



ELSEVIER

Contents lists available at ScienceDirect

## International Journal of Infectious Diseases

journal homepage: [www.elsevier.com/locate/ijid](http://www.elsevier.com/locate/ijid)

Short Communication

Clinical Characteristics of HIV-Associated *Talaromyces marneffe* Infection of Intestine in Southern ChinaZhiman Xie<sup>a,1</sup>, Jingzhen Lai<sup>b,c,1</sup>, Renping Peng<sup>a</sup>, Minhong Mou<sup>a</sup>, Hao Liang<sup>b,c,\*</sup>, Chuanyi Ning<sup>b,d,\*</sup><sup>a</sup> No. 4th People's Hospital of Nanning and the Affiliated Nanning Infectious Diseases Hospital of Guangxi Medical University, Guangxi Medical University, No. 1, Second Lane, Changgang Road, Nanning, Guangxi 530023, China<sup>b</sup> Guangxi Key Laboratory of AIDS Prevention and Treatment, Guangxi Medical University, No. 22 Shuangyong Road, Nanning, Guangxi 530021, China<sup>c</sup> Guangxi Biobank, Life Sciences Institute, Guangxi Medical University, No. 22 Shuangyong Road, Nanning, Guangxi 530021, China<sup>d</sup> Nursing college, Guangxi Medical University, No. 8 Shuangyong Road, Nanning, Guangxi 530021, China

## ARTICLE INFO

## Article history:

Received 30 January 2022

Revised 29 March 2022

Accepted 30 March 2022

## Keywords:

Talaromycosis

*Talaromyces marneffe*

HIV

AIDS

Intestinal

## ABSTRACT

Intestinal *Talaromyces marneffe* (TM) infection among patients with HIV/AIDS is rare. Herein, we report 31 cases of intestinal TM infection in Guangxi. Most patients exhibited fever, lymphadenectasis in the abdominal cavity, and chronic intestinal symptoms. CD4<sup>+</sup> T-cell counts <50 cells/ $\mu$ L were reported in 28 patients. TM was cultured from the blood of 23 patients and from the marrow of 7 patients, whereas TM-like fungal spores in the cytoplasm of tissues with erosion, ulceration, and/or polyps were found in all 31 patients. We suggest that intestinal TM infection should be considered among patients infected with HIV with extremely low CD4<sup>+</sup> T-cell counts (<50 cells/ $\mu$ L) who are manifesting fever, chronic gastrointestinal symptoms, and endoscopic evidence of erosion and/or ulceration.

© 2022 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

Talaromycosis is an invasive mycosis that is endemic to Southeast Asia and South China and is caused by *Talaromyces marneffe* (TM). It primarily affects individuals infected with HIV with advanced conditions and individuals with other immunocompromising conditions (Narayanasamy et al., 2021). Despite a mortality rate of up to 50%, which is a higher mortality rate than that of most HIV-related complications (Hu et al., 2013, Jiang et al., 2019), TM has received little attention from regional and global researchers. Diagnostic and treatment modalities remain extremely limited. Common manifestations of disseminated TM infection include fever, weight loss, skin lesions, and gastrointestinal abnormalities (Cao et al., 2019). Approximately 1.9% of all talaromycosis cases are intestinal infections (Zhou et al., 2021). However, the clinical features of intestinal TM infection have rarely been reported in detail. Here, we report the clinical characteristics of 31 patients infected with HIV with disseminated intestinal TM infec-

tion who were diagnosed by identifying TM in intestinal biopsies by microscopy.

## Methods

A retrospective survey was performed to identify cases of patients with HIV/AIDS with intestinal TM infection in No. 4th People's Hospital of Nanning between 2011 and May 2021. Intestinal talaromycosis was confirmed by identifying TM spores in intestinal biopsies. Clinical characteristics, treatment regimen, and outcomes were reported in the current study. The G test was used to detect the levels of the fungal cell wall component (1,3)- $\beta$ -D-glucan, which indicates deep mycosis.

## Case series

## Clinical characteristics

Of the 31 included patients, 77.42% were male, and the median age was 42 years. Most patients presented with abdominal pain (38.71%), fever (38.71%), and diarrhea (25.81%) that prompted their hospital visit (Table 1). On physical examination, intestinal symptoms were present in 29 patients, including abdominal pain in 19

\* Correspondence author:

E-mail addresses: [lianghao@gxmu.edu.cn](mailto:lianghao@gxmu.edu.cn) (H. Liang), [ningchuanyi@126.com](mailto:ningchuanyi@126.com) (C. Ning).<sup>1</sup> Zhiman Xie and Jingzhen Lai contributed equally to this manuscript.

