

A Case of Disseminated *Talaromyces marneffe* in the Host with Normal Immunity

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Rec date: October 9, 2017; Acc date: October 15, 2017; Pub date: October 22, 2017

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Citation: Zhao Y, Sun X, Wu X. A Case of Disseminated *Talaromyces marneffe* in the Host with Normal Immunity. J Clin Radiol Case Rep 2017, Vol.1 No.1:02.

Abstract

Introduction: Disseminated *Talaromyces marneffe* is a rare disease caused by conditional pathogen *Talaromyces marneffe* (*T. marneffe*) which hazards immunocompromised persons more than healthy ones.

Objectives: To report a case of disseminated *Talaromyces marneffe* in the host with normal immunity.

Methods: The patient with cough, fever and cervical lymph nodes enlargement was diagnosed by lymph node biopsy and culture and treated with Amphotericin B and itraconazole.

Results: After lymph node biopsy and culture, she was diagnosed with disseminated *Talaromyces marneffe* and she was cured successfully after treatment with Amphotericin B and itraconazole.

Conclusion: Disseminated *Talaromyces marneffe* involves lung tissue, liver tissue, lymph node and skin, leading to cough and fever.

Keywords: Disseminated *Talaromyces marneffe*; Host with normal immunity; Cough; Fever

transplantation and stem cell transplantation, as well as those who receive immunosuppressive therapy or are critically ill. As a result, the number of patients with invasive aspergillosis and candidiasis has significantly increased [1,4,5].

The burden of invasive fungal infection including *candidaemia*, chronic pulmonary aspergillosis, and invasive aspergillosis following leukaemia therapy, transplantations, and chronic obstructive pulmonary disease is increasing.

Talaromyces marneffe (*T. marneffe*, TM), formerly known as *Penicillium marneffe*, can cause fatal disseminated TM in immunocompromised individuals more than healthy ones particularly those with Acquired Immunodeficiency Syndrome (AIDS) [1-3]. Recent studies suggest that the most probable mode of entry is via inhalation of airborne environmental conidia. Many reports describe the frequency of lower respiratory tract TM infection among patients with AIDS [6]. However, the literature seldom described the infection in normal immunity. Given the limited clinical experience, we aimed to describe the clinical features of disseminated TM with lung invasion in normal immunity to increase knowledge and promote effective diagnostic and therapeutic strategies.

Case Report

The patient, a 17-year-old female student, was admitted on January 10, 2012 due to cough and expectoration for 3 months and fever with cervical lymph nodes enlargement for 10 days.

The patient has no primary immunodeficiency (such as interferon gamma autoantibodies) and secondary immunodeficiency, especially medications need to be mentioned such as NSAIDs, antimalarial drugs, anti-epileptic drugs and some herbal medicine, and corticosteroids. She has never trip to anywhere before admission. Without obvious predisposing factor, the patient had cough and expectoration which were not obviously relieved after oral medicine treatment (detail unknown) in the last 3 months without fever, and then had intermittent chills and fever, especially at night, with the maximum body temperature of 39.8°C.

Introduction

Invasive fungus diseases (IFDs) have become more prevalent and are a major cause of hospital death, especially in individuals with immunocompromised conditions [1,2]. In the past, most IFDs were associated with Human Immunodeficiency Virus (HIV) infection, including cryptococcosis and pneumocystosis [3]. Almost all HIV-infected patients now days have access to antiretroviral therapy (ART). Therefore, the rising incidence of IFDs seems to be associated with the increasing number of patients who undergo organ

Ten days ago, and the patient had cervical lymph node enlargement, and the symptoms were not obviously relieved after the cefminox and reduced glutathione treatment. The chest CT scan in a local hospital showed large patch of infiltration in bilateral lungs. Both alanine aminotransferase and aspartate aminotransferase were elevated. The patient was previously healthy without any special diseases, history of immunodeficiency or history of long term use of immunosuppressive drugs.

The pre-admission cervical lymph nodes biopsy showed granulomatous changes and a large number of round and oval spores in macrophages and vacuolization of cells, and so histoplasmosis might be diagnosed. The physical examinations at admission showed cyanotic lips. There were several well circumscribed dark red papules on her forehead (centrally umbilicated maculopapular lesions), which were crusted at the edges, characteristic of lesions seen in TM infection, several palpable lymph nodes of which the larger one was about 4.5 × 3 cm in the size in the submandibular and bilateral necks, bilateral mild stained yellow sclera's, dullness of percussion at bilateral lungs, decreased breath sounds in auscultation, no moist and dry rales, heart rate 132 beats/min, rhythm regular, no cardiac murmurs; slight abdominal distention, no palpable or enlarged liver and spleen below the ribs, positive shifting dullness; moderate edema in lower limbs.

