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CASE REPORT

Recurrent Disseminated *Talaromycosis* Mimicking Liver Disease in a STAT3-Mutated HIES Patient: A Case Report

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Background: Talaromycosis is increasingly recognized in immunocompromised individuals beyond those with HIV, including patients with primary immunodeficiencies such as Hyper-IgE syndrome (HIES). However, diagnosing disseminated infection remains challenging due to nonspecific clinical manifestations and limitations of conventional diagnostic methods.

Case Presentation: We report a rare case of recurrent disseminated *Talaromyces marneffei* (*T. marneffei*) infection in a 25-year-old male with STAT3-mutated HIES. Initially presenting with abnormal liver function tests, the patient had a history of *T. marneffei* pulmonary infection successfully treated with itraconazole. During the current admission, he developed intermittent fever, jaundice, and splenomegaly. Initial evaluations led to a misdiagnosis of chronic drug-induced liver injury (DILI). Subsequent fever recurrence and worsening liver function prompted further investigation. Metagenomic next-generation sequencing (mNGS) and histopathology of liver revealed *T. marneffei*, confirming disseminated infection involving the liver. Histopathological examination of the liver showed granulomatous inflammation with IgG4-positive plasma cell infiltration, further complicating the differential diagnosis. The patient responded well to intravenous voriconazole, with significant improvement in liver function and radiological findings.

Conclusion: Disseminated talaromycosis should be considered in immunocompromised patients presenting with unexplained fever, hepatosplenomegaly, or organ dysfunction, even in the absence of classic symptoms. Integration of mNGS into diagnostic workflows enhances pathogen detection, and long-term antifungal prophylaxis may be necessary in patients with persistent immune deficiencies.

Keywords: *Talaromyces marneffei*, hyper-IgE syndrome, disseminated talaromycosis, metagenomic next-generation sequencing, HIV-negative

Introduction

Talaromycosis, a systemic mycosis caused by *Talaromyces marneffei* (*T. marneffei*), is highly endemic in Southeast Asia but is rarely reported elsewhere.[1] *T. marneffei* infection commonly occurs in individuals positive for human immunodeficiency virus (HIV). However, an increasing number of cases have been reported among immunocompromised patients, including those who have undergone hematopoietic stem cell or solid organ transplantation, those receiving corticosteroids or immunosuppressive agents, and those with anti-interferon-gamma autoantibodies or Hyper-IgE syndrome (HIES).[2,3] HIES caused by STAT3 gene mutation is a primary immunodeficiency disorder characterized by markedly elevated serum IgE levels, recurrent pneumonia, cutaneous abscesses and eczema, and skeletal abnormalities.[4] Diagnosing disseminated *T. marneffei* infection remains challenging due to its nonspecific clinical manifestations, which may include fever, cough, lymphadenectasis, hepatomegaly, splenomegaly, and skin lesions. Previous studies have suggested the presence of *T. marneffei* latent infection highlighting the urgent need for a rapid detection method. Traditional diagnostic approaches for *T. marneffei* infection mainly rely on clinicopathological analysis, culture of clinical specimens and polymerase chain reaction (PCR). Recently, Metagenomic next-generation sequencing (mNGS)

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has become a widely used tool for identifying fungal infections in immunocompromised individuals.[5] Herein, we present a rare case of recurrent *T. marneffei* infection in a patient with *STAT3* mutated HIES.

Case Presentation

A 25-year-old male was admitted to our hospital presenting with abnormal liver function tests.

Two and a half years prior to the current presentation, the patient developed fever, non-productive cough, and dyspnea, and sought care at a local hospital. The patient presented to the local hospital. A chest computed tomography (CT) scan revealed multiple high-density nodular opacities in both lungs. Laboratory findings showed markedly serum immunoglobulin (Ig)E levels (7766 IU/mL, reference range: 1.27–241.3 IU/mL) and eosinophilia (1.95×10^9/L; reference range: $0.02–0.52\times10^9$/L). HIV testing was negative. *Talaromyces marneffei* (*T. marneffei*) was identified in bronchoalveolar lavage fluid (BALF) using metagenomic next-generation sequencing (mNGS) with a read count of 478. Cultures of lung tissue biopsy specimens also confirmed the presence of *T.marneffei*. Genetic analysis of peripheral blood gene detection revealed a mutation in the signal transducer and activator of transcription 3 gene (STAT3). Based on these findings, the patient was diagnosed with Hyper-IgE syndrome (HIES) and pneumonia caused by *T.marneffei*-associated pneumonia. He was treated with itraconazole (200 mg twice daily) for 6 months, after which a follow-up chest CT scan showed complete resolution of his pulmonary lesions.

