Uncommon Invasive *Penicillium* Species Infection in a Patient with Advanced HIV: A Rare Case Report

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Abstract: - *Penicillium* species are ubiquitous worldwide and constitute one of the largest fungal genera. Typically benign, *Penicillium* (*P.*) non-*marneffei* species can become a serious threat in immunocompromised hosts with the potential for high mortality. We present a rare care of disseminated *P.* non-*marneffei* infection in a Honduran patient with advanced HIV, initially manifesting as nonspecific symptoms. After a thorough and unrevealing workup, an inguinal lymph node biopsy resulted in positive fungal staining of tissue. However, expanded polymerase chain reaction (PCR) amplification of fungal 28S rDNA was necessary to confirm the diagnosis. Here we describe the first reported case of disseminated infection in a patient with HIV/AIDS presenting with lymphadenitis and propose treatment recommendations as no standards have been developed yet.

Key-Words: - *Penicillium* non-*marneffei*, HIV/AIDS, fungal lymphadenitis, disseminated infection, opportunistic infections, PCR, 28S rRNA.

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1 Introduction

Penicillium species are ubiquitous fungi found in human environments, including air and soil, and represent one of the largest fungal genera, [1], [2]. Notably, all *Penicillium* species (*spp.*) within the subgenus *Biverticillium* have been recently reassigned to the genus *Talaromyces,* [3], [4]. Among these, *Penicillium (P.) marneffei* has been officially reclassified as *Talaromyces (T.) marneffei,* [1], [2], [4], [5]. This dimorphic fungus is endemic to Southeast, East, and South Asia and is associated with the development of an AIDS-defining illness, [4], [6], [7].

The reclassification of *P. marneffei* is particularly significant in the context of the ongoing HIV pandemic. While the global incidence of HIV has declined, *T. marneffei* infections have not, especially in Southeast Asia, [8]. By the end of 2018, 288,000 cases were reported by 33 countries—excluding the United States (US)—with an estimated 17,300 cases per year, [8]. Detecting these infections is challenging due to their nonspecific clinical presentations. Additionally,

Penicillium spp. are not typically included in the differential diagnosis for people living with HIV (PLWH) presenting with nonspecific symptoms in non-endemic countries like the US.

Conversely, *P.* non-*marneffei spp.* are generally non-pathogenic and often identified as laboratory contaminants [2], [5]. However, in immunocompromised individuals, these species can cause severe and potentially fatal fungal infections globally, [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19]. The clinical presentations of these infections are diverse, including pneumonia, bloodstream infections, fungus balls, pericarditis, rhinosinusitis, intestinal invasion, endocarditis, and other systemic invasive diseases, [5], [18].

A review of the medical literature found only one reported case of disseminated *P.* non-*marneffei* infection in an immunocompromised patient without HIV in Malaysia in 2017, highlighting the rarity of such infections not only in the US but also worldwide, [20]. To our knowledge, our case is likely the first documented instance of disseminated *P.* non-*marneffei* infection in a patient with HIV. In the US, fungal infections in PLWH typically include cryptococcosis, histoplasmosis, and pneumocystis pneumonia, [21]. The advent of antiretroviral therapy (ART) has significantly reduced the incidence and mortality of fungal diseases among people with advanced HIV in the US since the 1980s, [21]. For instance, the incidence of cryptococcosis in PLWH decreased by approximately 90% in the 1990s, although fungal infections remain a significant source of morbidity and mortality globally, especially in low- and middle-income countries, [21], [22].

Diagnosis of *Penicillium* infections typically involves microscopy, histology, and culture. Rapid diagnosis can be achieved using antigen detection and polymerase chain reaction (PCR) methods when available, [4], [5]. Left untreated, *Penicillium spp.* infections can be fatal, [4], [6]. Currently, no standardized treatment guidelines exist for *P.* non-*marneffei* species. A comparative study on the antifungal susceptibility of *T. marneffei* and non-*marneffei* Penicillium species found that itraconazole and voriconazole are the drugs of choice for managing infections caused by these species, [20]. However, in the case of disseminated *P.* non-*marneffei* infection in Malaysia, the patient deteriorated on this initial therapy, and amphotericin B was subsequently added, leading to clinical improvement, [20].

