

Drug-related talaromycosis: A case report

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Abstract

Talaromycosis is a rare deep fungal infection caused by *Talaromyces marneffeii*. Currently, methamphetamine has become the second-largest drug abuse category in the world after cannabis and has become a serious public health problem. Methamphetamine can inhibit human immune system and increase the probability of pathogenic microorganism infection. On 8 October 2016, a 20-year-old man with a fever history of 2 months was admitted to our hospital. He had bloody stools and abdominal pain during hospitalization. There was no significant abnormality in physical examination. Because of the misdiagnosis, he underwent improper treatment. Periodic acid-Schiff stain (PAS) staining showed that the mucosa of distal ileum, ascending colon, transverse colon, and sigmoid colon were infiltrated by a large number of tissue cells, which contained a large number of blue purple particles. In addition, a large number of histiocytes and multinucleated giant cells can be seen in the lamina propria of ileum mucosa, and fungal spores can be seen in histiocytes. Finally, he was diagnosed as talaromycosis and took itraconazole 0.2g twice a day. After 5 days, the temperature dropped to normal and the inflammation disappeared, and he continued to take itraconazole for 6 months. Due to the neglect of the history of drug abuse and the concealment, drug-related talaromycosis is often misdiagnosed. Pathological examination is warranted for diagnosis talaromycosis. This condition requires a long-term anti-fungal therapy.

Keywords

histoplasmosis, immunosuppression, methamphetamine, *Penicilliosis marneffeii*, talaromycosis

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Introduction

Talaromycosis, a rare deep fungal infection caused by *Talaromyces marneffeii*, is popular in Southeast Asia.¹ This disease rarely occurs in healthy person, and it is more common in immunocompromised person.² People who have not HIV infection and underlying disease with talaromycosis are rare in clinic.³ At present, methamphetamine has become the second-most widely abused drug class after cannabis, and it has become a serious public health problem, with an estimated 24 million users worldwide.⁴ Methamphetamine can inhibit body's immune system and increase the probability of pathogenic microorganism infection.⁵ Because of neglect of the history of drug abuse and the concealment, clinicians often fail to understand the causes of immune deficiency and cause some obstacles in the process of clinicians' diagnosis and

treatment. Here, we reported a case of drug abuse-related talaromycosis.

Case presentation

Written informed consent was obtained from the patient. A 20-year-old man who presented with 2 month history of fever was admitted in our hospital on 8 October 2016. Without obvious cause, the patient had repeated chills and fever 2 months

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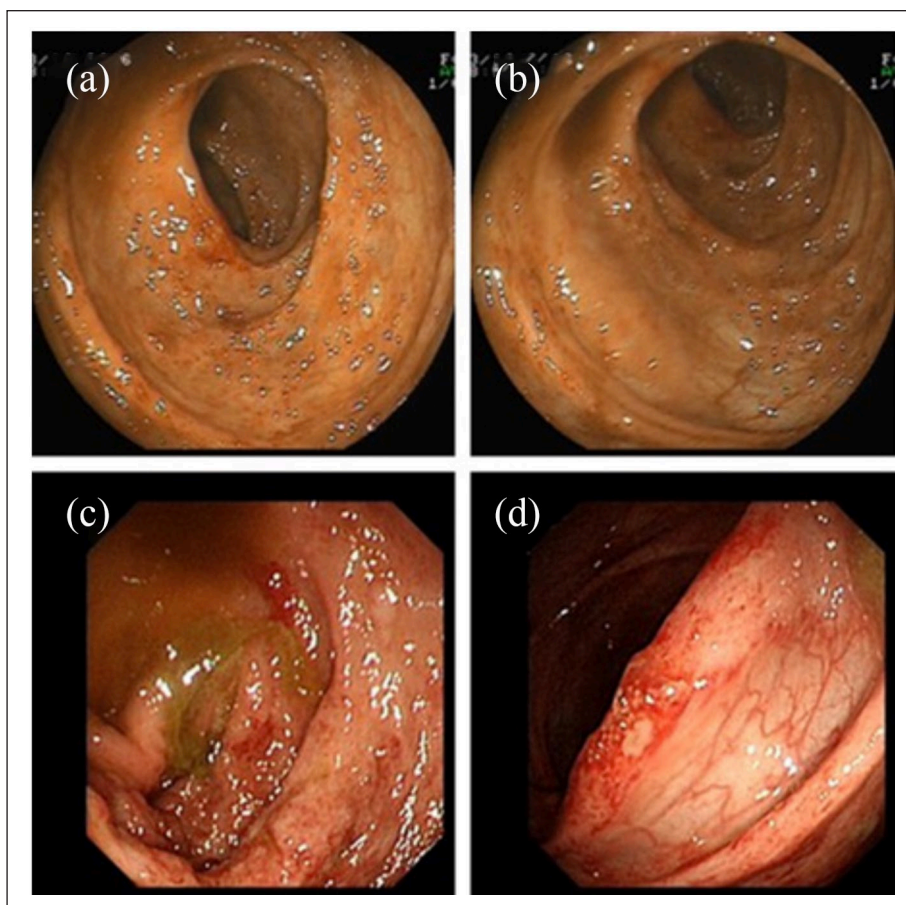


