

## Penicillium marneffeii infection during immune reconstitution inflammatory syndrome after HAART in HIV infected soldier of Northeastern India

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**Abstract :** Background: Immune reconstitution inflammatory syndrome (IRIS) occurs commonly with the use of antiretroviral therapy in HIV positive individual with low CD4 count and *Penicillium marneffeii* infection can occur as manifest immune reconstitution inflammatory syndrome in endemic areas of the fungus.

Case presentation: A 33 years old soldier of Northeastern India with HIV presented with severe pallor, oral and oesophageal candidiasis with CD4 count of 26 cells/mm<sup>3</sup>. He was started on antiretroviral therapy and four weeks post therapy developed erythematous nodules and papules with central necrosis over the face. His repeat CD4 count was 147 cells/mm<sup>3</sup> with histopathological examination and fungal stain of the skin biopsy lesion suggestive of *Penicillium marneffeii* infection. Diagnosis was confirmed by fungal culture of skin biopsy lesion showing growth of *Penicillium marneffeii*. 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 complete resolution after three weeks of start of oral itraconazole therapy.

Conclusion: Immune reconstitution inflammatory syndrome from *Penicillium marneffeii* 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, itraconazole, *Penicillium marneffeii*.

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### I. Background

*Penicillium marneffeii* 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<sup>1</sup>.

The typical manifestation of *P. marneffeii* infection consists of weight loss, anemia, fever, skin lesions, hepatomegaly and generalised lymphadenopathy<sup>2,3</sup>. 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<sup>4</sup>.

Introduction of HAART has been able to reduce morbidity and mortality in AIDS but also led to improved immune function of HIV infected individuals<sup>5</sup>. Immune reconstitution inflammatory syndrome (IRIS) occurs due to ART induced immune restoration and can present as paradoxical worsening of previously treated opportunistic infection as paradoxical IRIS or unmasking of sub clinical infections present in the individual as unmasking IRIS<sup>6-9</sup>.

We describe a case of HIV associated *Penicillium marneffeii* infection who developed the infection as unmasking IRIS after four weeks of starting the HAART.

### II. Case Report

33 years old male soldier, resident of Mizoram and presently working at Manipur in Northeastern India presented at the composite hospital in April 2015 with complaints of generalised malaise and significant weight loss of 12 kgs in three months. He also had odynophagia for one month duration. There was past history of Herpes zoster infection one month ago.

On examination he was frail and weak but hemodynamically stable. He had pallor and hypo-pigmented patches of previous Herpes zoster infection on the chest wall. Oral examination revealed thrush and systemic examination was unremarkable.

On laboratory investigation his hemoglobin was 7.4 gm/dl, total leucocyte count was 2500 /dl with adequate platelets. Peripheral blood smear for anemia typing showed normocytic normochromic anemia with leucopenia. Renal function tests and liver function tests were within normal limits. HIV 1 antibody test was positive by three rapid tests (Signal HIV, SD Bioline, Comb AIDS). HIV1 ELISA was also positive. HIV Viral

load was 642428 copies/mm<sup>3</sup> and CD4 count was 26 cells/mm<sup>3</sup>. HbsAg and anti HCV antibody tests were non reactive. VDRL was non reactive. Stool examination for ova and cyst was unremarkable. Chest Xray and fundus examination was normal. Sputum for AFB stain was negative. Upper GI endoscopy revealed adherent white patches in hypopharynx and throughout the esophagus suggestive of esophageal candidiasis. Culture from oral swab showed growth of *Candida albicans*.

The individual was diagnosed as a case of AIDS in WHO clinical stage 4 and was having anemia of chronic disease. He was started on TDF 300 mg/day, 3TC 300 mg/day and EFV 600 mg/day as HAART along with OI prophylaxis of cotrimoxazole and macrolide. He was started on tab fluconazole 200 mg/day along with oral clotrimazole mouth paint for oral and esophageal candidiasis. He was also been put on adequate nutritional support with oral hematinics.

