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**Research Paper**

# Penicillium marneffei infection manifesting as immune reconstitution inflammatory syndrome (IRIS) in HIV Infected soldier on HAART

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***ABSTRACT*:-**
***Introduction**: Immune reconstitution inflammatory syndrome(IRIS) occurs commonly with the use of antiretroviral therapy in HIV positive individual with low CD4 count and Penicillium marneffei infection can occur as manifest immune reconstitution inflammatory syndrome in endemic areas of the fungus.*
***Case presentation**: A 43 years old soldier of Northeastern India with HIV presented with low to moderate grade fever, anorexia , generalized malaise , significant weight loss with pallor and oral candidiasis with CD4 count of 10 cells/µl. He was started on antiretroviral therapy and ATT and four weeks post therapy developed erythematous nodules and papules with central necrosis over the face. His repeat CD4 count was 163 cells/µl with histopathological examination and fungal stain of the skin biopsy lesion suggestive of Penicillium marneffi infection. Diagnosis was confirmed by fungal culture of skin biopsy lesion showing growth of Penicillium marneffi .He was treated with oral itraconazole therapy of 400 mg/day for four weeks and thereafter continued on secondary prophylaxis of oral itraconazole 200 mg/day along with continuation of antiretroviral therapy. The skin lesions due to dimorphic fungus responded clinically by almost complete resolution after four weeks of start of oral itraconazole therapy.*
***Conclusion**: Immune reconstitution inflammatory syndrome from Penillium marneffei can occur in HIV positive patients residing in endemic areas for the fungus with low CD4 count on start of antiretroviral therapy. Early recognition and treatment with oral itraconazole in resource poor settings has good prognosis*

***Keywords:-** HIV, IRIS, HAART,ATT, Itraconazole, Penicillium marneffei.*

## I. INTRODUCTION

*Penicillium marneffei* was first discovered in 1959 by G.Segretain at the Pasteur Institute in Paris.The strain was isolated from bamboo rats dying of disseminated mycosis in Vietnam. The new species was named *P.marneffei* in honour of Hubert Marneffe, the Director of Pasteur Institute in Indochina [1, 2]. The first natural human infection was reported in 1973 from a patient with Hodgkin lymphoma who lived in Southeast Asia [3]. Before the first case was reported in 1988 in a patient infected with the human immunodeficiency virus (HIV) [4], human penicilliosis was uncommon with less than 40 cases reported in the Southeast Asia [5,6].

Penicillium marneffei infection is caused by dimorphic fungus and has been reported in immunocompromised population of Thailand, China, Vietnam, Singapore, Taiwan and India as endemic infectious disease.[7]The typical manifestation of P marneffei infection consists of weight loss, anemia, fever, skin lesions, hepatomegaly and generalised lymphadenopathy[8,9]. If left untreated it is a fatal disease.The primary treatment consists of Amphotericin B and itraconazole with secondary prophylaxis with oral itraconazole preventing relapse [10].

Immune reconstitution inflammatory syndrome (IRIS) is a complication related to antiretroviral therapy (ART)-induced immune restoration. IRIS manifests as a paradoxical exacerbation of previously treated opportunistic infections (paradoxical or worsening IRIS) or as an unmasking of subclinical, untreated infections (unmasking IRIS)[11-14]. We describe a case of HIV associated Penicillium marneffei infection who developed the infection as unmasking IRIS after four weeks of starting the HAART.

## II. CASE REPORT

43 years old male soldier, resident of Manipur working in Northeastern part of India known case of HIV + since 2013 on irregular treatment (Zidovudine 300 mg BD , Lamivudine 150 mg BD and Nevirapine 200 mg BD) and irregular follow up presented at our centre with complain of low to moderate grade fever , anorexia , generalized malaise and significant weight loss of more than 10%.