This case report describes a Honduran patient recently diagnosed with HIV/AIDS who developed an invasive infection caused by a *P.* non-*marneffei* species. This case is novel as it represents the first reported instance of disseminated *P.* non-*marneffei* infection in a patient with HIV/AIDS. Due to the vague symptomatology and clinical presentation, physicians in non-endemic areas may not consider *Penicillium spp*. infection in the initial differential diagnosis, posing delayed idenitification and treatment. The fungal organism in this case was identified only after PCR amplification of fungal 28S rDNA from an inguinal lymph node biopsy. Prompt diagnosis, timely treatment, and initiation of HAART contributed to the patient's rapid recovery. This case underscores the need for heightened clinical awareness and the development of specific treatment guidelines for *P.* non-*marneffei* infections.

2 Case Presentation

A 46-year-old Honduran man, recently diagnosed with HIV by his primary care physician one week prior to admission, was referred to the emergency department due to a hemoglobin level of 5.5 g/dL. He reported experiencing fatigue and dizziness over the past seven months, along with two instances of fever and an unintentional weight loss of thirty pounds. He also reported not yet starting antiretroviral therapy (ART) since receiving the HIV diagnosis. He declined any headaches, chills, or syncopal episodes. Of note, he reported having condomless sex with two men in the past six months. Born in Honduras, he immigrated to Miami in 2015.

The physical examination revealed palpable lymphadenopathy in the bilateral inguinal region, massive splenomegaly, and hyperpigmented violaceous lesions with indurated nodules in the right lower extremity (Figure 1). His laboratory findings were significant for pancytopenia, with a white blood cell count of 2 x $10^3/\mu L$, absolute neutrophil count of 1.2, hemoglobin level of 5.5 g/dL, platelet count at 72 x $10^3/\mu L$, CD4 count of 36 cells/mm^3, and an HIV viral load of 1530 copies/mL. Given a normal value of lactate dehydrogenase, bilirubin, and haptoglobin, hemolytic anemia was ruled out. Computed tomography (CT) with intravenous (IV) contrast of the abdomen was ordered given his abnormal physical exam findings and pancytopenia. It revealed splenomegaly measuring 24.5 cm, along with mesenteric, retroperitoneal, and inguinal lymphadenopathy (Figure 2). CT chest with contrast was also ordered which showed evidence of prior granulomatous disease and several tiny calcified lymph nodes. The calcified granulomas varied from 2 to 9 mm in size and were located in the right and

left lobe. At this point, it was thought that HIV infection was likely causing an impairment in the production of hematopoietic lineage and suppression of bone marrow proinflammatory cytokines.

The patient was initiated on bictegravir/emtricitabine/tenofovir alafenamide for HIV/AIDS treatment, as well as atovaquone for *Pneumocystis jirovecii* prophylaxis (trimethoprim-sulfamethoxazole was avoided due to thrombocytopenia). The patient also received a transfusion of 2 units of leukoreduced packed red blood cells.

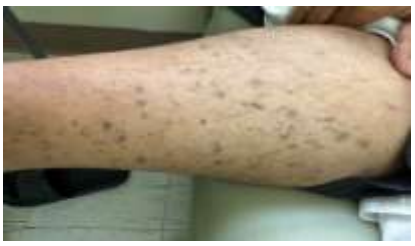

Fig. 1: Cutaneous findings involving hyperpigmented violaceous lesions with indurated nodules in the right lower extremity

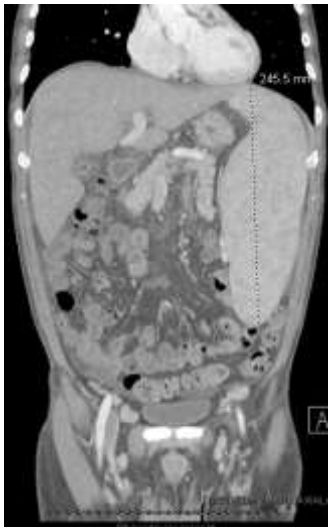

Fig. 2: CT with IV contrast of the abdomen demonstrating splenomegaly measuring 24.5 cm, along with mesenteric, retroperitoneal, and inguinal lymphadenopathy