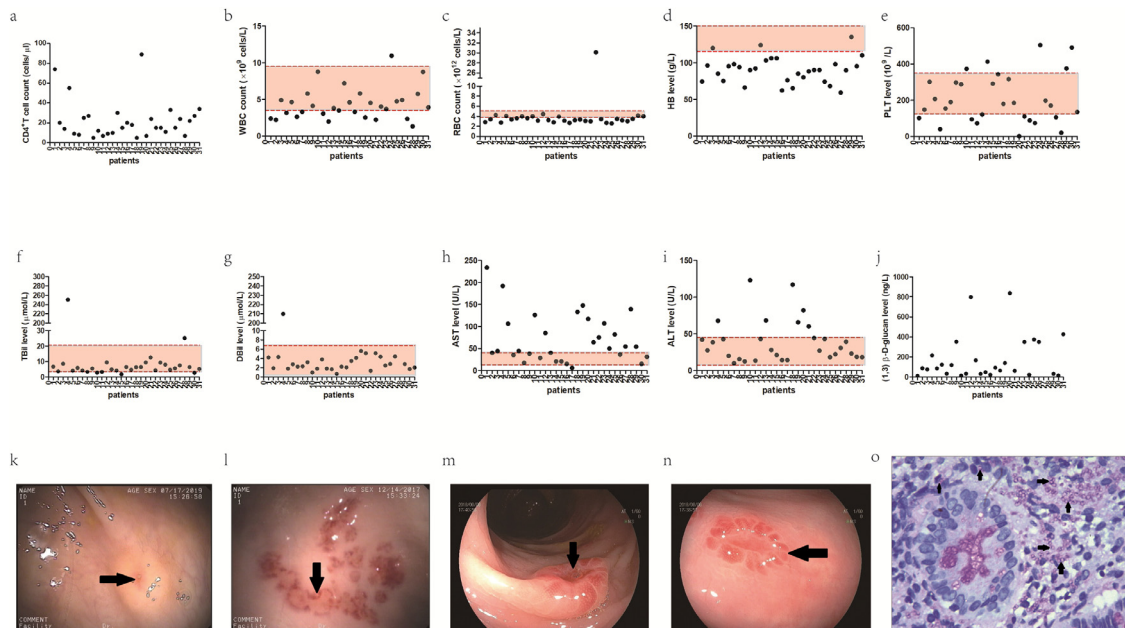
**Table 1**  
Clinical characteristics of HIV/AIDS patients co-infected with intestinal *Talaromyces* Marneffeii

Sex	
Male (%)	24 (77.42)
Female (%)	7 (22.58)
Age (years) (median, IQR)	42 (35, 52)
Main presenting symptoms	
Abdominal pain (%)	12 (38.71)
Fever (%)	12 (38.71)
Diarrhea (%)	8 (25.81)
Abdominal distension (%)	5 (16.13)
Cough (%)	3 (9.68)
Main clinical manifestation	
Abdominal pain (%)	19 (61.29)
Hepatomegaly and/or splenomegaly (%)	16 (51.61)
Fever (%)	16 (51.61)
Abdominal distension (%)	11 (35.48)
Diarrhea (%)	9 (29.03)
Nausea (%)	6 (19.35)
Emesis (%)	3 (9.68)
Enlargement of lymph nodes in the abdominal cavity (%)	15 (48.39)
Diagnostic methods	
Talaromyces Culture from blood (%)	23 (23/30,)
Talaromyces Culture from marrow (%)	7(7/9, 77.78)
Found Talaromyces spores by biopsies (%)	31 (100.00)
PAS+ (%)	23 (23/23, 100.00)
DPAS+ (%)	23 (23/23, 100.00)
Endoscopy	
Erosion /ulceration (%)	27 (27/30, 90.00)
Polyps (%)	9 (9/30, 30.00)
ART initiated before admission	12 (12/29, 41.38)
ART duration (months) (median, IQR) (n=10)	41 (0.875, 63.25)
Anti-fungal treatment	
Amphotericin B, followed by Itraconazole (%)	17 (54.84)
Itraconazole only (%)	11 (35.48)
Fluconazole, followed by Itraconazole (%)	3 (9.68)
Duration of hospitalization (days) (median, IQR)	19 (12, 25)
Outcome	
Lost to follow up (%)	16 (51.61)
Cured (%)	12 (38.71)
Died (%)	3 (9.68)
Follow up time (months) (median, IQR)	41.5 (23.75, 52)

