Epidemiology of *Talaromycosis (Penicilliosis) Marneffei* in India: An Update

Harish C. Gugnani, Neelam Sood

ABSTRACT

Talaromycosis marneffei (*Penicilliosis marneffei*) caused by a thermally dimorphic fungus, *Talaromyces (Penicillium) marneffei* is emerging as an important systemic opportunistic mycosis in HIV infected patients in several countries in Southeast Asia and in northeast India. This study presents an update on epidemiological and clinical aspects of *talaromycosis marneffei* in India. A thorough search of literature was done in Medline, PubMed, and Google Scholar, for accessing relevant data. Fifty-three cases of this disease have originated from the Manipur State. Several cases have been reported from Assam, a few are also known from Meghalaya, Mizoram, Nagaland, Sikkim, Delhi and Maharashtra. Clinical manifestations of disseminated infection in AIDS patients are fever, anemia, weight loss, weakness, lymphadenopathy, hepatosplenomegaly, respiratory signs, and characteristic skin lesions. The bamboo rat (*Cannomys badius*) has been found to be a natural host of *Talaromyces (Penicillium) marneffei* in Manipur. It is noteworthy that one of the ten *T. marneffei* isolates from bamboo rats shared the genotype with a human isolate from that area providing evidence for common source of infection for the rats and humans and host to host transmission. Natural reservoir of *T. marneffei* has not been established, though it has been demonstrated that the fungus can survive in sterile soil for several weeks, but only for a few days in unsterile soil. There is need for comprehensive investigation of *T. marneffei* infection in humans, and for occurrence of the fungus in bamboo rats and in soils of the rat burrows in India employing conventional and molecular techniques.

Keywords: *Talaromycosis marneffei*, epidemiological and clinical aspects, India, update.

Published Online: September 16, 2020

ISSN: 2593-8339

DOI: 10.24018/ejmed.2020.2.5.478

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I. INTRODUCTION

Talaromycosis marneffei (*Penicilliosis marneffei*) is caused by a thermally dimorphic fungus, *Talaromyces (Penicillium) marneffei*, a member of the family **Trichocomaceae**, order *Eurotiales*, class *Eurotiomycetes* of division *Ascomycota*. It is the only dimorphic species in the genus *Talaromyces* [25]. Infection caused by *Talaromycosis marneffei* is emerging as an important systemic opportunistic infection, being potentially life-threatening in HIV+ patients with low CD4 counts [32]. *Talaromycosis marneffei* is geographically restricted to Southeast Asian countries such as Thailand, Vietnam, Hong Kong, Taiwan, Philippines, Malaysia, Myanmar, Cambodia, Laos, and Northeast India. In northern Thailand, it is the third commonest opportunistic infection after tuberculosis and cryptococcosis in HIV-infected patients [32]. A large number of cases have also occurred in non-HIV-infected patients [6]. This infection is rare in Europe and all the cases described were residents or had stayed in an endemic area.

Talaromyces marneffei was first isolated in 1956 from the hepatic lesions of a bamboo rat (*Rhizomys sinensis*) in Vietnam, the rat had died spontaneously from the infection

[4]. The first case of human infection was reported in 1973 from a patient (an American priest) with Hodgkin lymphoma who lived in Southeast Asia [7]. *T. marneffei* grows in the infected tissues and at 37 °C (body temperature) as a fission yeast i.e. arthroconidia formed from hyphae. At room temperature (25-30 °C) it grows as a filamentous form (mold) and produces a diffusible red pigment; microscopically biverticillate and monoverticillate penicillii bearing curved chains of conidia are observed. An infected patient does not act as a source of infection. The first four cases in India were of disseminated infection in HIV+ patients from Manipur State in northeast (NE) India [29], the patients had fever, weight loss, anorexia, hepatosplenomegaly, and molluscum contagiosum like lesions on face and upper trunk.

II. MATERIALS AND METHODS

A thorough search of literature was done in Medline, PubMed, Biomed lib, Cochrane library and Google Scholar using different sets of keywords, viz. *talaromycosis marneffei*, *Talaromyces marneffei*, rodent carriers, environmental reservoir, for accessing relevant data from

different states of India. Cross references in the collected research publications were also accessed extracting relevant information.