Given the lack of improvement in the patient's symptoms and the persistence of his anemia, an extensive workup was undertaken in collaboration with infectious disease and hematology/oncology specialists. Overall, the patient was found to be negative for *Aspergillus*, *Blastomyces*, *Cryptococcus*, *Histoplasma*, *Leishmania*, parvovirus, *Toxoplasma*, and *Coccidioides*. Blood cultures for bacterial, fungal, and anaerobic infection remained negative as well. The hematology/oncology team was initially consulted due to a concern for an underlying malignancy given the negative infectious disease workup. Two bone marrow biopsies were conducted, both yielding no evidence of viral, fungal, or mycobacterial infiltration, nor possible malignancy. Bilateral inguinal lymph node biopsies were also pursued, revealing positive findings for reactive hyperplasia with atypical megakaryocytes, likely secondary to HIV infection. The right groin biopsy specifically showed minute fragments of fibroadipose tissue with crushed lymphoplasmacytic infiltrate with negativity for HHV-8, EBV, and fungal infection. However, the patient's left inguinal lymph node biopsy indicated fungal lymphadenitis with atypical paracortical hyperplasia and plasmacytosis (Figure 3A-B, Figure 4).

In response to the fungal lymphadenitis findings, the patient was initiated on empiric treatment with IV liposomal amphotericin B at 3 mg/kg. The left inguinal node biopsy specimen was sent to the University of Washington for further evaluation through tissue PCR for additional fungal, acid-fast bacilli, and leishmaniasis testing. Results from the University of Washington's comprehensive fungal PCR workup revealed positivity for a *Penicillium* species. Notably, the specific *Penicillium* species could not be identified. However, the laboratory noted that the tissue sample tested negative on PCR for *T. marneffei*. Therefore, the patient's pancytopenia, lymphadenopathy, splenomegaly, and overall fatigue in the setting of advanced HIV were diagnosed as infections from *P.* non-*marneffei* fungi.

The patient's treatment regimen for *P.* non-*marneffei* infection was developed from guidelines for the treatment of systemic *T. marneffei* infection. The patient received IV liposomal amphotericin B at a dosage of 3 mg/kg daily totaling four weeks. However, different from the above-cited guidelines, we extended the amphotericin B duration from 2 weeks to 4 weeks as a clinical judgment due to the patient's slow initial clinical improvement. During the remainder of his hospitalization, the patient's pancytopenia remained unchanged.

However, his splenomegaly and hyperpigmented violaceous lesions in his lower extremities showed improvement. After completing induction therapy with Amphotericin B for 4 weeks, the patient was clinically improved and discharged home on oral itraconazole at 200 mg twice daily for a period of ten weeks, with subsequent dose change to 200 mg once daily until achieving virologic suppression and a CD4 count greater than 100

cells/mm^3 for at least six months. The patient maintained regular follow-ups in the infectious disease outpatient clinic.

During subsequent appointments, the patient reported improvement in symptoms of fatigue and dizziness with no new complaints. He demonstrated compliance with the prescribed medications, including bictegravir/emtricitabine/tenofovir alafenamide, itraconazole, and atovaquone. Four months post-initiation of ART, his CD4 count rose to 73 cells/mm^3 (from an initial value of 36 cells/mm^3), and his HIV viral load decreased to 26 copies/mL (initially 1530 copies/mL). Ten months after his initial diagnosis, his pancytopenia improved markedly, with hemoglobin of 11.3 g/dL, white blood cell count 2.6 x 10^9/L, and platelet count 56 x 10^3/μL . His HIV viral load was undetectable and his CD4 count was maintained at 116 cells/mm^3, at which point itraconazole was discontinued. He reported resolution of his fatigue and dizziness.