On examination he was frail and weak with dry skin but hemodynamically stable. Clinically he had pallor, oral thrush and systemic examination was unremarkable except palpable liver ( 4cm below Right costal margin). On laboratory investigation his hemoglobin was 7.1 gm/dl, total leukocyte count was 4800 /dl with adequate platelets. Urine and stool R/E was –WNL , sputum for AFB x 3 – Neg ,ESR -119, Monteux test-Negative, Peripheral blood smear for anemia typing showed normocytic normochromic RBC with polychromatic cells and normal leucocytes ,platelets and no haemohagocytes .Repeat complete blood count revealed Hb of 7.2gm/dl with raised MCV of 102 fl. USG abdomen revealed mild hepatosplenomegaly. Rapid Malaria Test and IgM/IgG for S typhi was Negative. Renal function tests and liver function tests were within normal limits. CD4 count was 10 cells/µl . HbsAg ,anti HCV antibody tests and VDRL were non reactive. Among Torch profile , IgG antibody for rubella/ CMV/HSV1 were positive however Toxoplasma IgG/IgM ,Rubella IgM, CMV IgM, HSV1 IgM , HSV2 IgM/IgG were negative . HIV viral load was not done due to poor financial condition of the patient .Chest X-ray revealed area of faint cotton wool opacities in LLZ s/o pneumonitis LLL and fundus examination revealed cotton wool spots and dot and blot retinal hemorrhages in both fundus s/o HIV microangipoathy .

The individual was diagnosed as a case of AIDS in WHO clinical stage 4 with HIV associated anemia likely of drug induced (Ziduvidine) and/or HIV per se. Since there was clinical and immunological failure on First line HAART (ZLN) , he was started on 2$^{nd}$ line ART (Tenofovir 300 mg/day, Lamivudine 300 mg/day and Lopinavir/ritonavir 400 mg + 100 mg BD) along with empirical ATT (Rifabutin based) , OI prophylaxis of cotrimoxazole , macrolide and also put on adequate nutritional support with oral hematiminics and inj Erythropoietin.

After start of HAART and Rifabutin based ATT, there was marked improvement in his general condition , Individual shown improvement in his appetite and started gaining weight ,his Hb has risen to 9.2 gm /dl but four weeks post HAART he developed non pruritic erythematous papules and nodules with central umbilication and necrosis.(Fig.1,2,3 and 4).There was no associated lymphadenopathy.

**Fig: 1&2-** Nodules with central umbilication and necrosis (Anterior View of face)
**Fig: 3-** Nodules with central umbilication and necrosis (Lateral View of face) also showing biopsy site **Fig: 4-** Nodules with central umbilication and necrosis at back of scalp and neck(posterior view)

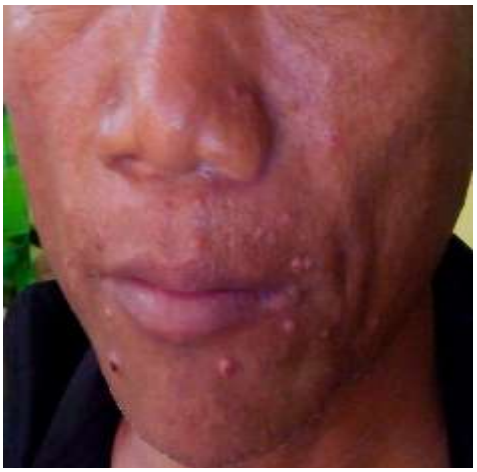
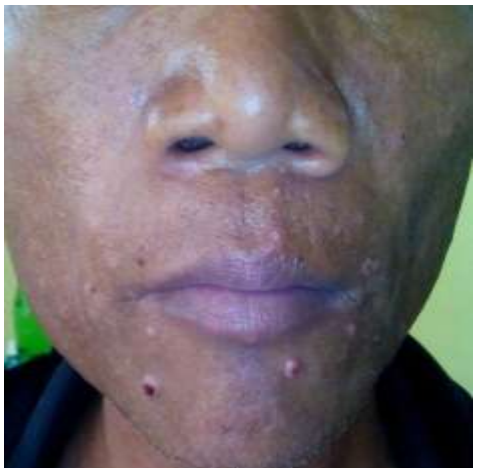


