University Journal of Medicine and Medical Specialities

ISSN 2455- 2852 2021, Vol. 7(6)

Epidemiological and clinical characteristics of Talaromyces marneffei infection: A case series from a tertiary care hospital in South India.

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Abstract

Introduction: Talaromyces marneffei, previously known as Penicillium marneffei is a dimorphic fungi mainly affecting immunocompromised individuals and is endemic in North-Eastern regions of India. It is the third most common infection among individuals infected with acquired immunodeficiency syndrome (AIDS). It is acquired by inhalation of conidia. After an initial respiratory infection, it can disseminate. We are describing here the different spectrum of talaromycosis, as seen in our centre.

Methods: Fourpatients who hadlaboratory confirmed diagnosis of Talaromyces marneffei infection, presenting to Christian Medical College, Vellore over a period of 4 years are included.

Results & Discussion: Threepatients (75%) were from the North-Eastern regions of India, with the remaining one hailing from Bangladesh. All patients were immunosuppressed with AIDS being the predominant underlying cause (in 3 patients). CD_4 counts of the patients ranged from 7-50 cells/µl. One patient was co-infected with human immunodeficiency virus (HIV) and hepatitis B virus.The clinical presentations of the patients ranged from generalised weakness, multifocal osteomyelitis, papular skin eruption or fever with necrotic nodules over skin. T. marneffei was isolated from bone marrow of first patient, skin biopsy of second and T10 vertebral tissue of the third patient. The organism was cultured from bothbone marrow and skin biopsy from the fourth patient, suggesting dissemination. Three out of 4 patients (75%) survived aftertreatment with amphotericin B and itraconazole. However, one patient succumbed to the infection.

Conclusion: Talaromycosis is endemic in North-Eastern regions of India but with increased medical tourism, there is need for awareness of varying clinical presentations of thisdisease. This will aid in early diagnosis and appropriate management of these immunocompromised patients.

Introduction

Talaromyces marneffei, previously known as Penicillium marneffei(1), is a dimorphic fungi that was first discovered in 1956 in Vietnamfrom a bamboo rat (Rhizomys sinensis)(2). It predominantly affects individuals with weakened immune system and was considered a rare disease until the 1980s with less than forty cases reported over few decades(3). With the advent of acquired immunodeficiency syndrome (AIDS), the cases started to increase at an alarming rate(3). It is present in the environment as mould and changes to the yeast forms (8-13 µm, with large transverse septum) on entering the human body.Penicilliosis was the previous name given to the disease with the organism being known as Penicillium marneffei. The nomenclature was changed on the basis of genomic studies done on RPB1 gene. The organism was then reclassified in the genus Talaromyces(1,4).

Talaromyces marneffeienters the human body through the respiratory system. Infection sets up when the conidia are inhaled. It spreads to other organs through haematogenous route. The disease caused is known as talaromycosis. Its clinical course is rapid and more severe in immunocompromised individuals. A more indolent course is seen in immunocompetent persons. Necrotizing reactions aremainlyseen in individuals with any type of immunodeficiency, with the yeast forms of the organism being present both extracellularly and intracellularly. Granulomatous reactions are present in individuals who are immunocompetent (5). It usually affects the reticulo-endothelial system but other sites such as lungs, skin, osseous tissues and subcutaneous tissue can also be involved(6,7). A few case reports of keratitis due to T. marneffei have also been described in the past (8,9).

Talaromycosisis known to be endemic in China, India and South East Asian countries such as Thailand, Vietnam, Mayanmar, Malaysia, Cambodia and Indonesia (3,10). Over the period of years, cases have slowly increased, with an abrupt rise seen after AIDS pandemic (11). Few sporadic cases have also been reported from France, Switzerland, Germany, United Kingdom, Australia and United States but most cases have been attributed to travel to endemic countries (12). In India, it is predominantly seen in North-Eastern states with Singh et al. reporting four indigenous cases from Manipur in 1998 (13). Michael et al., in 2005 reported three cases of talaromycosis with different clinical presentations (previously known as penicilliosis), from Vellore, with all three patients belonging to North-Eastern states of India (14).

In our study, we present four cases of talaromycosis presenting to Christian Medical College, Vellore in the past 4 years.

Aim and Objectives

Aim: The aim of our study was to evaluate epidemiology and clinical features of patients presenting with talaromycosis.

Objectives: The objectives of our study were:

To describe the cases of talaromycosis presenting to our hospital in the past four years.

To evaluate the various epidemiological and clinical presentations of T. marneffei Infection

Materials and Methods: Four cases of talaromycosis, presenting to Christian Medical College, Vellore over a period of four years i.e. January 1, 2013 to November 30, 2017 were included in our study. These cases were selected based on the presence of yeast form in microscopy and culture positivity of samples sent for microbiological investigations. The clinical details were taken from the electronic patient records.