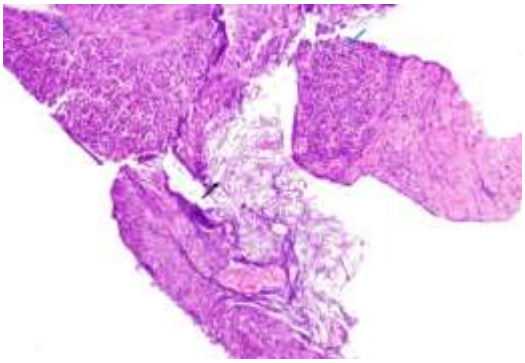

Fig. 3A: Inguinal Lymph Node Biopsy, Hematoxylin and eosin stain (H&E) 100x magnification. On low power, aggregates of fungal hyphae (black arrow) are seen in the background of lymphoid proliferation (blue arrows)

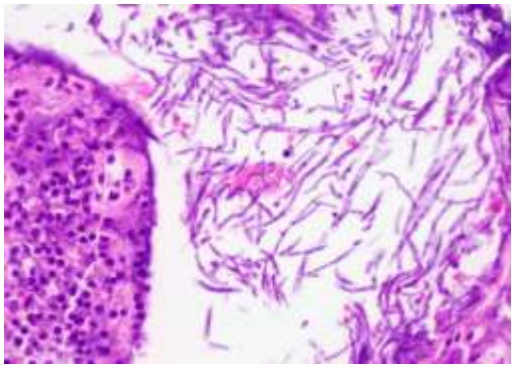

Fig. 3B: Inguinal Lymph Node Biopsy, H&E 400x magnification. At higher power, the hyphae can be better appreciated. They appear to be hyaline (i.e., lack pigmentation) and narrow. Septations are seen, along with occasional branching. This morphology is typical of the mold form of *Penicillium* species

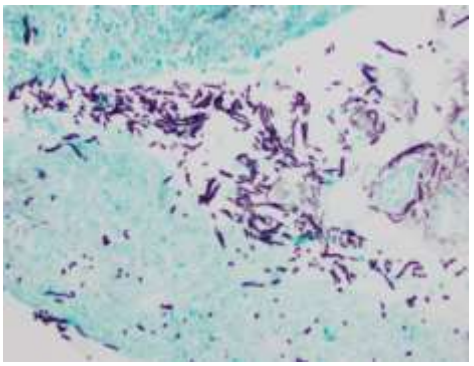

Fig. 4: Inguinal Lymph Node Biopsy, Grocott's methenamine silver (GMS) special stain. The hyphae stain is diffusely positive for GMS, confirming fungal origin

3 Discussion

While *P.* non-*marneffei* fungi typically pose minimal health risks to humans, they can cause severe infections, especially in individuals with compromised immune systems [2], [4], [5]. Our patient faced a substantial risk factor due to his immunocompromised state from uncontrolled HIV [23], [24]. HIV, being a retrovirus, has the capability to target and eliminate CD4 T lymphocytes, leading to profound immunosuppression in affected individuals. This heightened vulnerability exposes those with advanced HIV to a significant risk of infection, particularly when the CD4 count falls below 200, as observed in our patient with an initial CD4 count of 36 cells/mm^3.

While *T. marneffei* is a prevalent fungus-causing disease in the HIV/AIDS population in Southeast Asia, it is not endemic to North or South America, the regions where our patient has resided [4], [6], [7], [25]. Notably, he repeatedly declined to traveling to Asia. The University of Washington microbiology laboratory's expanded PCR amplification of fungal 28S rDNA of lymph node tissue resulted in positivity for a *Penicillium* species. Although the specific *Penicillium* species could not be identified, the tissue PCR testing resulted negative for *T. marneffei* species. Given the patient's lack of exposure to an endemic region for *T. marneffei*, we deduced that he likely contracted an infection from a *P.* non-*marneffei* species.

While infrequently associated with human disease, certain *P.* non-*marneffei* species hold significance in immunocompromised hosts. A study conducted in the United States analyzed 100 isolated specimens from clinical sources, revealing that the most frequently encountered *Penicillium* species were *P. citrinum* and *P. rubens,* [2]. Various

case studies and literature reviews have identified common disease-causing species, including *P. citrinum, P. chrysogenum, P. digitatum*, and *P. expansum*, with *P. chrysogenum* being highlighted as one of the most prevalent disease-causing species overall [2], [5], [26]. Additionally, pathogenic species such as *P. oxalicum* have been noted, with some cases even indicating resistance to voriconazole [2], [16]. Based on this data, it is reasonable to consider that one of these frequently identified species may have been the causative agent responsible for our patient's illness. In our patient's case, even after utilizing an expanded PCR amplification of fungal 28S rDNA of lymph node tissue we were unable to identify the species of *Penicillium*. This points towards the overall difficulty of diagnosing *Penicillium* infections and identification at the species level; we highlight the need to expand on fungal and *Penicillium* rapid PCR databases [5].