**Figure 1**



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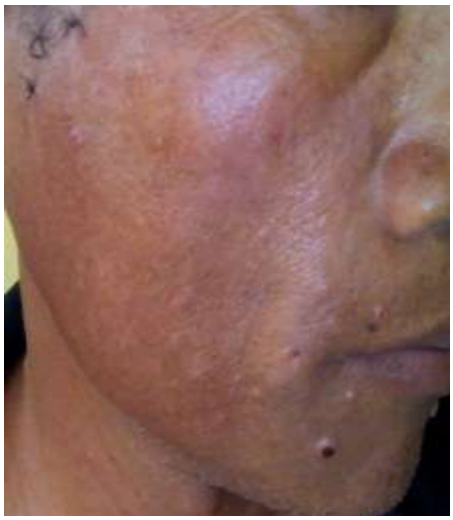


**Figure 3**

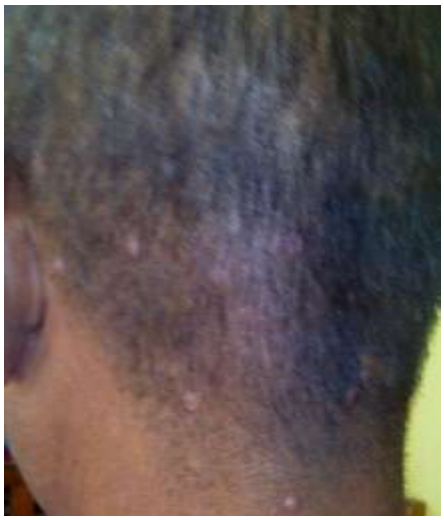


**Figure 4**

IRIS (unmasking) was considered and differential diagnosis of molluscum contagiosum,cutaneous cryptococcosis, penicilliosis and histoplasmosis was kept as likely opportunistic infections. Investigations were carried out accordingly. Repeat Chest Xray was NAD. His CD4 Count was raised to 163 cells / µl . Biopsy was obtained from the cutaneous face lesion and was also sent for fungal culture.HPE of the biopsy lesion showed skin with upper dermis displaying moderate to dense lymphohistiocytic cells infiltration. Numerous yeast forms of fungus are seen within the cytoplasm of the histiocytes in an extracellular location dividing by binary fission, morphologically resembling *Penicillium marneffei*. (Feature are of penicullosis) and culture grown *Penicillium marneffei* .He was started on oral itraconazole 400 mg/day for 4 weeks and there after continued with oral itraconazole 200 mg/day as secondary prophylaxis. After start of itraconazole therapy all the cutaneous lesions of *Penicillium marneffei* started regressing and by 4 weak almost resolved and there was no relapse. (Fig.5,6 and 7). Presently he is continuing ART with secondary prophylaxis of oral itraconazole.

**Fig:5-** Post Treatment (Lateral View),
**Fig:6-** Post Treatment (Anterior View)
**Fig:7-** Post Treatment (posterior View)

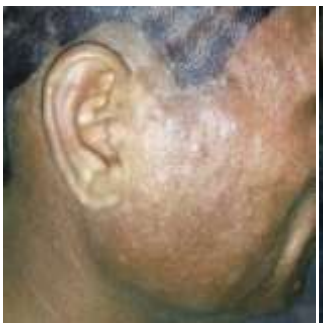


Figure 5

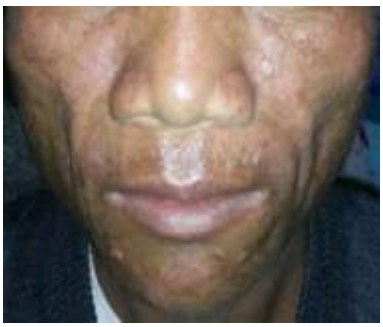
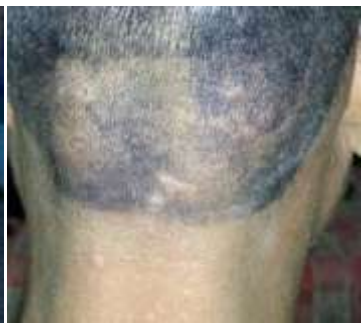


Figure 6


Figures 7

## III. DISCUSSION

Penicillium marneffei is a pathogenic dimorphic fungus, endemic in South East Asia, Manipur of North East India and is considered as an AIDS defining illness [15,16].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 [15,16]. 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) (8,15)

Immune reconstitution inflammatory syndrome is mostly seen in profoundly immune suppressed patients (with CD4 T-cell counts of less than 100 cells/µl) 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 (16,17) . Penicillium marneffei infection occurs late in the course of HIV infection when the CD4 cell count is consistently less than

50 cells/µl (8,15)]. Occult Penicillium marneffei 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 marneffei [18].