Figure 1. Twice colonoscopy showed segmental inflammation and shallow ulcers from distal ileum to sigmoid colon.

ago and the highest temperature raised to 39°C. He passed bloody stools and got abdominal pain during hospitalization. Physical examination was non-remarkable. Blood examination revealed 10.42×10^9 white blood cells/L, with 69.40% neutrophils and 16.17% lymphocytes. HIV antibody, immunochemistry, dengue antigen, hepatitis B, hepatitis C, influenza A, and influenza B antigen were all unremarkable. Chest and abdominal computed tomography (CT) scan showed ileocecus of ascending colon, and transverse colon showed diffuse thickening of the wall. The most obvious was in the transverse colon, which was considered as inflammation. On 13 October 2016, colonoscopy showed multiple segmental colon ulcers, which was considered as Crohn's disease or tuberculosis (Figure 1(a) and (b)). Pathology showed that there were a lot of acute and chronic inflammatory cells infiltration in lamina propria, submucosa, and muscle layer, and there were multiple granulomatous lesions without obvious caseous necrosis. In addition, the possibility of intestinal bacterial

infection, inflammatory bowel disease (IBD), intestinal tuberculosis, lymphoma, histoplasmosis, and other diseases were excluded. It tended to be Crohn's disease, but tuberculosis was not excluded (Figure 2). The CTE of the small intestine showed that ileocecus and distal ileum were thickened and strengthened obviously after injection, so that the patient was conformed to Crohn's disease (Figure 3(c) and (d)). From 8–25 October, we gave him antibiotic treatments. Taking small intestinal computed tomography enterography (CTE), colonoscopy, and pathology into consideration, he was diagnosed as Crohn's disease and given glucocorticoids and immunosuppressant therapy from 20 October. After 5 days of treatment, the patient still had repeated fever, and the anti-infection treatment was upgraded to imipenem. However, his symptoms still have not improved. Therefore, we rechecked the colonoscopy. On 30 October, IBD was considered by colonoscopy, but it was not confirmed (Figure 1(a) and (b)). Meanwhile, tuberculosis was not

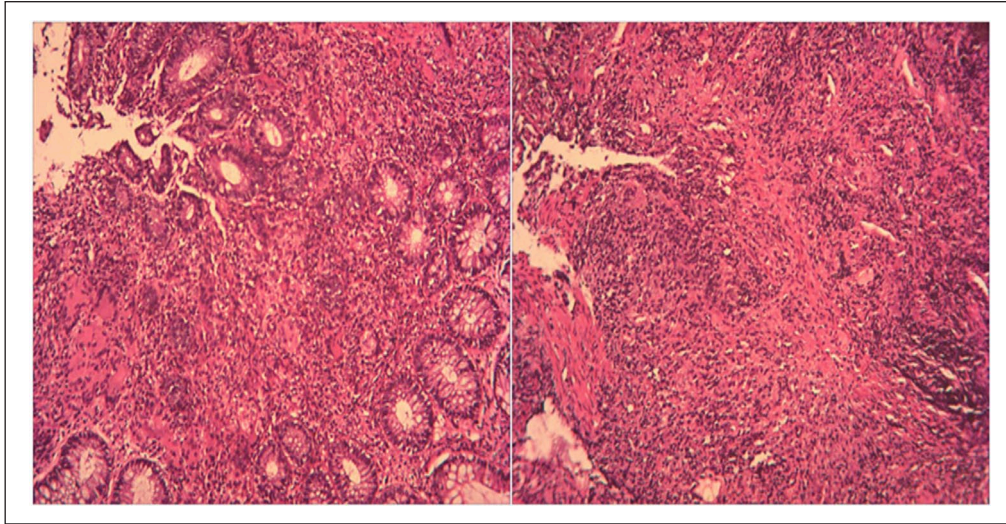


Figure 2. Inflammatory cells infiltration in intestinal wall and there were multiple granulomatous lesions without obvious caseous necrosis.

