CASE REPORT

# *Penicillium marneffei* infection involving liver

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## ABSTRACT

*Penicillium marneffei* (*P. marneffei*) is a pathogenic fungus that can cause fatal infections in humans, particularly immuno-compromised hosts. It is prevalent only in the Southeast Asian region. A 5-year-old boy was presented with diagnosed Acute Lymphoblastic Leukemia undergoing chemotherapy and suffering from high-grade fever for 15 days positively responded to antibiotics on the initial day, but later he became unresponsive. He was found negative for blood cultures of bacterial growth. Ultrasound of the abdomen showed a borderline enlarged liver with multiple small hypoechoic areas of variable sizes seen scattered in both lobes of the liver. Morphological and microscopic analyses of liver tissues showed multiple septate hyphae of *P. marneffei*. Amphotericin B was found to be effective in treating the child. Appropriate identification is essential to treat the pathogen-causing disease, especially in immuno-compromised conditions like a leukemic patient, and determine underlying mechanisms behind the pathogenesis.

**Key Words:** *Penicillium marneffei*, Immuno-compromised host, Liver

## 1. INTRODUCTION

*Penicillium marneffei* (*P. marneffei*), or *Talaromyces marneffei*, is the only dimorphic fungus of the genus *Penicillium*. Its thermal transformation from mold to yeast characterizes the distinctive dimorphic feature.[1] It was first isolated from bamboo rats, and the first natural infection of *P. marneffei* in humans was presented in immuno-compromised Hodgkin lymphoma patients in 1973.[2] It has been evident in humans *P. marneffei* infection usually occurs in immuno-compromised patients having cancer or HIV infection.[3] *P. marneffei* is endemic to Southeast Asia and Southern China.[4] Inside the immuno-compromised human body, it has been found to reside in fluid-filled or unfilled body cavities like the esophagus, bone marrow, abscesses, axial skeleton, and chylous ascites (a rare condition in which milky white lymphatic fluid known as chyle starts accumulating in the abdominal cavity).[5–7] This pathogenic fungus has been reported to cause Penicillosis, spreading throughout the body via the lymphatic system to the skin, liver, reticuloendothelial, digestive, and respiratory systems. Hence, the symptoms of *P. marneffei* are night sweats, chills, low or high-grade fever, skin lesions, fatigue, chest pain, shortness of breath, abdominal pain, hepatosplenomegaly, and lymphadenopathy in the neck particularly. It has non-specific and overlapping symptoms with other infections. But the clinical manifestation of Penicillosis depends upon the immuno-compromised condition of the body and local or disseminated infection.[8]

## 2. CASE REPORT

A 5-year-old boy diagnosed with Acute Lymphoblastic Leukemia (ALL) undergoing chemotherapy presented with continuous high-grade fever and was unresponsive to any antibiotic. Blood cultures were found negative for bacterial growth. Complete blood count (CBC) showed 25% hema-

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tocrit, 8.3 g/dl hemoglobin, 0% absolute neutrophil count, 0% absolute lymphocyte count, $46 \times 10^9$ platelet count, and $0.9 \times 10^9$ white blood count. Abdominal ultrasound showed borderline enlarged spleen and liver with multiple small hypoechoic areas of variable sizes scattered in both lobes of the liver. Fine needle aspirations cytology (FNAC) of the liver stained with Periodic Acid – Schiff (PAS) showed epitheloid granuloma with the fungal organism. No malignant cells were seen. A liver biopsy showed necroinflammatory slough with numerous fungal hyphae infiltrated in sinusoids, shown in Figure 1.