patients, diarrhea in 9 patients, and abdominal distension in 11 patients. Fever was the main extraintestinal symptom. Splenomegaly, hepatomegaly, or hepatosplenomegaly was reported in 16 patients. Enlargement of lymph nodes in the abdominal cavity was found in 15 patients by ultrasonography. Blood tests (Figure 1a–j and Supplementary Table 2) showed that a low CD4<sup>+</sup> T-cell count was present in all 31 patients. Anemia and abnormal platelets were detected in 28 and 16 patients, respectively. High aspartate aminotransferase levels were present in 19 patients, and high alanine aminotransferase levels were present in 7 patients. The G test was performed in 28 patients, and positivity was reported in 25 patients. TM was cultured from the blood of 23 patients and from the marrow of 7 patients. Endoscopy revealed that erosion and ulceration were scattered in the large intestines of 27 patients, and polyps were found in 6 patients (Supplementary Table 1). The erosion was elevated or flat, with some visible fusion (Figure 1k–l). The ulceration was peripherally swollen, which indicated proliferative swelling or hyperemia edema (Figure 1m–n). Biopsies of tissues with erosion, ulceration, and/or polyps showed TM-like fungal spores in the cytoplasm of cells in all 31 patients. Most of the spores were small, round, or oval. Sometimes the transverse septum was seen in the spores. D-PAS staining was clearly visible (Figure 1o).

### Outcomes

Twelve patients received antiretroviral therapy (ART) before admission, and the median ART duration was 41 months. The median duration of hospitalization was 19 days. All patients received antifungal therapy during hospitalization or after hospital discharge, including fluconazole, amphotericin B, and itraconazole (Supplementary Table 1). After their discharge, 12 patients were followed up for a median duration of 41.5 months, whereas 16 of them were lost to follow-up. Most of the patients who were followed up improved or were cured after receiving therapy, ex-



**Figure 1. Results of blood tests, endoscopy, and histopathologic biopsies.** a) CD4<sup>+</sup>T cell count of the patients; b) white blood cell (WBC) count of the patients; c) red blood cell (RBC) count of the patients; d) hemoglobin (HB) level of the patients; e) platelet (PLT) level of the patients; f) total bilirubin (TBil) level of the patients; g) direct bilirubin (DBil) level of the patients; h) aspartate aminotransferase (AST) level of the patients; i) alanine aminotransferase (ALT) level of the patients; j) (1,3)-β-D glucan level of the patients; Red dotted line in b–i) showed the threshold of the normal range of different indicators, while the red background in b–i) showed the normal range of different indicators. k–n) were shot by endoscopy. k) showed erosive erosion; l) showed simple erosions, some were partial fused; m) showed ulceration with obvious proliferative and bulging lesions around; n) showed ulceration with obvious hyperemia and edema of mucosa around; o) pathological section stained with D-PAS (× 400) showed many round or oval spores with transverse septum.

cept three who died during hospitalization or after against-advice discharge.

## Discussion

We described a rare TM infection in the intestine of HIV-infected patients. Although gastrointestinal symptoms are common in talaromycosis, TM in the intestine identified via histopathology or cultured from intestinal tissue is rare. To the best of our knowledge, this is the first report of a large number of histopathologically confirmed intestinal TM infection cases among patients with HIV. Patients with HIV with intestinal TM infection exhibited fever, lymphadenectasis in the abdominal cavity, and chronic intestinal symptoms of abdominal pain, diarrhea, and abdominal distension. Fever, diarrhea, and abdominal pain are the top three symptoms of intestinal talaromycosis (Zhao et al., 2020). The patient had no intestinal symptoms that distinguished this condition from other intestinal diseases. Hepatosplenomegaly is a common but nonspecific symptom in talaromycosis, but abdominal lymph node enlargement may be an indirect indication of possible intestinal lesions. Blood tests confirmed poor immunity, common anemia, and abnormally high AST levels in these patients. The extremely low CD4 cell count ( $<50$  cells/mm<sup>3</sup>) directly indicates that the patients have very poor immunity and are vulnerable to pathogens. The prevalence of anemia in TM-HIV coinfection was 95.6% (Ying et al., 2020), which is close to what we reported. Elevated AST level usually indicates impaired liver function and poor prognosis in TM infection (Wei et al., 2021, Ying et al., 2020). TM cultures from blood, marrow, or feces are not always positive. However, erosion and ulceration are the most common intestinal lesions. TM can be identified from biopsies of intestinal tissue with erosion and ulceration. Early antifungal therapy with amphotericin B and itraconazole can effectively treat talaromycosis and improve patient survival (Le et al., 2017). In conclusion, patients with HIV with unexplained intestinal symptoms with CD4  $<50$  cells/mm<sup>3</sup> should be considered to have intestinal talaromycosis.

