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Talaromycosis (Penicilliosis): A formidable challenge in Southeast Asia

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Abstract
Talaromyces marneffei a dimorphic fungus causes systemic mycoses (Talaromycosis) among immunocompromised individuals especially in HIV infected individuals. Talaromycosis is endemic to Southeast Asia and China. Bamboo rats act as the reservoir and the infection is probably transmitted by inhalation and inoculation with varied incubation period (weeks to years). The signs are manifested as mild fever, anaemia, weight loss, molluscum contagiosum lesions to fatal lymphadenopathy, splenomegaly if left untreated. The infection is diagnosed mainly by isolation and identification of the agent by culturing on Sabouraud's Dextose Agar. Serum detection of antigenemia, PCR and RT-PCR are confirmatory in diagnosing. Amphotericin B and itraconazole are drugs of choice for talaromycosis. Primary prophylaxis with itraconazole (200 mg/kg body weight) among HIV infected individuals with CD_4 count less than 200 cells/mm^3 is recommended to be beneficial. However, with mysterious epidemiology talaromycosis is still not clearly understood and hence further studies should focus towards understanding the epidemiology, developing rapid diagnostic techniques and effective treatment regime.

Keywords: molluscum contagiosum, penicilliosis, Southeast Asia, *Talaromyces marneffei*, talaromycosis

1. Introduction
Human infections due to fungal etiology are showing an upward trend in incidence. Now fungal infections are considered as one of the major cause for global burden and morbidity among immunocompromised population. *Penicillium* an ascomycetous saprophytic fungus is found worldwide. These *Penicillium* species are considered as a boon to the society as they revolutionized the medical field with its component penicillin having antibacterial property. On contrary many of the species in this genus are attributed as the cause for food spoilage and production of harmful mycotoxins in food. *Talaromyces marneffei* (formerly *Penicillium marneffei*) is the only dimorphic pathogenic fungi in the genus Penicillium responsible for systemic mycoses called Talaromycosis (formerly Penicilliosis). Recently *Talaromyces marneffei* has emerged as an invasive opportunistic fungal pathogen which is endemic to Southeast Asia and China and reported occasionally in non-endemic areas. The fungi are highly pathogenic particularly in patients with weak immune status and its isolation from blood is considered as an indicator of Human Immunodeficiency Virus (HIV) infection especially in endemic areas [1]. Effective antiretroviral therapy has reduced the incidence of talaromycosis among HIV positives [2]. However, talaromycosis is been still reported among individuals unaware of their HIV infection or who do not undertake proper anti-retroviral therapy as well as among other immunocompromised individuals.

2. Epidemiology
Talaromycosis is considered as one of the AIDS defining illness as the highest incidence is noticed in HIV infected population. Talaromycosis ranks third opportunistic infection associated with AIDS next to Tuberculosis and Cryptosporidiosis [3]. In Asia, talaromycosis gained its importance as human disease only after epidemics of HIV infection. *Talaromyces marneffei* was first isolated from the bamboo rat that died of reticuloendothelial mycosis in Vietnam in 1956. First human case was identified in the year 1959 when a researcher pricked his hand accidentally with needle contaminated with yeast cells of *P. marneffei* [4]. Later in 1973 an American minister suffering from hodgkin's disease was diagnosed for talaromycosis [5]. Second naturally infected case identified was also an American who visited Southeast Asia during 1984 [6]. In the same year five cases were reported from Thailand and later higher incidences were noticed in Southeast Asian regions *viz*., Thailand, China, Hong Kong, Malaysia, Taiwan, Vietnam and North East India [7]. Till today more than 500 cases have been reported form China [8]. In India cases were predominantly identified in Manipur a north eastern state which shares border with Myanmar, a country with high rate of HIV infection [9, 10]. Now Manipur is considered as the endemic foci for talaromycosis which can be attributed to highest number of HIV cases found in the state among drug abusers. During 1990's highest cases were reported among HIV infected individuals and later the patients with transplantation and autoimmune diseases were at risk. Aftermath of the improved health care system and antiretroviral therapy (ART) in Southeast Asia, the incidence of HIV associated talaromycosis has decreased to a great extent. At present (2010 - 2015) highest occurrence is noticed among non-HIV immune-

compromised individuals *viz*., adults treated with immunosuppressive therapy (anti - IFN-γ autoantibodies, anti-CD20 monoclonal antibodies and or kinase inhibitors), chemotherapy, organ transplantation and autoimmune disorders [11].