Six months after discontinuation of therapy and 18 months prior to the current presentation, the patient was readmitted to the local hospital due to recurrent fever. His fever resolved three days after initiation of oral itraconazole (200 mg twice daily), and he was discharged two weeks later with continuation of the same dosage for 13 months.

Unexpectedly, three weeks prior to the current presentation, the patient was again admitted to a local hospital due to recurrent fever. On admission, his body temperature was 37.8°C. Liver function tests showed elevated alanine aminotransferase (ALT: 181 U/L), aspartate aminotransferase (AST: 104 U/L), alkaline phosphatase (ALP: 552 U/L), and gamma-glutamyltransferase (GGT: 467 U/L). Total bilirubin (TB) and direct bilirubin (DB) levels were within normal limits. A chest CT scan revealed newly detected nodular lesions in both lungs (Figure 1A). Cultures of both blood and BALF for bacteria and fungi were negative. mNGS of BALF detected 2 reads corresponding to *T.marneffei* nucleotide sequences. Despite the absence of antifungal therapy, the patient's temperature normalized on the fourth day of hospitalization. He received polyene phosphatidylcholine for three weeks, but liver enzymes remained elevated (ALT: 210 U/L, AST:124 U/L, ALP:653 U/L, GGT: 510 U/L). Additionally, he noted progressive jaundice of the skin and sclera. Serological testings for hepatitis A virus IgM antibodies, hepatitis B virus core IgM antibodies, hepatitis B surface antigen, hepatitis C virus antibodies, and hepatitis D virus antibodies were all negative. Consequently, the patient was referred to our hospital for further evaluation.

On evaluation, the patient denied symptoms including anorexia, nausea, abdominal cramping, cough or dyspnea. He had a prior diagnosis of drug-induced liver injury (DILI) associated with itraconazole use. The patient's medical history was significant for a lifelong eczematous dermatitis that began in infancy. There was no history of exposure to individuals with

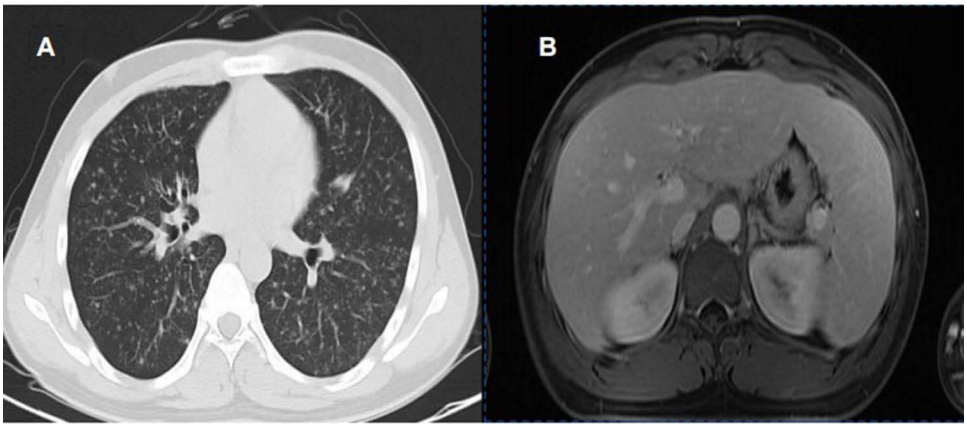

Figure 1 Chest CT and Spleen MRI. (**A**) Chest CT revealed nodular lesions in both lungs. (**B**) Upper abdominal MRCP demonstrates splenomegaly with diffuse abnormal signal intensity.

infectious illnesses, and the patient did not use dietary or herbal supplements. He denied recent travel, alcohol consumption, or illicit drug use. There was no known family history of consanguinity, similar recurrent infections, or other inherited conditions.