## Funding source

This work was supported by the National Natural Science Foundation of China (grant numbers 81760602 and 81803295), Guangxi Natural Science Foundation (grant number 2018GXNSFAA138031), the Research Basic Ability Enhancement Project of Young and Middle-Aged Teachers in Guangxi Universities in 2021 (grant number 2021KY0081), and Nanning Scientific Research and Technology Development Program (grant number 20193008).

## Ethical approval

The study was approved by the Ethical Committee of No. 4th People's Hospital of Nanning. Written informed consents were obtained from all included patients.

## Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2022.03.057](https://doi.org/10.1016/j.ijid.2022.03.057).

## References

- Cao C, Xi L, Chaturvedi V. Talaromycosis (Penicilliosis) Due to *Talaromyces* (Penicillium) *marneffei*: Insights into the Clinical Trends of a Major Fungal Disease 60 Years After the Discovery of the Pathogen. *Mycopathologia* 2019;184(6):709–20. doi:[10.1007/s11046-019-00410-2](https://doi.org/10.1007/s11046-019-00410-2).
- Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffei* infection: an emerging disease in mainland China. *Mycopathologia* 2013;175(1-2):57–67. doi:[10.1007/s11046-012-9577-0](https://doi.org/10.1007/s11046-012-9577-0).
- Jiang J, Meng S, Huang S, Ruan Y, Lu X, Li JZ, et al. Effects of *Talaromyces marneffei* infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2019;25(2):233–41. doi:[10.1016/j.cmi.2018.04.018](https://doi.org/10.1016/j.cmi.2018.04.018).
- Le T, Kinh NV, Cuc NTK, Tung NLN, Lam NT, Thuy PTT, et al. A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. *The New England journal of medicine* 2017;376(24):2329–40. doi:[10.1056/NEJMoa1613306](https://doi.org/10.1056/NEJMoa1613306).
- Narayanasamy S, Dat VQ, Thanh NT, Ly VT, Chan JF, Yuen KY, et al. A global call for talaromycosis to be recognised as a neglected tropical disease. *The Lancet Global health* 2021;9(11):e1618–e1e22. doi:[10.1016/S2214-109X\(21\)00350-8](https://doi.org/10.1016/S2214-109X(21)00350-8).
- Wei HY, Liang WJ, Li B, Wei LY, Jiang AQ, Chen WD, et al. Clinical characteristics and risk factors of *Talaromyces marneffei* infection in human immunodeficiency virus-negative patients: A retrospective observational study. *World journal of emergency medicine* 2021;12(4):281–6. doi:[10.5847/wjem.j.1920-8642.2021.04.005](https://doi.org/10.5847/wjem.j.1920-8642.2021.04.005).
- Ying RS, Le T, Cai WP, Li YR, Luo CB, Cao Y, et al. Clinical epidemiology and outcome of HIV-associated talaromycosis in Guangdong, China, during 2011–2017. *HIV medicine* 2020;21(11):729–38. doi:[10.1111/hiv.13024](https://doi.org/10.1111/hiv.13024).
- Zhao YK, Liu JY, Liu JH, Lu S, Wu HH, Luo DQ. Recurrent *Talaromyces marneffei* Infection Presenting with Intestinal Obstruction in a Patient with Systemic Lupus Erythematosus. *Mycopathologia* 2020;185(4):717–26. doi:[10.1007/s11046-020-00469-2](https://doi.org/10.1007/s11046-020-00469-2).
- Zhou Y, Liu Y, Wen Y. Gastrointestinal manifestations of *Talaromyces marneffei* infection in an HIV-infected patient rapidly verified by metagenomic next-generation sequencing: a case report. *BMC infectious diseases* 2021;21(1):376. doi:[10.1186/s12879-021-06063-1](https://doi.org/10.1186/s12879-021-06063-1).