Laboratory diagnosis of the disease was done by direct microscopy and culture. The various samples that were sent to microbiology laboratory, for diagnosis of these patients were;bone marrow (from two patients), skin biopsy samples (from two patients) and tissue from T10 vertebrae from one patient. These samples were visualised using Calcofluor white stain and Gram stain. Many yeast like organisms (of about 3X6.5µm in size) were seen. The samples were also cultured on Sabouraud's dextrose agar (25^{o}C) and Brain heart infusion agar (37^{o}C).

Culture on Sabouraud's Dextrose Agar at 25^{o}C showed bluish-green, filamentous, flat colonies with white periphery within 48 hours. Red, rapidly diffusible pigment or wine red pigment was visualised on the reverse. Microscopic examination of the culture showed thin hyaline septate hyphae with hyaline conidiophore that were biverticillate and located laterally and terminally. Each verticilli had 3-5 metulae which in turn produced several phialides which bore lemon shaped conidia in chains. Yeast forms of about 3 µm in size were seen on histopathology examination of the tissues, which is consistent with talaromycosis.

Results: The 4 patients with T. marneffei infection included in our study, are described as follows;

Case 1: A 53 year-old-man from Itanagar, Arunachal Pradesh, presented to the outpatient department with history of generalised weakness since 5 months, swelling over both the legs since 15 days and history of significant loss of weight, i.e. about 20 kgs over a period of two months. On examination, he was emaciated and had hepatomegaly.On laboratory evaluation, the patient was found to have a haemoglobin of 9 gm/dL and raised liver ezymes. He was found to be positive for human immunodeficiency virus-1 (HIV-1) antibodies and the CD_4 count was 12 cells/µl. Bone marrow biopsy was sent for culture to the microbiology lab and it grew T. marneffei. The patient went into shock, DIC and severe metabolic acidosis and ultimately succumbed to infection.

Case 2:A 36 year-old-male from Cachar, Assam presented with the complaints of fever and loose stools since one year, with skin lesions over right upper limb since 20 days. The patient also had a history of weight loss with a loss of about 8 kgs over the year. There was a history of tuberculous pleural effusion 10 years back, for which he had received anti-tubercular treatment. On examination, bilateral pitting edema was seen. Many necrotic nodules of 1X1 cm size were seen on the skin of dorsal aspect of left forearm. Oral candidiasis was also present. Laboratory investigations showed that he had a haemoglobin of 9.5 gm/dL. He was found to be positive for HIV-1 antibodies, with CD_4 count of 50 cells/ µl. Investigation for tuberculosis was negative with normal chest X-ray and Xpert Mtb/Rif assay on sputum was negative for M. tuberculosis. On further investigations his bone marrow culture grew Mycobacterium intracellulare and punch skin biopsy grew T. marneffei on culture. The patient was treated with liposomal amphotericin B and oral itraconazole and anti-retroviral therapy was started. The patient was started on amikacin, clarithromycin, moxifloxacin and ethambutol for disseminated atypical mycobacterium infection. He presented to our hospital again two months later with amikacin induced nephrotoxicity and the drugs were adjusted and patient was advised to continue ethambutol, moxifloxacin, azithromycin and clofazimine instead. The patient has since then been lost to follow-up.

Case 3:A 16 year-old-malefrom Dhaka (Bangladesh), had a history of recurrent childhood infections and

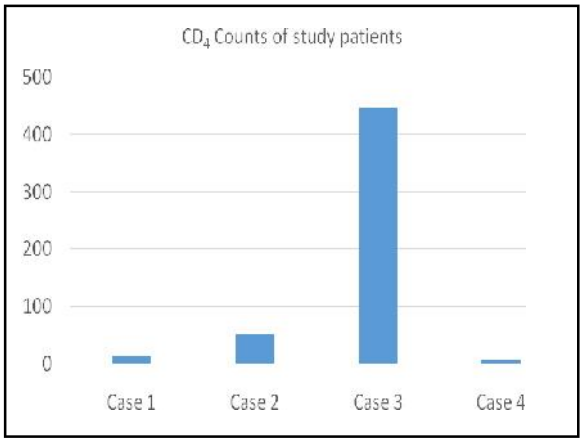
probable primary immunodeficiency, presented with lower back ache and fever since 3 months and loss of sensation in both the legs and difficulty in walking since three weeks. On examination, touch and pain sensations were absent below L1, temperature sensation was reduced below L1 level and deep tendon reflexes were exaggerated. MRI spine showed multilevel infective spondylodiscitis. Haemoglobin was 12.7 gm/dL. He was however found to be negative for blood borne viruses and had a CD_4 count of 446 cells/µl. CT guided biopsy of T10 vertebrae was taken and vertebral tissue was sent for culture. The ulture grew T. marneffei. Granulomatous spondylodiscitis with focal acute inflammation and occasional yeast forms were observed on pathological examination. The patient was treated with liposomal amphotericin B for 4 weeks and oral itraconazole 200 mg, b.i.d.