3. Reservoir of *T. marneffei*

Bamboo rats *viz*., *Rhizomys pruinosus*, *R. sinensis*, *R. sumatrensis*, and *Cannomys badius* are considered as the natural reservoirs for the fungi *T. marneffei* [12, 13]. Prevalence of infection in bamboo rats vary depending on the geographical area. The species *R. sinensis* and *R. pruinosus* were noticed in southern China to Thailand and Myanmar whereas *R. sumatrensis* in Indonesia [14]. In India *C. badius* is the natural animal reservoir for *T. marneffei* [15]. Major environmental reservoir for infection is the soil of bamboo rat burrow [16]. For humans, exposure to the soil in the premises of infected bamboo rat is the predisposing factor rather than direct exposure to bamboo rats [17]. Very recently dogs are also suspected as reservoir for infection in northern Thailand as 13 per cent of nasal swabs of dogs were positive for *T. marneffei* [18].

4. Etiology and its cultural charecteristics

T. marneffei (*P. marneffei*) is a dimorphic pathogenic fungus which grow as mycelia at 25°C and yeast at 37°C. It belongs to Domain – Fungi, Phylum – Ascomycota, Class – Eurotiomycetes, Order – Eurotiales, Family – Trichomonaceae, Genus – *Talaromyces*, and Species – *marneffei*. On Sabouraud's Dextose Agar (SDA) the mycelia appear as velvety green colony with radial folds and diffusible red pigment on reverse. At 37°C the fungus grows as white colonies of yeast on blood agar [10].

5. Risk group for infection

Immunocompromised individuals are highly susceptible for this opportunistic invasive pathogen. During initial period of disease epidemics, HIV infected individuals were considered as most susceptible and later other non-HIV immunosuppressed individuals who were under chemotherapy, organ transplantation and autoimmune disorders are also considered as high risk group for infection [11]. The farmers of endemic area engaged in agricultural activity are having likelihood of acquiring infection through inoculation [19]. Risk of infection is not only restricted to the persons living in the endemic area but also to those individuals who visit the endemic area. In Belgium, a case study revealed the spread of talaromycosis from organ donor to the recipient [20].

6. Transmission and pathogenesis

T. marneffei being a saprophyte in the soil in and around the area inhabited by bamboo rats, environmental exposure to the soil borne conidiospores through inhalation is the most probable route of infection to humans. There are no evidence regarding transmission of infection through direct exposure to bamboo rats or eating of bamboo rats. Talaromycosis infection showed seasonality in occurrence with increased number of cases being reported during rainy season. This may be due to the existing favourable environmental condition for fungal growth during that season which needs further investigation [2, 21]. Inoculation is another possible route of acquiring the infection through occupational exposure among clinicians, lab technicians, waste handlers, farmers and drug abusers [4, 7, 19].

Upon inhalation of conidiospores, they get phagocytized by pulmonary histiocytes. Fungus evades the host immune response and survives within the phagosome. Later these conidia develop into small yeast cells as that of *Histoplasma capsulatum* which may lead to misdiagnosis. But they divide by fission in contrast to histoplasma, which divides by budding and aids in differential diagnosis. After establishment in phagosome, they get disseminated throughout the body and result in systemic infection upon immunosuppression. The incubation period varies from few weeks to years. The pathogenicity is mainly attributed to the phase transition and survivability within the phagosome which helps in overcoming the host defence mechanism [22, 23].

7. Clinical manifestations in man

The severity of the infection varies among patients with different degrees of immunosuppression. In HIV-infected patients, *T. marneffei* infection is often disseminated and involves multiple organs. Clinical manifestations in HIV associated talaromycosis includes fever, anaemia, weight loss, characteristic molluscum contagiosum-like lesions, diffuse pulmonary involvement, and frequently concomitant fungemia, lymphadenopathy and spleenomegaly. Most common are skin lesions often noticed on upper face, neck and trunk characterized by generalized papular rashes with central necrotic umbilication. Rarely genital and pharyngeal ulcers are noticed [7, 24] and in few cases mesenteric lymphadenitis has been reported [25]. Manifestations in HIV-negative patients include lymphadenopathy, osteomyelitis and septic arthritis, pulmonary infection and disseminated infection with multi organ involvement [26]. Severe anaemia, thrombocytopenia, and osteomyelitis seem to be more common in children than in adults [27]. Recently dissemination of infection to brain was noticed in immunocompetent patient in China [28].

8. Diagnosis

Talaromycosis is a curable disease if diagnosed and treated early. Mortality rate in untreated individuals with HIV is 100% and in non HIV patients it is 90% [29]. Hence prompt and early diagnosis is at most important to curtail mortality. Gold standard test for diagnosis is isolation and identification of fungi from the clinical samples. Clinical specimens that are commonly used for culture include bone marrow aspirate, blood, lymph node biopsies, skin biopsies, skin scrapings, sputum, bronchoalveolar lavage, pleural fluid, liver biopsies, cerebrospinal fluid, pharyngeal ulcer scrapings, palatal papule scrapings, urine, stool samples, and kidney, pericardium, stomach, or intestine specimen's impressions [10, 27].