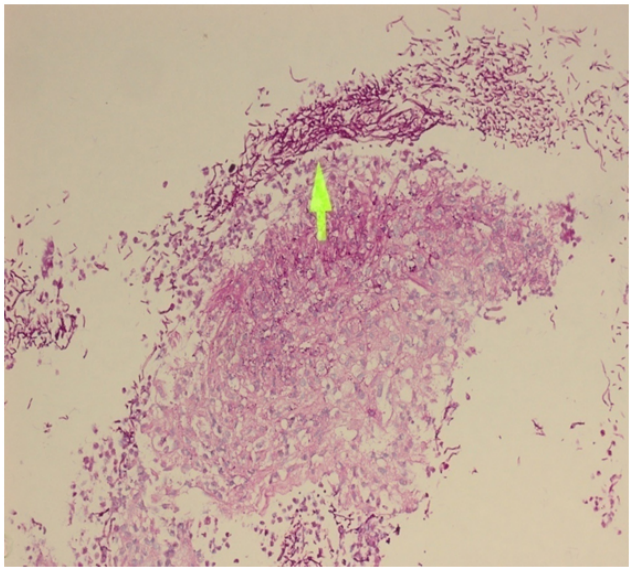

**Figure 1.** Periodic Acid-Schiff stained section of liver tissue. Yeast-form fungi filling the cytoplasm of macrophages are PAS-reactive.

To characterize fungal hyphae, tissue sections were then inoculated on two sets of Sabouraud Dextrose Agar (SDA) and Sheep Blood Agar (SBA). One group was incubated at room temperature, and the other was incubated at 37 °C in an ambient air incubator. After two weeks of incubation, colonies of *Penicillium* appeared on SDA. Gross morphology showed grayish-white or wooly colonies on SDA, as shown in Figure 2.

Further verification of *P. marneffei* morphology was performed through the tease mount method, in which a part of fungal growth was teased with a needle and observed under a microscope. To avoid cross-contamination, the tease mount was prepared in a biosafety cabinet. It revealed multiple hyaline septate hyphae, short conidiophores located laterally and terminally to the central transverse septum, as depicted in Figure 3. The patient was orally administered Amphotericin B 0.7 mg/kg for two weeks, followed by Itraconazole 5 mg/kg BD. Although the patient initially responded positively, he succumbed to multiple co-morbidities on the $25^{th}$ day of hospitalization.

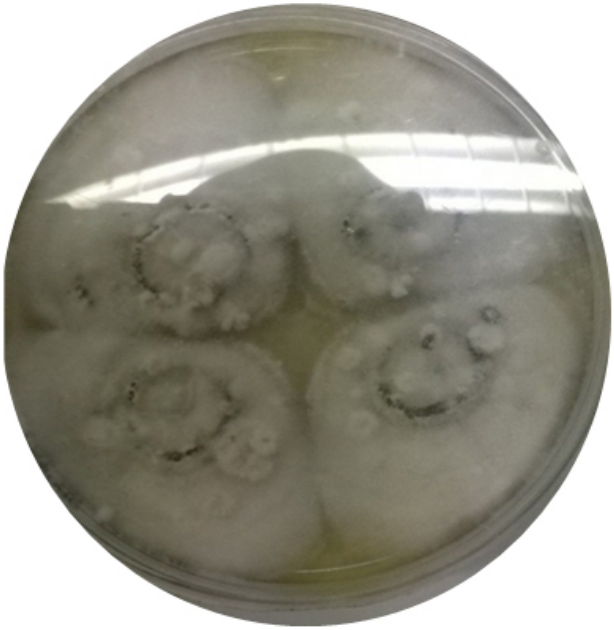

**Figure 2.** Colony morphology *P. marneffei* on SDA. The pigment diffused into the agar, which has a light green coloration. The surface tends to be granular to fluffy, depending on the degree of sporulation; note the distinct white apron at the margin of peripheral new growth.

