranasal sinuses and abdominal ultrasonography. Skin biopsy from a nodule on the arm revealed pseudoepitheliomatous hyperplasia and intraepidermal granulomas with giant cells. Periodic acid–Schiff staining was positive for spores and short fungal hyphae. An additional sample of the excised nodule was sent for microbiological examination.

A 10% potassium hydroxide wet mount of tissue revealed septate, hyaline and branched fungal hyphae. The specimen was cultured on two sets of Sabouraud dextrose agar, incubated at 37°C and 25°C. After 4 days of incubation, a heavy growth of fungal colonies was seen at 25°C in the form of a white and cotton obverse and orange reverse suggestive of *Fusarium* [Figure 2]. Growth was observed on successive subcultures performed on potato dextrose agar. Lactophenol cotton blue mount showed septate, branched hyphae producing microconidia (oval small 2–4 × 4–8 μm with

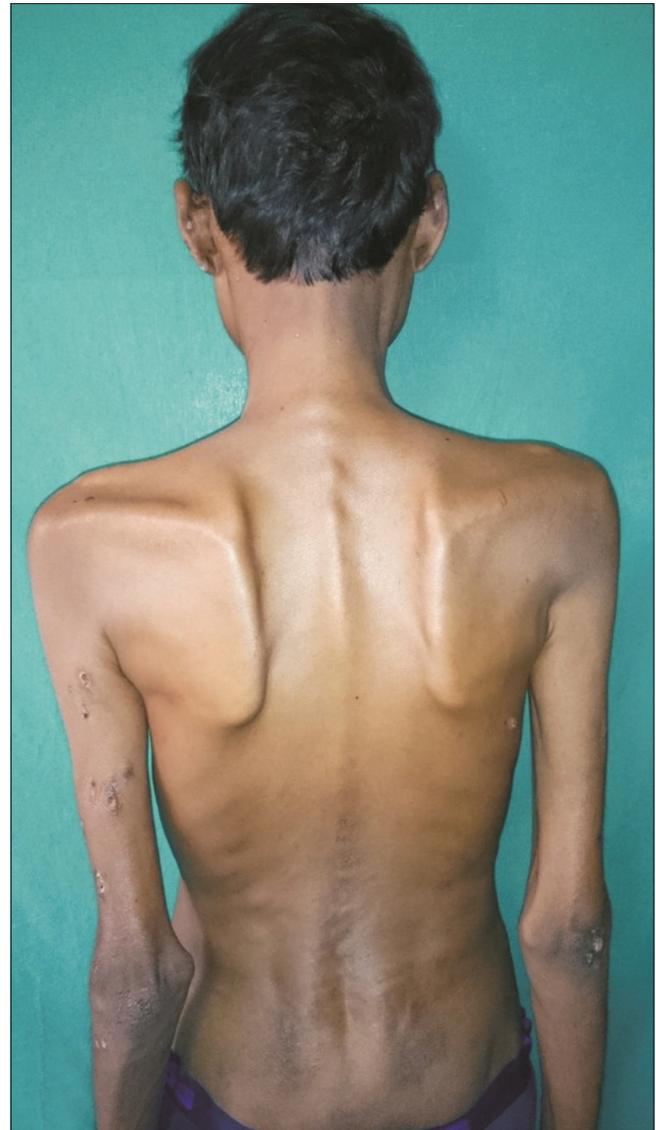


Figure 1b: Similar lesions over arms

1–2-celled reniform conidia singly and in clusters) and many branched conidiophores with phialides producing 2–4 × 11–60 μm multiseptate (3–4), sickle or boat-shaped macroconidia typical of *Fusarium solani* [Figure 3]. Later, another tissue sample was sent for repeat isolation of fungus in order to confirm the species.²

Minimal inhibitory concentrations and minimal effective concentration were determined following the microdilution method recommended by Clinical and Laboratory Standards Institute document M38-A2 with minor changes.³ Fluconazole, amphotericin-B and terbinafine were ineffective in inhibiting growth of *F. solani*. Among sensitive drugs, itraconazole, ketoconazole and voriconazole had minimal inhibitory concentration 90 of 2 μg/ml each [Figure 4].^{4,6}