Physical examination, revealed a temperature of 36.8°C, blood pressure of 123/79 mmHg, pulse rate of 80 beats per minute, and respiratory rate of 18 breaths per minute. The patient exhibited jaundice with subtle scleral icterus. The abdomen was soft and non-tender, with palpable masses or hepatosplenomegaly. The remainder of the physical examination was unremarkable. Laboratory investigations showed ALT 162 U/L, AST level 127 U/L, ALP 820 U/L, GGT 670 U/L, and TB 37.3 μmol/L. Inflammatory markers including C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6), were within normal limits. Serum cryptococcal antigen was negative. The white-blood cell differential count and platelet counts were normal, as were renal function, electrolytes, thyroid-stimulating hormone (TSH), coagulation parameters and ceruloplasmin levels. Cytomegalovirus IgM antibody, Epstein-Barr virus antibodies, and herpes simplex virus antibodies were negative. Serum immunoglobulin levels showed IgG at 31.15 g/L, IgE at 2500 IU/L, and IgG4 at 3.5 mg/dL. Autoimmune markers including antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver kidney microsome type 1 antibodies were negative. CD4+ T-lymphocyte count was 641 cells/μL, within the normal reference range. Antibodies to schistosome and Clonorchis sinensis were negative. Major laboratory findings are summarized in Table 1. Abdominal ultrasonography demonstrated mild, diffuse heterogeneous echotexture of the liver parenchyma and splenomegaly.

The patient remained afebrile after admission and initial febrile episode was attributed to an upper respiratory tract infection. A provisional diagnosis of chronic DILI due to itraconazole was made. He received a one-week course of polyene phosphatidylcholine, magnesium isoglycyrrhizinate, and ademetionine was prescribed for one week without improvement in liver function. Differential diagnoses including IgG4-related sclerosing cholangitis and liver involvement in *T.marneffei* infection were considered. On hospital day 10, the patient developed fever without concomitant respiratory symptoms; the peak temperature was 38°C. Repeat laboratory testing showed the normal results of the white-blood cell differential, CRP, PCT, and IL-6 levels. Magnetic resonance cholangiopancreatography (MRCP) did not reveal choledocholithiasis but

Table 1 Summary of Key Laboratory Findings

Parameter	Result	Reference Range
White Blood Cell Count	4.62	3.5 −9.5 $\times 10^9$/L
Neutrophil Count	2.81	1.8 −6.3 $\times 10^9$/L
Lymphocyte Count	1.90	1.0 −3.0 $\times 10^9$/L
Hemoglobin	119	130 −175 g/ L
Platelet Count	139	125 −350 $\times 10^9$/L
CRP	8.16	< 10mg/ L
PCT	0.03	< 0.05 μg/ L
IL-6	5.04	< 7 pg/ mL
ALT	210 (peak)	< 40 U/ L
AST	127 (peak)	< 40 U/ L
ALP	820 (peak)	40 −150 U/ L
GGT	670 (peak)	9 −48 U/ L
TB	51.8 (peak)	3.4 −20.5 μmol/ L
Creatinine	76	45 −90μmol/ L
IgE	2500	1.27 −241.3 IU/mL
IgG	31.15	7.0 −16.0 g/ L
IgG4	3.5	0.03 −0.84 mg/dL
CD4+ T-lymphocyte count	641	500 −1,200 cells/ μL
Autoimmune markers	Negative (ANA, SMA, LKM-1)	–
Viral hepatitis serology	Negative (HAV, HBV, HCV, HDV)	–
EBV, CMV, HSV antibodies	Negative	–

Abbreviations: CRP, C-reaction protein; PCT, procalcitonin; IL-6, Interleukin 6; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TB, Total bilirubin; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV hepatitis C virus; HDV, hepatitis D virus; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; HSV, herpes simplex virus; ANA, Anti-Nuclear Antibody; SMA, Anti-Smooth Muscle Antibody; LKM-1, Anti-Liver/Kidney Microsomal Antibody Type 1/.