The laboratory examinations after the admission: blood routine test: WBC 15.66×10^9 , hemoglobin 10^8 g/L, liver function: alanine aminotransferase 150 U/L, aspartate aminotransferase 196 U/L, alkaline phosphatase 2365 U/L, total bilirubin 63.7 $\mu\text{mol/L}$, direct bilirubin 14.5 $\mu\text{mol/L}$, total protein 46.1 g/L, albumin 26.8 g/L. Abdominal CT showed hepatosplenomegaly. HIV, ten indexes of hepatitis and syphilis were negative. The proportion of CD3 is 58% and the ratio of CD4/CD8 is 1.33. Tumor biomarkers were normal. Gynecological ultrasound was normal. Head CT and X-ray plain film of lower limbs were normal.

Amphotericin B liposomes were given at doses from 0.1 mg/kg/day to 3 mg/kg/day and gradually increased to 0.5-1 mg/kg/day after the admission. Meanwhile, hepato-protective, hypoproteinemia correcting and nutrition support therapy were also given and the tissue culture of the cervical lymph node was identified to be *T. marneffe*.

The lesions of chest CT reexamination were absorbed and the cervical lymph nodes were shrunk significantly after two weeks of amphotericin B liposome therapy. Meanwhile, the liver function was recovered after 16 days treatment and the rashes were subsided after 20 days treatment. The white blood cells were normal. The hemoglobin was 85 g/L and the lesions of chest CT reexamination showed slow absorbing after one month of amphotericin B liposome therapy.

Hepatic dysfunction occurred (3 times of the normal) in 10 days after the replacement of amphotericin B, and then itraconazole capsules (200 mg 2 times/day) and hepatoprotective treatment were given rather than amphotericin B. The patient was discharged in significantly-improved general condition with the maintain treatment of

itraconazole 200 mg bid after the lesions of bilateral lungs were mostly absorbed within 4 months with the total amount of 6000 mg amphotericin B liposome therapy which was reused when liver function returned to normal after 10 days of hepato-protective treatment.

Discussion

Penicillium species are common and generally non-pathogenic laboratory contaminants that are widely found in nature. Among *Penicillium* species, *Penicillium marneffe* (*P. marneffe*) is the only dimorphic and pathogenic species. This species was recently transferred to the *Talaromyces* genus along with other *Penicillium* species belonging to the *Biverticillium* sub-genus.

T. marneffe is a thermally dimorphic fungus, normally appearing as a mould at temperatures of 25-30°C and as a yeast at a temperature of 37°C. It is an opportunistic pathogen, mainly related to HIV infection, but acquired infection in endemic regions has been described in solid organ transplant recipients. Most of the published cases from other regions had previously travelled to South-East Asia, notably Thailand, Vietnam, Hong Kong, Southern China, Taiwan, India, Indonesia, Cambodia or Laos.

Some 10% of AIDS patients in Hong Kong and 30% of patients in Thailand will present with *T. marneffe* infections. Thus, far the only known hosts for *T. marneffe* are humans and bamboo rats. Although many aspects of the ecology and potential reservoirs of *T. marneffe* and its relationship with human infection remain unknown. Airborne inhalation of conidia and direct inoculation are known modes of transmission.

Most patients with penicilliosis present with symptoms related to infection of the reticuloendothelial system, including generalized lymphadenopathy, hepatomegaly and splenomegaly. Initial presenting features of the disease are usually non-specific, like fever, anaemia and weight loss. Molluscum contagiosum like skin lesions are seen in most patients, and may be the best clue to diagnosis.

T. marneffe which hazards immunocompromised persons more than healthy ones is a rare deep mycosis caused by conditional pathogen TM which parasitizes cells [1-5]. Multiple re-examination of HIV, tumor biomarkers, ten indexes of hepatitis and immunization series (CD4/CD8) were normal, except for the absence of factors of hypo-immunity, such as the use of immunosuppressant for the patient. The domestic and overseas literatures reported that the disease often occurred in AIDS patients or patients without AIDS but with the factors of hypo-immunity, such as the use of steroid [6-23]. Although disseminated penicilliosis usually affects the monocyte-macrophage system, [2-5] the exact mode of *T. marneffe* transmission remains unknown.