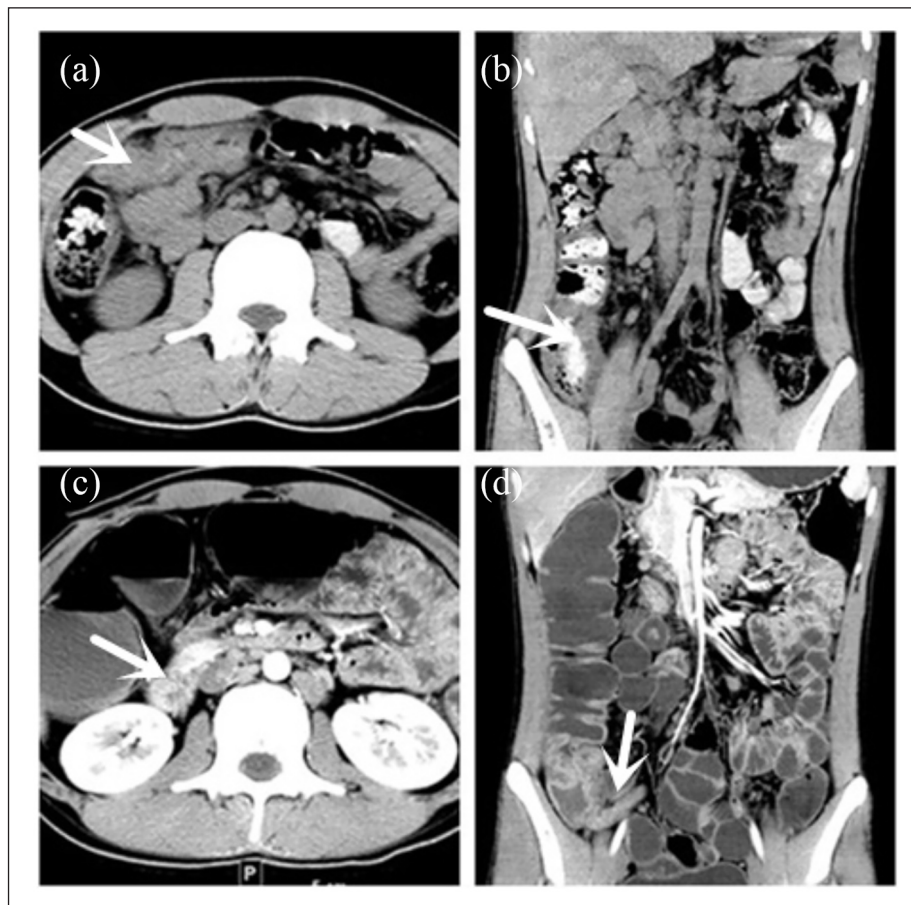


Figure 3. CT and CTE showed multiple segmental thickening of the intestinal wall.

excluded. Sample of intestinal biopsy was sent to our hospital and the Southern Hospital of Southern Medical University for examination. In the oral

report of intestinal pathology in our hospital, the microbes with positive Periodic acid-Schiff (PAS) staining were examined, which were also seen in