8.1 Microbial culture

Dimorphic nature of *T. marneffei* is greatly employed in diagnosis where culture on SDA at 25°C produce velvety green mycelia with a diffusing red pigment onto the solid medium and at 37°C grow as yeast like colonies on blood agar.

8.2 Cytology and histopathology

A Giemsa stained touch smear of a skin biopsy or bone marrow aspirate is a rapid and sensitive diagnostic method that readily demonstrates the presence of typical yeast-like cells with a central septum, either within histiocytes or scattered through the tissue. The yeast-cells are spherical to ellipsoidal, 2 to 6 µm in diameter, and divide by fission rather than budding, a characteristic visible feature on stained touch smears that distinguishes *T. marneffei* from *Histoplasma capsulatum.* Organism can be identified in histopathology of tissue sample stained with hematoxylin and eosin, Grocott methenamine silver or Periodic Acid-Schiff (PAS) stain which appear as fission arthroconidia or unicellular round to oval cells, which may divide by cross wall formation in macrophages or histiocytes [22].

8.3 Serological and molecular test

Various serodiagnostic tests are employed which mainly aim at detecting antigenemia as the titer of antibodies to fungus are lower in HIV infected individuals. Hence monoclonal antibodies (MAb 4D1S) against 30–150-kDa protein are used which is highly specific without cross-reactiv ity.

Recent investigations suggest that the inhibition ELISA also facilitates rapid detection of the mannoprotein specifically recognized by MAb 4D1 and aid as a rapid test for the diagnosis of *T. marneffei* infection in the clinical laboratory [30]. Various molecular techniques like nested PCR and RT – PCR are also employed in diagnosis. Altogether, PCR-based technologies offer a good alternative to conventional diagnosis of *T. marneffei* infection [31].

9. Treatment

Untreated cases of talaromycosis show 100% mortality. This highly fatal disease of immune-compromised individuals can effectively be treated if diagnosed early. The drug of choice is liposomal amphotericin B at 3 to 6 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole (400 mg/day) for a subsequent duration of 10 weeks. Alternatively, intravenous voriconozole at 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks can be used. For minor illnesses use of oral itraconozole (400mg/day) for 8 weeks is recommended [24, 32, 33] (Table No. 1).

10. Prevention and control

To prevent systemic fungal infections among HIV infected individuals, patients with CD4 counts <200 cells/mm^3 primary prophylaxis should be initiated (Oral itraconozole at 200 mg/day). Primary prophylaxis is mandatory among HIV infected individuals dwelling in endemic area (Thailand, Vietnam, southern China) and whose CD4 counts <100 cells/mm^3 while it is not recommended in other geographical area.

In order to obtain better outcome and for immune restoration, antiretroviral therapy should be administered simultaneously. Also awareness should be created among the risk group regarding personnel protective measure.

Table 1: Treatment and prevention regimen for *Talaromycoses* [33]

Infection Stage	Indication	Preferred therapy	Alternative therapy
Prevention (Primary prophylaxis)	HIV infected patients residing in endemic area with CD4 count <100 cells/mm^3	Itraconazole (200 mg o.d. Per Orum)	Fluconazole (400 mg QWK, Per Orum) for 8 weeks
Acute cases	Severely ill with systemic signs	Liposomal amphotericin B (3-6 mg/kg o.d., Intravenous) for 2 week followed by Itraconazole (200 mg o.d. Per Orum) for 10 weeks	Voriconazole (6mg/kg Intravenous q12h)for 1 day then, 4mg/kg q12h for 3 days followed by 200 mg bid Per Orum for 12 weeks
Mild cases	Mild clinical signs like anaemia, loss of body weight, skin lesions	Itraconazole (200 mg bid Per Orum) for 8 weeks	Voriconazole 400 mg bid Per Orum for 1 day followed by 200 mg bid Per Orum for maximum of 12 week
Chronic maintenance therapy (Secondary prophylaxis)	Recurrence of infection with CD4 count <100 cells/mm^3	Itraconazole (200 mg bid Per Orum) daily until recovery	-

11. Conclusion

Systemic mycosis caused by *Talaromyces marneffei* is an important fungal disease endemic to Southeast Asian countries which has jeoparadized the life of immonocompromised humans. This saprophytic fungal infection possesses high risk of zoonotic transmission and is likely to be transmitted through exposure to the soil of bamboo rats inhabited area. Though advancements in anti-retroviral therapy has reduced the incidence, still there has been lack of sufficient studies on epidemiology, rapid diagnosis and therapy. Hence further studies should focus towards understanding the global distribution, epidemiology, developing rapid diagnostics techniques and effective treatment regime.

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