

Talaromyces marneffe Infection in Systemic Lupus Erythematosus Patients: Report of Two Cases and Review of the Literature

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Jingshan Wei¹
Ye Qiu¹
Wen Zeng¹
Mianluan Pan¹
Jianquan Zhang^{1,2}

¹Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, People's Republic of China; ²Department of Respiratory and Critical Care Medicine, The Eighth Affiliated Hospital of Sun Yat-Sen University, Shenzhen, Guangdong 518033, People's Republic of China

Purpose: *Talaromyces marneffe* is a highly invasive fungus, causing fatal mycosis in patients with or without HIV in Southeast and Eastern Asia. However, its presence in patients with systemic lupus erythematosus is rarely reported.

Methods: We reported two SLE patients infected by *T. marneffe* and reviewed other patients reported in the English literature. All cases were pooled for analysis.

Results: Eleven patients with SLE infected with *T. marneffe* infection were identified, including the two presented here. Three were male and eight were female; all were HIV negative. All the patients, except two where data were missing, had received immunosuppressants before *T. marneffe* infection. The main clinical features included fever, cough, lymph node enlargement, gastrointestinal symptoms, and rash. Five patients were misdiagnosed as having SLE exacerbation. *T. marneffe* was detected via culture or histopathologic analysis, with the fungus most commonly found in the blood. Seven of the 11 patients were successfully treated by timely antifungal therapy with concomitant SLE control, while four patients who did not receive antifungal therapy died.

Conclusion: *T. marneffe* infection should be excluded when SLE patients, especially if on long-term immunosuppressants, present with fever, cough, lymph node enlargement, gastrointestinal symptoms, and rash. Controlling the lupus and timely antifungal treatment can improve the outcomes of SLE patients with *T. marneffe* infection.

Keywords: *Talaromyces marneffe*, systemic lupus erythematosus, immunosuppressant

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple systems and is characterized by pathogenic autoantibodies and uncontrolled inflammatory response.¹ Intrinsic immune system defects combined with immunosuppressive therapy predispose SLE patients to various infections, including bacterial, fungal, parasitic, and viral infections.¹⁻⁴

Talaromyces marneffe is a highly invasive fungus endemic to Southeast and Eastern Asia.^{5,6} It commonly occurs in human immunodeficiency virus (HIV)-positive patients, but has been reported in both immunocompetent and immunocompromised HIV-negative patients.^{7,8} Reports of its presence in SLE patients are rare,⁹⁻¹⁵ and risk factors remain unclear. The diagnosis is challenging owing to non-specific manifestations that are similar to those of active SLE.

Here, we report two SLE patients infected with *T. marneffe* and review the literature with a focus on risk factors, clinical characteristics, treatments, and

Correspondence: Jianquan Zhang
Department of Respiratory and Critical Care Medicine, The Eighth Affiliated Hospital of Sun Yat-Sen University, Shenzhen, Guangdong 518033, People's Republic of China
Tel +86 139 7812 3845
Fax +86 0771 535 0031
Email jqzhang2002@126.com

outcomes. We hope this article will serve as a reference for its early diagnosis and treatment.

Methods

We reported two SLE patients who had been diagnosed with *T. marneffe*i infection at the First Affiliated Hospital of Guangxi Medical University. Other reported cases of *T. marneffe*i infection in SLE patients were identified by searching the PubMed, Wanfang, and Google Scholar databases up to June 2020 using the keywords “*Penicillium marneffe*i or *Penicilliosis marneffe*i or *Talaromyces marneffe*i” and “Systemic lupus erythematosus or SLE.” Only articles published in the English language were selected. The retrieved cases were pooled with the two cases in this report for analysis.

Results

Case 1

A 49-year-old Chinese man, who had a 2-month history of SLE and treated with oral prednisone (30 mg/day), was admitted to a local hospital in February 2017 due to repeated fever, cough and fatigue. He was a farmer living in Guangxi. During hospitalization, Gram-negative bacteria were isolated from his blood culture and antibiotic (meropenem) for septicemia administered during a period of 3 weeks without improvement. He was then referred to our hospital for further treatment.

Upon admission to our hospital, physical examination showed annular erythema of the inner canthus and eyelids, a mouth ulcer and massive ecchymosis of the forearms. Routine blood examination revealed the following: white blood cells, $3.65 \times 10^9/L$ with 81.4% neutrophils; hemoglobin, 85.80 g/L; and platelets, $649.20 \times 10^9/L$. The c-reactive protein (CRP) level (38.99 mg/L) and erythrocyte sedimentation rate (>140 mm/hour) were elevated. The 24-hour urine protein level was 2655.0 mg, anti-dsDNA antibody titers were normal, and serum complements were low (C3, 0.519 g/L; C4, 0.125 g/L). Assessment for anti-nuclear antibody and anti-SS-A indicated positivity while anti-HIV antibody was not detected. The liver functions (alanine aminotransferase, 144 U/L; aspartate aminotransferase 677 U/L) were deranged, and blood coagulation (thrombin time >120 s, fibrinogen 0.69 g/L) was impaired. The CD4+ T-lymphocyte count (95 cells/ μ L) was lower than normal. A sputum smear contained hyphae. Chest computed tomography (CT) scan revealed infiltration in the upper

lobes of the lungs, swollen mediastinal lymph nodes, and a slight pleural effusion. A diagnosis of active SLE with lupus nephritis, pneumonia, and septicemia was established.