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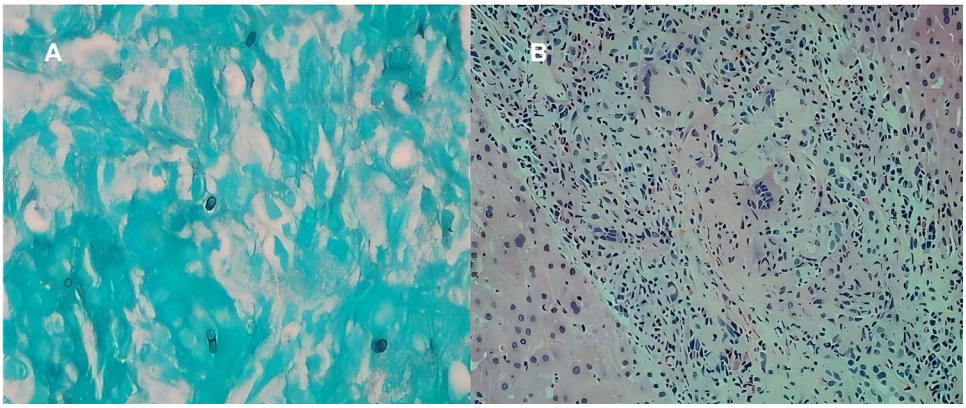

Figure 2 Microscopic examination of liver. (**A**) *Talaromyces marneffei* was visible under the microscope (Grocott's methenamine silver). (**B**) Epithelioid granulomas with multinucleated giant cell reaction.

confirmed splenomegaly (Figure 1B). Ultrasound-guided liver biopsy was performed Ultrasound-guided on hospital day 13. Fever recurred on hospital day 14, with temperature reaching 38.5°C. Clinical review identified a prior diagnosis of *T. marneffei* pulmonary infection in addition to current manifestations of intermittent fever, abnormal liver function, and splenomegaly. These findings prompted a high clinical suspicion for diagnosis of disseminated *T. marneffei* infection. Due to concerns regarding potential adverse effects, the patient declined amphotericin B therapy. Consequently, intravenous voriconazole was administered at a dose of 200 mg twice daily. Afebrile status was achieved the next day following initiation. mNGS of the liver tissue confirmed the hepatic *T.marneffei*. On hospital day 16, microscopic examination revealed multiple portal epithelioid granulomas with prominent lymphocytic, plasmacytic, and eosinophilic infiltration (Figure 2A). Immunohistochemical staining demonstrated 8 $IgG4^+$ plasma cells per high-power field. Grocott's methenamine silver (GMS) stain demonstrates the presence of yeasts compatible with *T. marneffei* (Figure 2B).

In consideration of all the facts, we finally diagnosed the patient with disseminated *T.marneffei* infection, which invaded the liver, spleen, and lung. Intravenous voriconazole, magnesium isoglycyrrhizinate, and ademetionine were administered continuously. A third liver function test on hospital day 19 (5 days after administered) was significant improved (AST: 41 U/L, ALT: 45 U/L, ALP: 387 U/L, GGT: 601 U/L). On day 24 of hospitalization, liver function tests had markedly improved (AST: 40 U/L, ALT: 36 U/L, ALP: 220 U/L, GGT: 100 U/L, TB:11.7μmol/L, DB:2.9μmol/L). The patient was discharged with oral voriconazole (200mg, twice daily). At a 2-month follow, the patient remained afebrile and n good general condition, with normalized liver function. A chest CT showed a marked decrease in bilateral pulmonary nodular lesions compared to prior imaging. The patient has shown no signs of recurrence after 10 months of continuous oral voriconazole therapy.

Discussion

We report a rare case of STAT3-HIES complicated by recurrent *T.marneffei* infection, ultimately presenting as disseminated disease predominantly involving the liver. The diagnostic and therapeutic course highlights challenges associated with managing opportunistic infections in immunocompromised hosts and provides insights into the variable clinical manifestations and treatment strategies for of *T.marneffei* infection.

T. marneffei is an opportunistic pathogen, capable of invading multiple organs, including the lungs, liver, spleen, lymph nodes, blood, and bone marrow.[6] In recent years, increasing numbers of *T. marneffei* infections have been reported in HIV-negative individuals, highlighting its emergence as an important infection in immunocompromised populations. The clinical manifestations and laboratory findings of *T. marneffei* infection are often nonspecific and variable, leading to misdiagnosis and delayed treatment. According to data from a systematic review, the average time to diagnosis was 5.39 months, and among 78 cases HIV-negative cases, 48.1% were initially misdiagnosed as tuberculosis, bacterial pneumonia, lung cancer, or other conditions.[6] Conventional diagnostic methods for *T. marneffei* infection include histopathological examination and culture of clinical specimens, which may be limited by low sensitivity and prolonged turnaround time. In contrast, mNGS has emerged as a powerful tool for the rapid and accurate diagnosis of *T. marneffei* infection.[7,8]

STAT3 mutations impair Th17 cell differentiation, which compromises host antifungal immunity and represents a key risk factor for *T. marneffei* infection.[4] STAT3 signaling is essential for the differentiation of Th17 cells, which produce IL-17 and orchestrate neutrophil recruitment and activation. Therefore, the prevalence of *T. marneffei* infection is particularly high in HIV-negative patients with HIES.[9] These cases highlight the importance of considering *T. marneffei* as a potential pathogen in patients with primary immunodeficiencies, especially those with defects in the Th17 pathway.

