

Atypical cutaneous lesions of *Penicillium marneffe* infection as a manifestation of the immune reconstitution inflammatory syndrome after highly active antiretroviral therapy

Lahari Saikia, Reema Nath, Debeeka Hazarika¹, J. Mahanta²

Departments of Microbiology and ¹Dermatology, Assam Medical College, Dibrugarh - 786 002, India. ²Regional Medical Research Centre, Lahowal, Dibrugarh - 786 002, India

Address for correspondence: Dr. Lahari Saikia, Department of Microbiology, Assam Medical College, Dibrugarh - 786 002, India. E-mail: lahari.saikia@yahoo.com

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ABSTRACT

Penicillium marneffe infections normally manifest as molluscum contagiosum like skin lesion in HIV-infected persons. We report a case with verrucous lesions over nose and face due to *Penicillium marneffe* infection after HAART treatment. A 28-year-old man presented, after two weeks of HAART treatment, with multiple erythematous, scaly, papules and nodules with central necrosis predominantly in face and both extremities and scrotum. Microbiological investigations confirmed the diagnosis of *Penicillium marneffe* infection. This is perhaps the first case report with such manifestation due to *Penicillium marneffe* infection.

Key words: Highly active antiretroviral therapy, immune reconstitution inflammatory syndrome, *Penicillium marneffe*

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has markedly decreased the overall morbidity and mortality of HIV-infected patients.^[1] Treatment of HIV infection with HAART appears to restore pathogen specific immune response resulting in prevention or regression of diseases caused by opportunistic pathogens. However, some patients experience a dysregulated restoration of antigen-specific immunity leading to an exaggerated or inappropriate inflammatory response known as immune reconstitution inflammatory syndrome (IRIS), usually within a few weeks to months after the start of HAART.^[2] This occurs as a result of partial recovery of the immune system, manifested by increase in CD4 T-lymphocyte count and decrease in plasma HIV-1 viral load.^[2] There is no generally accepted case definition for IRIS. In India, the agreed practical definition of IRIS would be the “occurrence

or manifestations of new opportunistic infections (OIs) or existing OIs within six weeks to six months after initiating ART; with an increase in CD4 count”.^[3] The inflammatory response can result in a spectrum of presentations ranging from clinical deterioration of previously treated opportunistic infection (OI) or atypical appearance of an unrecognized OI to even autoimmune disorders such as Guillain-Barre syndrome.^[2,4] Cutaneous immune reconstitution inflammatory syndrome is described in relation to a wide range of conditions, the commonest being herpes zoster and herpes simplex.^[5] We present a patient who developed extensive atypical cutaneous lesions of *Penicillium marneffe* infection as a manifestation of the immune reconstitution inflammatory syndrome after being started on HAART.

CASE REPORT

A 28-year-old man presented to integrated counselling

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and testing centre (ICTC) of Assam Medical College with a three-month history of fever, weight loss, loss of appetite, diarrhoea, cough and oral thrush without any skin lesions. The patient was counselled and after informed consent he was tested seropositive for HIV infection. His haemoglobin was 8.6 gm/dl, total leucocyte count 3,400/ μ l of blood and erythrocyte sedimentation rate (ESR) 30 mm at the end of first hour. Liver enzymes were raised (aspartate aminotransferase [AST] 171 IU/L; alanine aminotransferase [ALT] 54 IU/L, serum alkaline phosphatase [SAP] 301 IU/L, total serum bilirubin 1.08 mg%) and ultrasound revealed hepatosplenomegaly with contracted gall bladder. Screening of blood for hepatitis B virus (HBsAg) and hepatitis C virus (anti-HCV) were negative. Chest X-ray was normal and sputum was negative for acid fast bacilli (AFB). The CD4⁺ cell counts were decreased to 47 cells/ μ l. Highly active antiretroviral therapy (HAART) was initiated with

three drugs (stavudine, lamivudine and nevirapine) along with fluconazole and cotrimoxazole. After two weeks of treatment, the patient developed multiple erythematous, scaly, papules and nodules with central necrosis predominantly in face and both the extremities and scrotum [Figure 1a]. Lesions on alae nasi showed crusting with verrucous plaque. A differential diagnosis of lupus vulgaris and discoid lupus erythematosus (DLE) with HIV infection was considered and skin biopsy was sent for histopathological examination which revealed focal areas of necrosis with few neutrophils and several Periodic acid Schiff positive yeast like cells [Figure 2a]. Leishman's stain and culture from aspirated skin material in Sabouraud's dextrose agar (SDA) was performed for isolation and confirmation of the fungus. Leishman's stain revealed plenty of intracellular and extracellular septate yeast like cells. Culture of aspirated material in Sabouraud's