The only known natural hosts for Penicllium marneffei are bamboo rats (Rhizomys and Cannomys spp.) and human beings [19,20]. Inhalation of conida (spores) with the help of pulmonary histiocytes disseminate in the host body to cause systemic infection [21-23]. Human infections occur due to soil exposure especially during rainy seasons [24].

Our patient is a soldier who had frequent occupational exposure to soil and jungles, thickly vegetated by bamboo in Manipur during military activities might have inhaled the spores of Penicillium marneffei. IRIS is a manifestation of immune recovery after initiation of potent ART when majority of patients present with unusual manifestations of opportunistic infection due to increase in CD4 count and fall in HIV viral load [25-28].

In our case also P marneffei infection manifested after 4 weeks of ART initiation and there was documented increase in CD4 count from 10cells/ µl at baseline to 163 cells/ µl ( four weeks after the start of HAART).HIV viral load was not done due to poor financial condition of the patient. The skin lesions which appeared during IRIS was umbilicated papular lesions with central necrosis similar to those in disseminated cryptococcosis or histoplasmosis [29-31]. Definite diagnosis of Penicillium marneffei infection in our case was based on mycological culture from skin biopsy lesions which has 90 % sensitivity according to studies [19] along with histo-pathological examination of biopsy lesion.

P marneffei is highly sensitive to itraconazole, voriconazole, ketoconazole,terbinafine and 5-Flurocytosine, intermediately sensitive to Amphotericin B and least sensitive to fluconazole [ 32]. Intravenous Amphotericin B for 2 weeks and followed by oral itraconazole 400 mg/day for 10 weeks is recommended for treatment of disseminated and severe P marneffei infection[33].Oral itraconazole has been shown to be successful in treatment of P marneffei with dose of 400 mg/day for 4weeks followed by 200mg/day as secondary prophylaxis[7].

In our case clinical remission of cutaneous lesions of P marneffei was seen after 4 weeks of oral itraconazole 400 mg/day also and thus have been found efficacious with less side effects compared to injection Amphotericin B therapy as recommended for initial 2 weeks of treatment.

During the pre-HAART era, over half of patients developed relapse of penicilliosis within 6 months after discontinuation of antifungal treatment [34,10]. Secondary prophylaxis with itraconazole 200 mg/day was shown to be well tolerated and highly effective with a reduction in relapse rate from 57% to 0% [10]. Therefore, it has been recommended that all patients who have completed treatment for penicilliosis should be put on secondary prophylaxis with itraconazole 200 mg/day[35].

With the introduction of HAART, there is growing data to suggest that secondary prophylaxis can be stopped after immune restoration [36,37]. It is suggested that secondary prophylaxis can be stopped for patients who are receiving HAART and have a CD4 count >100/uL for over 6 months. However, secondary prophylaxis should be reintroduced if the penicilliosis relapses or the CD4 count falls below 100/uL [35]

## IV. CONCLUSION

IRIS is not a rare condition especially in era of HAART use and IRIS due to P marneffei infection will be increasingly occurring in patients residing at endemic area for the fungus. Characteristic umbilicated popular rashes with central necrosis should alert the clinicians of possibility of P marneffei infection and investigate accordingly. Treatment with oral itraconazole 400 mg/day for 4 weeks followed by 200 mg/day as secondary prophylaxis is successful in clinical remission of the cutaneous lesions of P marneffei infection and can be used with lesser side effects than injection Amphotericin B as recommended for treatment during initial 2 weeks for P marneffei infection.

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