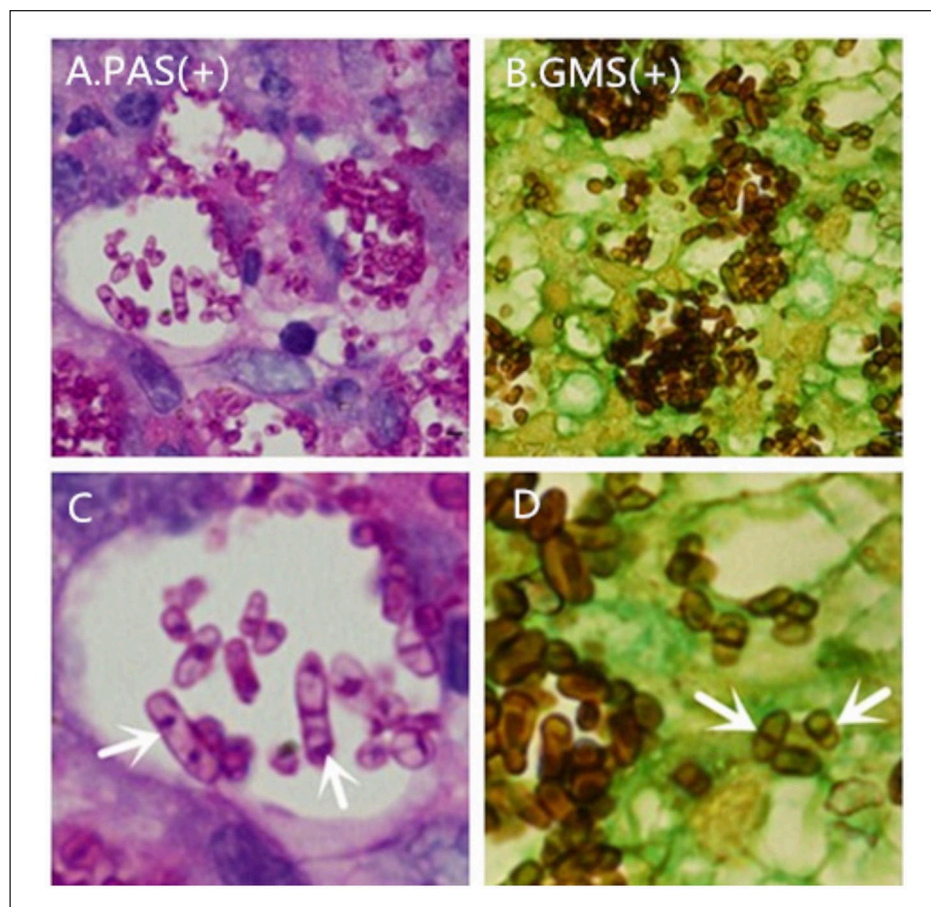


Figure 4. *T. marneffei*'s specific sausage-like cells and cross-walls can be observed by PAS staining and GMS staining.

the intestinal pathology on 13 October. Therefore, we thought that we made a wrong diagnosis. Pathology reported that distal ileum, ascending colon, transverse colon, and sigmoid colon mucosa were infiltrated by a large number of tissue cells that had a large number of blue purple granules. Special staining showed purple blue particles with positive PAS staining and Gomori's Methenamine-Silver (GMS) staining. It was considered to be histoplasmosis. On 7 November, Southern Hospital Pathology Consultation Report described that a large number of tissue cells and multinuclear giant cells were seen in the lamina propria of ileum mucosa, and fungal spores were found in tissue cells, so that he was diagnosed as talaromycosis (Figure 4). On 8 November, immunologic testing showed that CD3 cells accounted for 17.40%, CD4 cells accounted for 11.50%, CD8 cells accounted for 4.10% and a CD4/CD8 ratio of 2.8. According to the pathology consultation report, he was finally diagnosed as talaromycosis. A treatment of itraconazole 0.2g twice daily for a long

term was given to him. The temperature dropped to normal and bloody stools disappeared after anti-fungal treatment for 5 days. We knew that he used to have a history of taking methamphetamine many times between July and August after inquiring about his medical history again. He reviewed colonoscopy in the hospital again on 17 January 2017. The examination results suggested that the intestinal inflammation subsided.

Discussion

T. marneffei, formerly known as *Penicillium marneffei*, most found in patients with HIV positive but increasingly observed in patients without HIV-infected immunocompromise.⁶ A non-HIV-infected patient, without underlying disease, who had a history of taking methamphetamine 2 months was included in our report. In the T-lymphocyte subgroup examination, the levels of CD3+ cells were seriously low, and CD4+ cells and CD8+ cells were also decreased, indicating that his immune function