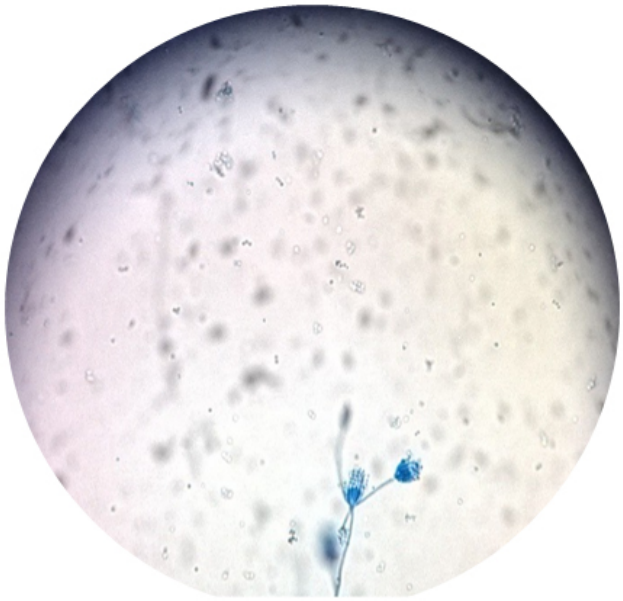

**Figure 3.** *P. marneffei* colony morphology in tease mount smear stained with Lacto-phenol Cotton Blue dye. Fruiting structure with branching phialides from which are produced chains of spherical conidia.


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## 3. DISCUSSION

The distinctive property of *P. marneffei* is its thermal dimorphic nature which discriminates it from other species of this genus. It is a pathogenic fungus for humans and causes a pathological condition called Penicillosis. It has fatal outcomes in immunosuppressive individuals.[9, 10]

Morphological and microscopic characterization revealed that it presents a cottony white colony. The conidiophores of *P. marneffei* have branched with ellipsoid to ovoid-shaped conidia, as shown in Figures 2 and 3. Contrary to this *Penicillium piceum (P. piceum)* offers greenish-blue to grayish-green colonies with less branched conidiophores and globose-shaped conidia. It shows inefficient growth on SDA and prefers malt extract agar for development. Moreover, the isolation source of *P. piceum* is soil, decaying plant material, and non-pathogenic to humans. Whereas the basis of isolated *P. marneffei* is the infected liver of an AIDS patient. The feature which discriminates it from every other species of the genus *Penicillium* is its thermally dimorphic nature.[11]

The infection usually occurs in the lungs by inhaling conidia; from the lungs, it spreads to other sites via a hematogenous route. The most common secondary site of infection is the liver. It infiltrates into hepatocytes through sinusoids and parenchyma via epitheloid granuloma.[2] The infection spreads to other organs, including lymph nodes, blood, lung, pericardium, and meninges.[8] It causes three distinct tissue reactions: granulomatous, suppurative, and necrotizing. The most common is a granulomatous reaction, usually in individuals with normal immunity.[1] Clinically, patients are presented with weight loss, anemia, and fever. The disseminated disease presents with skin lesions, painful non-productive cough, generalized lymphadenopathy, and hepatosplenomegaly.[8] Laboratory diagnosis of *P. marneffei* can be made by cytological and histological examination. The cytological demonstration revealed intracellular and extracellular basophilic, elliptical yeast-like organisms in the infected tissues, confirmed by microbiological cultures.[12]

The environmental source could be a possible route of airborne transmission of conidia. Center for disease control (CDC) has suggested Biosafety Level 2 (BSL-2) for the propagation and manipulation of *P. marneffei* cultures with limited access facilities.[2] It is susceptible to 5-flucytosine, the azole group of antifungal agents such as Itraconazole, Ketoconazole, and Miconazole. Management response of the azole appears to compare well *in vitro*. Amphotericin B has proved to have practical clinical implications, but the results of *in vitro* susceptibility testing are inconsistent.[2, 13]

The preferred options for Penicillosis treatment are Amphotericin B (0.6 mg/kg administered for two weeks) and oral Itraconazole (400 mg/day for ten weeks).[13] *P. marneffei* infection of the liver as a primary site is rare. However, it can spread to the liver as a secondary site of infection. Because of its propagative and disruptive nature, *P. marneffei* infection can spread to other organs and is associated with a high mortality rate. Hence, this life-threatening fungal infection necessitates prompt diagnosis, treatment, or management. This study paved the way for the whole genome sequencing of *P. marneffei* to identify and characterize genetic factors involved in its pathogenesis and thermally triggered dimorphic phenotype.

## CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

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