Despite the potentially high mortality rate associated with *Penicillium* species infections, reaching 62% in immunocompromised individuals according to one study, and 59% according to another review, our patient's prompt diagnosis and treatment likely played a crucial role in his swift recovery [5], [20]. Considering there is no standard of treatment established for *P.* non-*marneffei* infections, we utilized the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* for *T. marneffei* infection [4]. The treatment protocol involved induction with liposomal amphotericin B at 3-5 mg/kg IV daily for two weeks, followed by oral itraconazole at 200 mg twice daily for ten weeks, with subsequent de-escalation to a maintenance regimen of oral itraconazole at 200 mg daily. This maintenance therapy is intended to continue until virologic suppression and CD4 count reaches greater than 100 cells/mm^3 for a minimum of six months. The prompt initiation of ART is recognized as a significant contributing factor to the patient's recovery. It is important to acknowledge that the patient remains at continued risk for the reactivation of disease until the CD4 count is consistently maintained above 100 cells/mm^3 [10], [12], [27], [28], [29].

Additionally, given that our patient with severe disseminated *P.* non-*marneffei* infection showed significant improvement in the treatment regimen of *P. marneffei* infection among PLWH, we suggest it is reasonable to extrapolate treatment within the same genus, [4]. However, if clinical improvement is not observed, extending therapy or changing to a broader antifungal regimen may be required. In our case, we extended induction with Amphotericin B from 2 weeks to 4 weeks due to initial slow clinical improvement.

Here, we presented a novel clinical case of disseminated *P.* non-*marneffei* infection in a severely immunocompromised patient with advanced HIV. No previous cases of *P.* non-*marneffei* infection in PLWH have been cited in the literature. This case contributes to the diagnostics of opportunistic infection and management of PLWH. We have identified an atypical *P.* non-*marneffei* infection to be considered in the differential diagnoses of patients with advanced HIV with non-specific symptoms and lymphadenopathy. Here, we have documented the first successfully treated case of *P.* non-*marneffei* infection in a patient with HIV/AIDS.

4 Conclusion

Diagnosing *Penicillium* infections can be challenging given its nonspecific presentation [2], [5]. Unfortunately, due to these factors, many patients are diagnosed post mortem, with one study reporting a mortality rate of 62% in the immunosuppressed population [4], [5]. We strongly advocate for physicians to maintain a high index of suspicion regarding this pathogen, particularly in immunosuppressed patients, especially when symptoms persist after the administration of appropriate empiric antimicrobial courses.

The identification of *Penicillium* remains a difficult hurdle in the process of diagnosis and treatment. Shared morphological characteristics among various species make traditional identification methods of microscopy, culture, and histology difficult and often limit phenotypic results to the genus or family level. This underscores the growing importance of employing DNA sequencing for accurate identification. Unfortunately, molecular methods such as Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) still present challenges in species identification for clinical purposes, primarily due to the need for expanding commercial species databases in order to make accurate species-level identification [5], [30], [31]. Additionally, rapid PCR assays have not yet been validated or standardized for clinical or commercial use, adding another layer of complexity [4], [5].

Owing to the infrequency of cases, there is limited data and a scarcity of studies on an established standard of treatment for *Penicillium* non-*marneffei* diseases. Additional clinical trials and

in vitro studies are imperative to address this gap in knowledge.

Consent: Informed consent was obtained from the patient to publish case details, test results, and images.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work the authors used Microsoft Word and ChatGPT for language editing (i.e. spelling, grammar). After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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- Divya Pandya: Writing – original draft preparation, writing – review and editing.
- Amr Abulaban: Investigation, writing – review and editing.
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