III. RESULTS AND DISCUSSION

A. Geographic distribution of cases

Talaromycosis *marneffei* is geographically limited to Southeast Asian countries, viz. Hong Kong, Thailand, Vietnam, Taiwan, China, Laos, Cambodia, Philippines, Malaysia, Myanmar and northeast India. Majority of the cases (53) in India have originated from Manipur state in NE India [8], [26], [28], [33]. Twelve autochthonous cases have been reported from Assam [3], [9], [19], [21], [24], [25], [28], [33], a state bordering Manipur and a few cases in other NE states, viz. Nagaland -1 [18] Mizoram-2 [18], [30], and Meghalaya-1 [8], Sikkim-1 [28]. Cases reported from other parts of India include two each from Kerala [27] [31] and Maharashtra [2] [34], and one from Delhi [35]. In one additional case, there was history of travel to northeast India without mention of the specific state [28]. A study from Sikkim [1] reported 14.28% of 32 cases of onychomycosis due to *T. marneffei* but no details of the identification of the fungus in culture or tissue were mentioned, nor were these available on inquiry from the corresponding author of the article; hence identification of the etiologic agent as *T. marneffei* in these cases is doubtful.

B. Bamboo rats found to be natural hosts of *Talaromyces (Penicillium) marneffei*

Bamboo rats known to be carriers of *T. marneffei* in southeast Asia include *Cannomys badius* (The Lesser Bamboo rat), *Rhizomys pruinosus* (Hoary bamboo rat), *R. sinensis* (Chinese bamboo rat) *R. sumatrensis* (Large bamboo rat, Sumatran or Indo-Malayan rat [2]. In India only two species of bamboo rats, viz. *C. badius* and *R. pruinosus* are found in north eastern states, excepting Arunachal Pradesh and Nagaland [11]. Bamboo plantations harbor several species of rats other than bamboo rats. A study by Guignani et al [10] comprehensively investigated 182 sympatric rodents comprising five species (*Bandicota bengalensis*, *Rattus norvegicus*, *Rattus*, *Rattus nuditus*, *Mus musculus*, and indigenous reddish-brown bamboo rat *Cannomys. badius* from bamboo plantations in Manipur State, NE India. Ten of 110 *C. badius* rats were found to be asymptotically infected with *T. marneffei*. It is noteworthy that one of the 10 isolates from bamboo rats shared the genotype with that of a human isolate from that area [10]. This provides evidence for a common source of infection for the rats and human, and host to host transmission. A similar finding has been reported by Cao et al [5] in China. The bamboo rat, *Cannomys badius* is a very common in Manipur but is also known to occur in Arunachal Pradesh, Assam, Nagaland, Mizoram, and possibly it occurs in other States. There is no information on carriage of *Talaromyces marneffei* by this rat and other rodents in these States, though several indigenous human cases of *T. marneffei* have been recorded from Assam, and one from Nagaland.

C. Occurrence in soil and environmental reservoir of infection

Natural reservoir of *T. marneffei* has not been definitely established. In a study by Guignani et al [12], none of the 176 soil samples collected from bamboo plantations in several parts of India, including 25 collected from the burrows of the bamboo rat (*Cannomys badius*) in Manipur yielded *T. marneffei*. However, it has been demonstrated that the fungus can survive in sterile soil for several weeks, but only for a few days in unsterile soil [15]. Cao et al [5] were able to isolate *T. marneffei* from 5 of 43 samples of soil collected from the burrows and surrounding environment of bamboo rats in China. Thus, the most probable environmental reservoir for infection appears to be the soil of bamboo rat burrows. There is no evidence regarding transmission of infection through direct exposure to bamboo rats, or eating bamboo rats. Since bamboo rats come in contact with bamboo plants, it would be worthwhile to investigate possible carriage of *T. marneffei* on parts of bamboo plants.

D. Clinical spectrum of infections

Commonest symptoms in HIV+ patients in order of frequency are fever, weight loss, weakness, anemia, skin lesions, and hepatosplenomegaly and lymphadenopathy as reviewed by Ranjana et al [22] and Sethuraman et al [27], there were no respiratory symptoms in these cases. Skin lesions are typically centrally umbilicated generalized papules or nodules, which may be confused with molluscum contagiosum. A high index of suspicion in the presence of typical skin lesions can lead to early diagnosis. Cases of rare presentations include one of acute abdomen [22], another one with acute abdomen and mesenteric/retroperitoneal lymphadenitis [28] and the third one of total nail dystrophy [31]. Three HIV positive adult patients including two originating from Manipur [14] [18], and one from Assam [23], and another HIV positive 12-year-old boy from Assam [24] with *T. marneffei* infection, manifested as immune reconstitution inflammatory syndrome (IRIS).