Our patient was prescribed itraconazole 200 mg twice daily and response was seen in 2 weeks, with complete subsidence of lesions



Figure 1c: Similar lesions on lateral aspect of face



Figure 1d: Similar lesions on bilateral thighs



Figure 2a: Sabouraud's dextrose agar without cycloheximide at 25°C with white-cottony fungal colonies



Figure 2b: Orange reverse suggestive of *Fusarium*

in 1½ months, leaving postinflammatory hyperpigmentation and scarring [Figure 5]. Itraconazole was continued at a tapered dose of 100 mg twice daily for a further 3 months.

Discussion

Fusarium species are ubiquitous soil saprophytes and plant

pathogens that may cause infections in humans, in localized, locally invasive and disseminated forms. *Fusarium* species now represent the second most common mold causing opportunistic infections in immunocompromised patients.⁷ *F. solani* was the most frequent, followed by *Fusarium oxysporum*, *Fusarium verticillioidis* and *Fusarium moniliforme* among 12 species associated with infection.⁸

Skin involvement represents a frequent manifestation (>50%) of infection by *Fusarium* species and is also the most common source

Table 1: Cases of disseminated fusariosis in human immunodeficiency virus patients

Reference (Year)	Demography	Diagnosis	Treatment	Outcome
Eljaschewitsch et al. (1996)	HIV-infected patient with port-a-catheter	Port-a-catheter-related disseminated fusariosis	Liposomal amphotericin B (AmBisome) 2 mg/kg/day for 14 days	Successful treatment
Guarro et al. (2000)	HIV-positive patient with lymphoma who was neutropenic due to chemotherapy	Disseminated fusarial infection with two species of <i>Fusarium</i>	Amphotericin B in increasing dose up to 1.5 mg/kg	Patient died
Esnakula et al. (2013)	HIV-positive patient with nephropathy without neutropenia, skin lesions, or concomitant malignancy	Disseminated <i>Fusarium</i> infection	Amphotericin B deoxycholate	Patient died
Present case	HIV-positive patient without systemic features, neutropenia and concomitant malignancy	DCF	Itraconazole	Lesions healed completely in 45 days

DCF: Disseminated cutaneous fusariosis, HIV: Human immunodeficiency virus



Figure 3a: Lactophenol cotton blue mount showing septate, branched hyphae producing microconidia

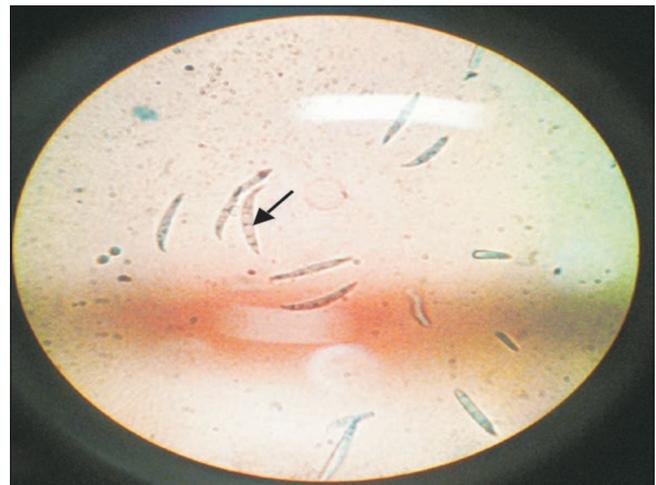


Figure 3b: Multi-septate sickle or boat-shaped macroconidia with 3–4 septae typical of *Fusarium solani*