Case 4:A 35 year-old-man from Senapati, Manipur, a known case of human immunodeficiency virus (HIV)& hepatitis B virus (HBV) co-infection (diagnosed in CMC, Vellore in 2010), presented with complaints of low grade intermittent fever and generalised skin lesions since past two weeks. He stopped the anti-retroviral treatment two years ago. On examination; 4-5 mm in size multiple, fleshy, dome shaped, papules were seen all over the body. The haemoglobin was 9.1 gm/dL and CD_4 count was 7 cells/µl.Skin biopsy and bone marrow biopsy were taken and both grew Talaromyces marneffei, suggesting dissemination. The patient was started on conventional amphotericin B with monitoring of renal parameters for two weeks and then itraconazole, 400 mg twice daily was advised.

Three of the patients (75%) were from North-Eastern states of India and one was from Bangladesh. On evaluation of the cases, all patients were found to be immunosuppressed. The cause of immunosuppression was HIV infection in three patients (75%), while one patient had primary immunodeficiency.

Degree of immunosuppression was evaluated by estimating the CD4 counts, which is depicted in Table 1, as follows:

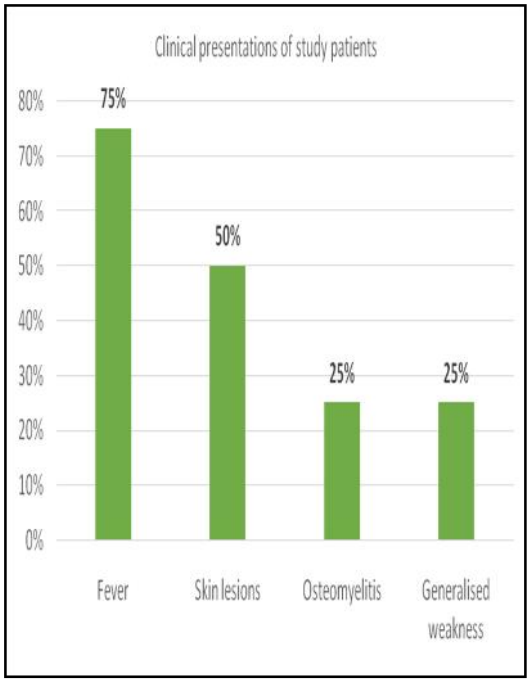
Table 1: CD_4 counts of study patients



The patient with the lowest CD_4 value of 7 cells/µl, had disseminated talaromycosis with generalised skin lesions. T. marneffei was isolated from both the bone marrow and skin biopsy specimens, in the said patient.

The clinical presentations ranged from generalised weakness to disseminated infections. Preponderance of fever was seen, with it being present in three cases. Skin lesions were present in 50% of the cases and other presentations were weakness and lower back pain (Osteomyelitis). The following table shows the various clinical presentations of the patients:

Table 2: Various clinical presentations of study patients



Discussion:T. marneffei is known to be endemic in South Asian countries, China and India.In India, it is endemic in North-Eastern states such as Manipur, Assam and Arunachal Pradesh. In our study, 3 out of 4 (75%) cases were from the North-Eastern states of India, with a single case from Bangladesh. This further corroborates the fact that talaromycosis is predominantly restricted to the areas of its endemicity(3).

Most of the cases of talaromycosis are associated with decreased immunity, with increased number of cases reported after the emergence of acquired immunodeficiency syndrome (AIDS)(11). In our study, immunodeficiency was present in all the study cases, with AIDS being the predominant cause (75%) and primary immunodeficiency being the cause in only one study patient. Severe disease or disseminated infections

are seen among patients with higher degree of immunosuppression, which is indicated by the CD_4 counts. The lowest CD_4 count that was observed in our study was 7 cells/µl and it resulted in disseminated infection, with T. marneffeiisolated from both the bone marrow and skin biopsy specimens of the patient; further validating the above stated fact.

Other immunodeficiency states, such as; transplant recipients, patients with primary immunodeficiency syndromes, patients on long term immunosuppressants and steroids are also at increased risk of acquiring Talaromyces infection. This has led to a rise in talaromycosis cases in non -HIV infected patients in the last decade(8,15,16), with a number of cases reported globally.An immunocompetent patient from France was recently diagnosed to have chronic pulmonary talaromycosis, which was attributed to his travels to the endemic regions in the past(16). From India, there has been a report of Talaromyces keratitis in an immunocompetent individual from Pune (8). The predominant clinical manifestations in such patients are fever, malaise, cough and cutaneous lesions (15).

Supparatpinyo et al., in their study spanning half a decade evaluated eighty cases of T. marneffei infections and found, fever (92%), anaemia (77%), weight loss (76%), and skin lesions (71%) to be the predominant presenting symptoms (10). Fever and loss of weight were also the predominantfeatures seen among our patients (in 75% of study patients). Skin lesions were seen among 50% of our study patients and anaemia was present in all cases, which reiterates the findings of previous studies.

Conclusion: Talaromycosis is predominantly an opportunistic infection, primarily restricted to the endemic regions. It can present as fever or can get disseminated and result in varied clinical manifestations. It is underdiagnosed in many instances, as it can mimic other diseases and have non-specific clinical features. There has been an increase in cases of talaromycosis in the past few years in areas where it is not endemic. Thus, there is a need to spread awareness regarding it among healthcare personnel which will in turn lead to early diagnosis and appropriate medical management of patients with talaromycosis.

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