Figure 1a: Facial skin lesions with verrucous plaques on the nose



Figure 1b: Skin lesions after two months of HAART and itraconazole

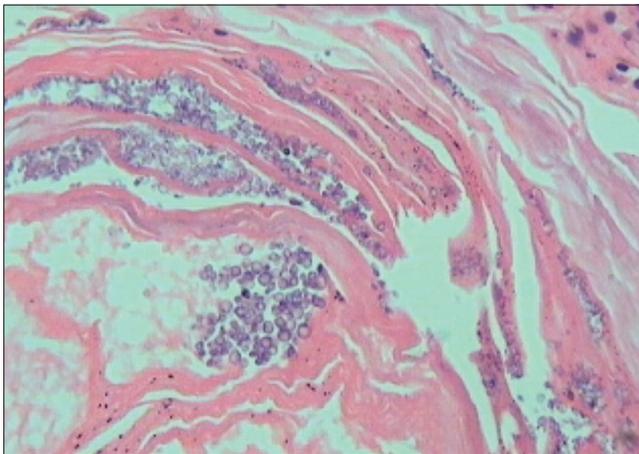


Figure 2a: Periodic acid schiff (PAS) positive yeast like cells in the skin biopsy ($\times 400$)

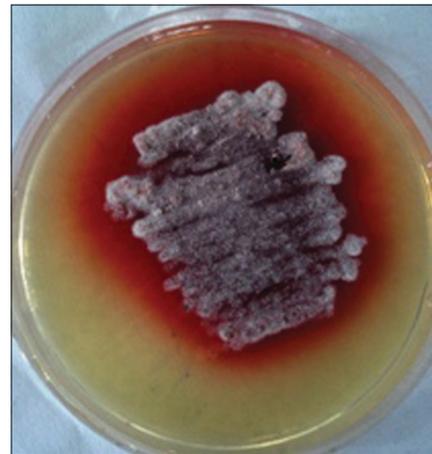


Figure 2b: Colonies of *Penicillium marneffe* with red diffusible pigment in sabouraud's dextrose agar medium

dextrose agar (SDA) showed flat, glabrous, moist, radially folded colonies with diffusible red pigment after 5 days of incubation at 25°C [Figure 2b]. Microscopic examination revealed septate hyphae with lateral and terminal conidiophores and chains of ovate conidia characteristic of *Penicillium* species. To confirm as *Penicillium marneffeii*, mold-to-yeast conversion was demonstrated by subculturing onto brain heart infusion agar and incubating at 37°C. His repeat CD4+ cell counts were 160 cells/ μ l of blood. Blood culture was done in duplicate and did not show growth of *Penicillium marneffeii* till 28 days of incubation.

He was admitted to the Dermatology department and fluconazole was stopped. He was treated with intravenous amphotericin B (0.6 mg/kg/day). After getting the first dose of amphotericin-B the patient refused to stay in the hospital; amphotericin B was stopped and followed up with oral itraconazole (400 mg/day). He was advised to come after two months. At follow-up, after two months, his skin lesions disappeared completely, weight had increased from initial 54 kg to 68 kg and general condition improved markedly [Figure 1b]. Oral Itraconazole was continued on maintenance with 200 mg/day along with HAART.

DISCUSSION

Penicillium marneffeii is a pathogenic dimorphic fungus, endemic in South East Asia, Manipur of North East India and is considered as an AIDS defining illness.^[6,7] Typically, penicillosis presents as a subacute febrile illness with or without pulmonary infiltration and characteristic molluscum contagiosum like skin lesions that occur on the face, upper trunk and extremities.^[6,7] There are several reports from South East Asia and Manipur with typical dermatological lesions that resolve after initiation of HAART and specific antifungal therapy (Amphotericin-B and itraconazole).^[6,7] This case report will add a new manifestation to the clinical profile of *Penicillium marneffeii* infection. Initially the lesions were confused with lupus vulgaris and discoid lupus erythematosus (DLE) by clinicians but diagnosis of *Penicillium marneffeii* as the aetiology could only be confirmed after laboratory help.

Immune reconstitution inflammatory syndrome is mostly seen in profoundly immunosuppressed patients (with CD4+ T-cell counts of less than 100 cells/ μ l) when put on HAART. As a consequence of restoration of the immune responses, dormant pathogens show overt clinical manifestation. Skin is the most common organ for visible manifestation of immune reconstitution syndrome after HAART.^[2,5] *Penicillium marneffeii* infection occurs late in the course of HIV infection when the CD4+ cell count is consistently less than 50 cells/ μ l.^[6,7] As these patients are commonly infected with multiple pathogens, diagnosis is often difficult. In these cases single etiologic agent may cause diverse clinical features, diverse etiologic agents may cause a single morphological presentation. Further, differential diagnosis in an HIV patient presenting with erythematous, scaly, papules and verrucous plaque can happen with multiple opportunistic infections like mycobacterial infection and histoplasmosis. These need epidemiological evidence for clinical suspicion. Occult *Penicillium marneffeii* infection during immune restoration often presents as a sudden onset of many skin lesions or exacerbation of inflammation of pre-existing lesions due to *Penicillium marneffeii*.^[8]

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