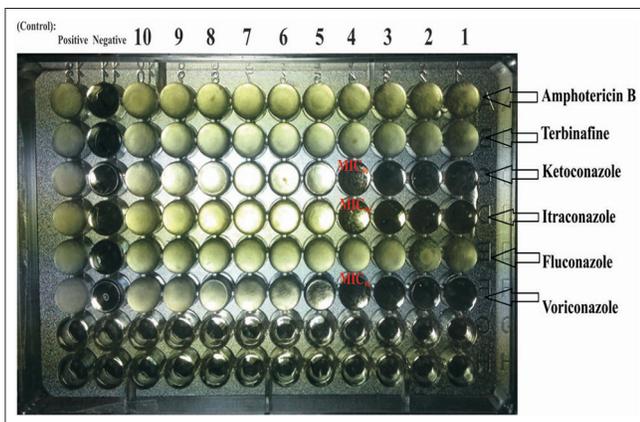


Figure 4: Minimal inhibitory concentrations by microdilution method in round-bottomed 96-well microdilution tray

of diagnostic material. Distinct patterns of skin involvement exist, depending on the immune status of the host.⁹ Sampathkumar and Paya classified the cutaneous lesions into three groups: violaceous nodules with central necrosis, ecthyma gangrenosum-like and target lesions.¹⁰ In immunocompromised patients, skin lesions evolve rapidly over a short period of time and can involve any site, with predominance in the extremities.

The principal portal of entry for *Fusarium* species is the airways, followed by skin at the site of tissue breakdown (trauma, burns

and onychomycosis) and foreign bodies (keratitis in contact lens wearers). Other sources are tap and hospital water system. The fact that we could not establish the entry portal of the fungus in our patient might be explained by the fact that skin breakdown may precede infection by up to 1 year.⁹

Disseminated infections occur when two or more noncontiguous sites are involved.⁹ Immunocompromised patients with prolonged and profound neutropenia (hematologic diseases) and/or severe T-cell deficiency (allogenic hematopoietic stem cell transplantation) and high-dose corticosteroid therapy are at the highest risk.^{1,9} So far, disseminated cutaneous fusariosis in human immunodeficiency virus-positive patients is very rarely known. In a review published in 2002, out of 259 patients with fusariosis, 232 (90%) patients were immunocompromised. Skin involvement was seen in 181 (70%) patients and was more common in immunocompromised group (72% vs. 52%).⁹ Out of 232 patients, only two were human immunodeficiency virus positive of which one had an infected port-a-catheter and other patient had non-Hodgkin’s lymphoma with neutropenia.^{11,12} Another case was reported in human immunodeficiency virus patient without skin involvement and neutropenia in 2013.¹³ Hence, we state that this is the first reported case of isolated



Figure 5a: Healed lesions with postinflammatory hyperpigmentation and scarring after 1½ month of itraconazole therapy over face



Figure 5b: Healed lesions over arms

disseminated cutaneous fusariosis and the third case of disseminated fusariosis in a human immunodeficiency virus infected patient [Table 1].

The most frequent pattern of disseminated disease is a combination of cutaneous lesions and positive blood cultures with or without involvement of other sites.⁸ Interestingly, in a previous review among patients with positive blood culture, skin lesions preceded fungemia in 11 patients by a median of 5 days, occurred on the same day (4 patients) and did not appear until after the diagnosis of fungemia was made (3 patients).⁸ In this case, the blood culture was negative for *Fusarium* similar to a previous review where 78 (52.7%) patients had blood cultures negative for *Fusarium* species.

Different patterns of susceptibility of different *Fusarium* species exist and there is not enough data documenting a correlation between minimal inhibitory concentrations and the clinical outcome. Amphotericin B has been used as the first-line drug but resistance to it has been reported and even our case was found to be resistant

to it.¹⁴ Newer antifungal triazole agents are available for *Fusarium* species including itraconazole, voriconazole and posaconazole. Susceptibility to itraconazole has been shown in some reports but at higher minimal inhibitory concentration which is even higher for *F. solani*.^{15,16} The results of itraconazole against localized fusariosis have been documented but rarely against disseminated cutaneous fusariosis. This variable susceptibility to these drugs poses a great problem for the physicians.

Our case of disseminated cutaneous fusariosis is being reported for the first time and is unique since the cause of immunocompromised state is only human immunodeficiency virus without any associated neutropenia, concomitant malignancy or any systemic involvement. Moreover, the excellent response of *Fusarium* to itraconazole is worth reporting.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the



Figure 5c: Healed lesions over lateral aspect of face



Figure 5d: Healed lesions over thighs

journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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