was decreased significantly. However, the proportion of CD4+/CD8+ was increased, which may be due to the fact that the levels of CD8+ cells were decreased more severely than CD4+ cells. Immune dysfunction or serious injury in drug addicts resulted in a marked increase in all kinds of opportunistic infections and tumor incidence. Studies have shown that long-term drug abuse can completely suppress the entire immune system, including non-specific and specific immune system functions.⁷ Through the determination of lymphocyte subsets, various types of antibodies, cytokines, and other immune indicators can understand drug abusers' function status of cellular immunity, humoral immunity, and non-specific immunity.⁸ It can lead to decrease in interleukin (IL)-2 secretion and Natural killer cell (NK) activity, an inhibition of mononuclear phagocyte phagocytosis, a decrease in T-lymphocyte-mediated lymphocyte proliferation response, and a damage in B-lymphocyte immune response.⁹ The patient in our report is characterized by its misdiagnosis rate, non-HIV infected and history of drug abuse. The time from admission to making a definitely diagnosis took 1 month. Twice misdiagnoses of colonoscopy and the pathological results in our hospital had misled the clinical treatment. The history of drug abuse was a blank area for clinicians to inquire and the patient always deliberately concealed the history of drug abuse when he was asked for medical advice, which may result in some obstacles in the clinical diagnosis and treatment process. The history of drug abuse may not have been explicitly excluded in the reported *T. marneffeii* literature of healthy host infection, so it is possible to report the drug addicts as normal hosts. When clinicians are faced with fungal infection, we should take drug abuse factors into account after excluding HIV, tumor, and taking immunosuppressants and should be further detailed medical history.

The conidia inhalation of *T. marneffeii* is the most important pathogenicity.¹⁰ This disease can also be transmitted through intestinal feeding, invaded through skin lesion and blood source. The clinical manifestations of talaromycosis are diverse, complex, and lacking of specificity, which often lead to misdiagnosis and missed diagnosis. Its clinical manifestations are divided into localized type and disseminated type. Localized type is often seen in skin and subcutaneous tissue infection. Disseminated type is more common. Disseminated type often involves respiratory system, digestive system,

lymphatic system, and bone system, which presents with fever, weight loss, lymphadenopathy, nonproductive, cough, hepatosplenomegaly, digestive symptoms, skin lesions, and anemia.¹¹ The patient was a localized case of *T. marneffeii* infection. Considering that the conidia of *Talaromyces marneffeii* entering the body through digestive tract and causing disease, there is no spread in the body. Therefore, the patient has no infection symptoms of respiratory tract and skin system. Although the patient had a transient skin lesion on face, the fungal culture was negative. This patient was fever-based disseminated talaromycosis and mainly caused digestive system lesions which colonoscopy showed non-caseous granulomatous lesions. It was misdiagnosed as IBD or intestinal tuberculosis twice under colonoscopy and the pathological examination of intestinal mucosa in our hospital also misdiagnosed as histoplasmosis by special staining. Even through laboratory tests, this disease was often misdiagnosed as histoplasmosis or other fungal diseases. The cases reported in literature were just the tip of the iceberg, which were more in fact than reported in the literature.

T. marneffeii is thermally dimorphic fungi such as *histoplasma capsulatum*. It grows as a yeast at 37°C and a mold at 25°C. The yeast cells are for pathogenic and mold conidia is for the transmission.¹² *T. marneffeii* shows the characteristics of invasion of blood vessels at 37°C, which is the cause of widespread dissemination in the body. The diagnostic gold standard of talaromycosis is the separation of *T. marneffeii* from the body. The clinical manifestations of talaromycosis are similar to histoplasmosis. And the morphology, size, and tissue distribution of these two fungi are also similar. *T. marneffeii* infection can be diagnosed by fungal culture, polymerase chain reaction (PCR) and direct observation under microscope. Differentiation from histoplasmosis by direct microscopy requires special stain (GMS stain or PAS stain) and observes the *T. marneffeii* specific sausage-like cells with cross-walls.¹³

In the treatment of talaromycosis, early diagnosis and effective anti-fungal therapy are the key, and the blood and tissue culture negative cannot be used as a basis for drug withdrawal.¹⁴ Despite available anti-fungal therapies, mortality rates often exceed 50%.¹¹ D-AmB, L-AmB, itraconazole, and voriconazole are effective drugs in talaromycosis.¹⁵ There is no definitive guide on the duration of anti-fungal therapy and to the patient

continued to receive anti-fungal treatment with itraconazole for 6 months.

Conclusion

Due to the neglect of the history of drug abuse and the concealment of patient, drug-related talaromycosis is often misdiagnosed. Pathological examination is warranted for diagnosis of talaromycosis. This condition requires a long-term anti-fungal therapy.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series. This study has been performed in accordance with ethical standard.

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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