T. marneffei infection can be categorized into disseminated and localized types. The disseminated talaromycosis often involves multiple organs and tissues, and patients present with fever, weight loss, cough, dyspnea, and gastrointestinal symptoms.[6] These nonspecific clinical manifestations may lead to misdiagnosis as tuberculosis or other fungal infections. Previous reports have described cases initially diagnosed as pulmonary tuberculosis but later confirmed as disseminated *T. marneffei* infection.[10,11] In contrast to the classical presentation characterized by skin lesions and respiratory symptoms, our patient primarily exhibited jaundice and abnormal liver function tests, resulting in an initial misdiagnosis of DILI. Additionally, the presence of elevated serum IgG4 levels and IgG4-positive cells in liver tissue may have contributed to a misdiagnosis of IgG4-related disease. The absence of typical clinical features may delay the recognition of *T. marneffei* infection, particularly in non-endemic areas or in patients without a known history of immunosuppression. Clinicians should maintain a high index of suspicion for opportunistic infections, especially in individuals with primary immunodeficiencies presenting with unexplained fever or organ dysfunction.

The use of mNGS in this case was pivotal in identifying *T. marneffei* in both BALF and liver tissue, particularly when conventional culture methods were negative. Initially, the low-abundance bacterial sequences (2 reads) detected by BALF-mNGS was deemed clinically insignificant and attributed to colonization in the absence of infection-related symptoms. However, clinical evidence confirmed that in immunocompromised hosts, even rare pathogens with low microbial burden, such as *T marneffei, Pneumocystis jirovecii*, and Leptospira, may still indicate active infection.[11–13] mNGS offers a rapid and comprehensive approach for diagnosing rare pathogens and should be considered earlier in the diagnostic workup of immunocompromised patients with unexplained febrile illnesses or organ dysfunction.

The mechanisms and predictive factors for recurrence in *T. marneffei* infection remain unstudied. Previous study indicated lower recurrence rates among HIV-positive patients.[14,15] This may be related to effective antiviral therapy and strict oversight of these patients. Conversely, HIV-negative individuals often present with refractory immune deficiencies and more comorbidities, which may contribute to their higher relapse incidence.[16] This patient experienced three *T. marneffei* infections (two pulmonary episodes and one disseminated infection) within a two-year period, suggesting the persistent risk of recurrence in STAT3-HIES patients despite standardized antifungal therapy. The recurrence may be attributed to the persistent pathogen colonization or activation due to the underlying immune deficiency. Furthermore, consolidation therapy and prolonged secondary prophylaxis might provide opportunities for the emergence of drug resistance.[17]

This case provides several important lessons for clinical practice. First, disseminated *T. marneffei* infection should be included in the differential diagnosis for immunocompromised patients presenting with unexplained fever, liver dysfunction, or splenomegaly, even in the absence of classic symptoms. Second, the integration of mNGS into routine diagnostic workflows can significantly improve the detection of elusive pathogens and reduce diagnostic delays. Finally, long-term antifungal prophylaxis should be considered in patients with persistent immune defects to prevent recurrence, although individualized treatment strategies are needed to balance efficacy and safety.

Conclusion

This case highlights the complex interplay between host immunity and opportunistic fungal infections, particularly in patients with primary immunodeficiencies such as STAT3-mutated HIES. The atypical presentation, diagnostic challenges, and recurrence of *T. marneffei* infection underscore the need for heightened clinical awareness, the integration of advanced diagnostic tools, and individualized therapeutic approaches in the management of immunocompromised patients.

Ethical Statement and Informed Consent

The study was approved by the Ethics Committee at the Shenzhen People's Hospital. The patient's written informed consent was obtained for publications of all the images and case details. No institutional approval was required to publish the case details.

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Disclosure

All authors agree with the submission and declare that they have no conflict of interest.

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