There have been 110 cases of talaromycosis *marneffei* in non-HIV subjects reported in world literature [6]; the major clinical features in these cases were fever, cough, malaise, anemia, thrombocytosis, cutaneous or subcutaneous lesions, lymphadenopathy, weight loss, and dyspnea. In a retrospective cohort study involving 116 HIV patients and 34 non-HIV patients infected with *T. marneffei* in Thailand, it was found that the non-HIV-infected patients were significantly older, less likely to have fever, splenomegaly and umbilicated skin lesions, and more likely to have Sweet's syndrome and osteoarticular lesions. [6]. The non-HIV-infected patients also had higher leukocyte, CD4 lymphocyte and platelet counts, and lower alanine transaminase level and blood culture-positive rate [6]. There are only four cases of talaromycosis *marneffei* in non-HIV patients from India, one a diabetic with probable early nephropathy with symptoms of chronic pneumonia, another one a post-renal transplant patient on immunosuppressive treatment both being from Sikkim [8]. The third case from Kerala [27] had a verrucous lesion on the foot with no history of trauma, tuberculosis, diabetes mellitus, HIV, hepatitis B or HCV infection, and the fourth one was an

immunocompetent patient with keratitis from Maharashtra [33].

The incidence of HIV-associated *T. marneffei* infection has decreased considerably with the use of potent antiretroviral therapy (ART). However, *T. marneffei* infection continues to cause considerable morbidity/mortality in AIDS patients who do not seek or have access to ART, or who have a suboptimal response to HIV therapy [35]. In India, indigenous cases of *Talaromyces marneffei* infection are known from NE states of Manipur, Assam, Mizoram, Nagaland, and Sikkim, but no case is known so far from Tripura. The maximum number of cases have been described from Manipur. The suggested association of the disease with rainy season [32] should be further explored. Two species of bamboo rats are found in the Northeast India, *Cannomys badius*, the Lesser Bamboo Rat and *Rhizomys pruinosus*, the larger Hoary Bamboo Rat. *Cannomys badius* is known to be carrier of the *Talaromyces marneffei* in Manipur. Carriage of *T. marneffei* by *R. pruinosus* in northeast India needs to be investigated. Further as described earlier, a few autochthonous cases of talaromycosis *marneffei* have been reported in the past decade from some states of India far away from the northeast, viz Delhi, Maharashtra, Tamil Nadu and Kerala. The stated species of bamboo rats are not found in these areas. Thus, an attempt should be made to investigate if other species of rats associated with bamboo plants in these areas harbor *T. marneffei*.

It is worth mentioning here that three locally acquired cases of talaromycosis *marneffei* in HIV infected patients have been reported from West Africa, one originating from Burkina Faso [13], another one from Ghana [17], and third one from Togo [20]; these patients had never travelled to Southeast Asia. Cases among Africans who have travelled to endemic countries in Southeast Asia are much more common [32]. It is possible that pockets of endemic foci of *T. marneffei* infection exist in other countries in Africa and elsewhere.

Several other *Talaromyces* species including *T. amestolkiae*, *T. decumbens*, *T. piceus* and *T. purpurigenus* and are common in soil, rotten fruits and air and have been reported to cause superficial and invasive fungal infection in humans in USA, Mexico, Argentina, UK and Turkey [16]. It would be worthwhile investigating occurrence of human infections caused by these species in India.

Our knowledge of the natural reservoir of *T. marneffei* and mode of infection has not been definitely established. It is possible that conidiospores of the fungus from soil or from direct contact with carrier bamboo rats are inhaled and then engulfed in alveolar macrophages via respiratory route.

IV. CONCLUSION

The need for comprehensive investigation of occurrence of human infections due to *T. marneffei* and occurrence of the fungus in environmental sources in different parts of India cannot be overemphasized. Diagnosis of infection can be challenging since other diseases like tuberculosis and histoplasmosis share many clinical features [28]. A definitive diagnosis should be made by correct identification

of the causative agent in tissue and culture as described in detail [28]. Molecular methods for diagnosing the infection at an early stage should also be explored. It has been demonstrated that MALDI-TOF mass spectrometry is a good choice for rapid, less expensive primary identification of *Talaromyces* species [16].

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