He was tolerating the medications well and his odynophagia and oral thrush improved after 2 weeks of therapy. On 21<sup>st</sup> May 2015 (four weeks post ART) he developed non pruritic erythematous papules and nodules with central umbilication and necrosis. (Fig.1 and Fig.2) There was no associated lymphadenopathy or hepatomegaly when re examined.



**Fig: 1-** Nodules with central umbilication and necrosis (Anterior View)



**Fig: 2-** Nodules with central umbilication and necrosis (Lateral View)

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 revealed discrete reticulonodular interstitial opacities involving both lung fields which also made us to consider TB IRIS a possibility. Repeat sputum for AFB was negative, XPERT MTB/RIF of sputum did not show any Mycobacteria. Serum for cryptococcal antigen was negative. Ultrasonography of abdomen did not reveal any organomegaly or retroperitoneal lymph nodes. Biopsy was obtained from the cutaneous face lesion and was also sent for fungal culture.

HPE of the biopsy lesion showed ulcerated skin with underlying dermis displaying moderate lymphohistiocytic cell infiltration and scattered neutrophils. Occasional foci display yeast forms dividing by binary fission morphologically resembling *P. marneffei*. Culture showed fungal hyphae and yeast-like cells suggestive of *Penicillium marneffei*. Chest Xray findings were attributed to the pneumonitis caused by *P. marneffei* infection.

He was started on oral itraconazole 400 mg/day for 4 weeks and thereafter continued with oral itraconazole 200 mg/day as secondary prophylaxis. After 3 weeks of itraconazole therapy all the cutaneous

lesions of *Penicillium marneffeii* resolved and there was no relapse.(Fig.3 and Fig.4).Presently he is continuing ART with secondary prophylaxis of oral itraconazole.



**Fig:3-** Post Treatment (Anterior View)



**Fig:4-** Post Treatment (Lateral View)

### III. Discussion

The only known natural hosts for *Penicillium marneffeii* are bamboo rats (*Rhizomys* and *Cannomys* spp.) and human beings<sup>10,11</sup>. Inhalation of conidia (spores) with the help of pulmonary histiocytes disseminate in the host body to cause systemic infection<sup>12-14</sup>. Human infections occur due to soil exposure especially during rainy seasons<sup>15</sup>.

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 marneffeii*.

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<sup>16-19</sup>.

In our case also *P. marneffeii* infection manifested after 4 weeks of ART initiation and there was documented increase in CD4 count from 26 cells/cumm at baseline to 147 cells/cumm (four weeks after the start of ART). HIV viral load was not done due to poor financial condition of the patient. The skin lesions which appeared during IRIS were umbilicated papular lesions with central necrosis similar to those in disseminated cryptococcosis or histoplasmosis<sup>20-22</sup>.

Definite diagnosis of *Penicillium marneffeii* infection in our case was based on mycological culture from skin biopsy lesions which has 90% sensitivity according to studies<sup>10</sup> along with histo-pathological

examination of biopsy lesion with fungal stain (Periodic acid-Schiff and Grocott silver methenamine stain) detecting non budding yeast cells with characteristic transverse septum.

*P. marneffei* is highly sensitive to itraconazole, voriconazole, ketoconazole, terbinafine and 5-Fluorocytosine, intermediately sensitive to Amphotericin B and least sensitive to fluconazole<sup>23</sup>.

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<sup>24</sup>. Oral itraconazole has been shown to be successful in treatment of *P. marneffei* with dose of 400 mg/day for 4 weeks followed by 200 mg/day as secondary prophylaxis<sup>25</sup>.

In our case clinical remission of cutaneous lesions of *P. marneffei* was seen after 3 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.

#### IV. Conclusion

IRIS is not a rare condition especially in era of ART use and IRIS due to *P. marneffei* infection will be increasingly occurring in patients residing at endemic area for the fungus. Characteristic umbilicated papular 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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