Not only clinical manifestations but also shape and size of pathogens and pathological changes between *T. marneffe* and histoplasmosis are very similar, so there have been many reports in which *T. marneffe* was misdiagnosed as

histoplasmosis in the literature [24]. This case was misdiagnosed as histoplasmosis before the admission, and then confirmed as *T. marneffeii* after the admission through the cervical lymph node culture, since the key point in identifying these two diseases is fungal culture. PM which grows as a mold form at 25°C and as a yeast form at 35°C and shows typical wine red on sabouraud medium at 25°C then turns into the coexistence of light gray, white and pink after 15 days, is the unique temperature dependent duplex bacteria in *T. marneffeii*. The microscopic structure shows slender separated transparent mycelium with typical double-whorled or single-whorled broom-like branches with the colonies characteristics of yeast form, characterized by round, oval or rectangular yeast-like thallus with sausage-like diaphragm partially at 35°C without pigment on sabouraud medium.

TM is mainly distributed in Southeast Asia, especially Thailand and domestic areas such as Guangdong, Guangxi, Hubei, Yunnan and other places with reports of sporadic cases [25,26]. The *Rhizomys* is considered to be a natural host now. The clinical manifestations after PM infection are localized or progressively disseminated usually disseminated leading to fatal infection of skin, lymph nodes and internal organs mainly due to chronic progressive involvement of monocyte-macrophage cells. The common symptoms are multiple popular skin lesions, fever, weight loss, pancytopenia, systemic lymphadenitis, hepatosplenomegaly, bone damage, central nervous system involvement and so on, if not treated, usually leading to death. Cases with cervical and mediastinal as well as abdominal lymph nodes enlargement, popular skin lesions, fever, pulmonary infiltrates and hepatosplenomegaly without bone damage and central nervous system involvement were considered to be typical disseminated infections.

Mortality of untreated *T. marneffeii* infection is reported to be 100%. Recommended drug options are amphotericin B 0.5-1 mg/kg/day for 2 weeks after itraconazole 400 mg/d for 10 weeks, then 200 mg/d orally even long-term use if infected with HIV [27-29]. The patient was given amphotericin liposome treatment considering amphotericin B toxicity.

The symptoms were relieved, lymph nodes were shrunk and pulmonary infiltrations were absorbed significantly at the beginning of the treatment, but hepatic dysfunction recurred during the treatment and then amphotericin liposome was replaced with itraconazole discontinuously with hepatoprotective treatment for 90 days but it was still part of the left lung lesion that was not absorbed even in the chest CT reexamination after 10 days of amphotericin B treatment, which caused hepatic dysfunction again, so itraconazole was reused before the discharge. Because the long-term treatment and the refractory lesions even after the amphotericin liposome treatment in the dose were much more than guidelines recommended in this case, we concluded that TM was easy to relapse and insisted on using amphotericin liposomes till the lesions absorbed mostly and then changed to oral itraconazole therapy with the intensive monitoring of hepatic and renal function in the course of the treatment.

Talaromyces marneffeii is an opportunistic fungal pathogen that poses a serious health threat to patients with AIDS and

the related penicilliosis usually affects the monocyte-macrophage system in multiple organs (e.g., skin, lungs and reticuloendothelial system). Although the mode of *T. marneffeii* transmission remains to be determined, inhalation of airborne conidia, exposure to soil, history of exposure to or consumption of bamboo rats, and inoculation have all been proposed as potential means.

Deficient CD4+T-cell-mediated immunity plays a key role in *T. marneffeii* infection among patients with AIDS. The lung, liver and spleen are rich in lymphoid tissue, which produces lymphocytes that play important roles in cellular and humoral immunity.

As mentioned above, in addition to non-specific symptoms, patients reported pharyngeal/laryngeal symptoms such as sore throat, dysphagia and lymph node enlargement.

As mentioned above, *T. marneffeii* infections in normal immunity are rarely reported. Therefore, histopathological and fungal culture analyses of tissues have become the most important methods used to diagnose invasive *T. marneffeii* infection.

Hematogenous dissemination can lead to hepatosplenic damage and lymph node enlargement. However, in Fujian, China, itraconazole treatment is not possible in most patients due to its high cost. Thus, this report expands our understanding of the pathogenicity of the genus *Penicillium* in this age of global warming [19]. Clinicians, mycologists and epidemiologists should be aware of the possibility of infection by uncommon fungal pathogens in patients because emerging pathogenic fungi are increasingly recognized as major threats to human health.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China 81270130 (to Wu X).

Declaration

Ethics approval and consent to participate: The study was done after the agreement from the local ethics committee (Ethics Committee of Shanghai Renji Hospital). The patient gave his informed consent prior to his inclusion in the study.

Consent for publication: We obtained consent to publish from the patient.

Availability of data and materials: Data and material in the manuscript were available for testing by reviewers if needed.

Conflicting interests: The Authors declare that there is no conflict of interest.

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