He received intravenous methylprednisolone (80 mg/day), empirical intravenous antibacterial (meropenem 1gq8h), and antifungal (fluconazole 200 mg/day). His temperature subsequently returned to normal. However, his platelet count progressively declined to $42.4 \times 10^9/L$ and he developed hemoptysis. Nine days post-admission, chest CT showed increased infiltration and pleural effusion. Finally, the sputum and bone marrow cultures were positive for *T. marneffe*i.

Methylprednisolone was changed to prednisone 50 mg/day. Intravenous amphotericin B (5 mg/day gradually increased to 25 mg/day) and oral voriconazole (400 mg/day) were administered for 2 weeks, followed by oral itraconazole (400 mg/day) for 11 months. His condition improved and there was no recurrence of *T. marneffe*i infection at the 3-year follow-up.

Case 2

A 27-year-old Chinese woman, who had received oral prednisone (30 mg/day) 4 years for SLE, was admitted to our hospital in July 2003 because of thigh swelling, pain, and fever for 3 weeks. She was a worker and born in Guangxi. On admission, her temperature was 38.8°C, and she had large scattered patches of edematous erythema on her swollen right thigh. Laboratory tests revealed the following: white blood cell count, $8.93 \times 10^9/L$ with 94.8% neutrophils; hemoglobin, 61 g/L; erythrocyte sedimentation rate, 138 mm/hour; a high CRP level (46.8 mg/mL); normal serum complements and anti-dsDNA antibody titers. Antinuclear antibodies were highly expressed (109.4 IU/mL), whereas anti-HIV antibodies were absent. Blood cultures were positive for coagulase-negative *Staphylococcus*. The histopathology of the skin lesions indicated vasculitis, which is consistent with SLE. Active SLE and septicemia were diagnosed. She responded to dexamethasone (10 mg/day) and antibiotics (levofloxacin and cefpiramide) and was discharged after 2 weeks of treatment.

In October 2003, she was readmitted to our hospital with recurrent swelling of her right thigh and cutaneous ulcers. The ulcer on her right thigh was 3 cm in diameter with purulent secretions. Her laboratory test results in the current admission were similar to those in July 2003. *T. marneffe*i was identified in cultures prepared from

blood and ulcer secretions, and coagulase-negative *Staphylococcus aureus* was isolated from ulcer secretions.

She received oral prednisone (40 mg/day), broad-spectrum antibiotics (intravenous cefuroxime and clindamycin), and intravenous fluconazole (300 mg/day). One month later, her clinical symptoms had significantly improved; fluconazole was reduced to 200 mg/day, and the antibiotics were discontinued. She was discharged 3 months after treatment and oral fluconazole (200 mg/day) was administered for an additional 6 months. There was no recurrence at the 1-year follow up.

Literature Review

Including our cases, 11 cases of SLE with *T. marneffe* infection have been reported in the English literature; their characteristics are detailed in Table 1. All patients were HIV negative and from southern China or Southeast Asia; three were male and eight were female, and the average age was 37.18 (range, 23–65) years. All patients presented with fever; four had cough, lymph node enlargement, and/or gastrointestinal symptoms and two had rashes. The duration of SLE ranged from 2 months to 24 years.

Chronic immunosuppression preceded *T. marneffe* infection in nine cases; data were unavailable for the remaining two cases. All nine patients had received prednisone prior to infection, with three concomitantly receiving additional immunosuppressants (eg, mycophenolate mofetil, azathioprine, or hydroxychloroquine). All patients with CRP data ($n = 7$) had an elevated level. Five patients including ours were initially misdiagnosed with SLE exacerbation, leading to delayed treatment of the infection and consequent increase of the immunosuppressant dosage and eventual worsening of the condition.

T. marneffe infection was diagnosed via culture or histopathologic examination, with the fungus most commonly found in the blood (five patients). Seven patients were expeditiously treated with antifungal drugs after *T. marneffe* infection was confirmed. The duration of the antifungal treatment was 12–80 weeks, with continuous control of the SLE. The treatment eliminated the infection in these patients. The four patients who did not receive antifungal therapy died. One died from multiple organ failure, while the second patient died from bleeding and disseminated intravascular coagulation. Data on the cause of mortality were not available for the remaining two patients.

Discussion

T. marneffe can invade various organs in HIV-negative patients, including lungs, skin and lymph nodes.^{7,14} The common clinical manifestations of infection are fever, malaise, weight loss, skin and soft tissue lesions, hepatosplenomegaly, lymphadenopathy, cough, and dyspnea.⁷ These manifestations are shared by SLE, which involves multiple organs; and fever is a typical symptom of an SLE flare-up.¹ Consequently, diagnosing *T. marneffe* infections in SLE patients is challenging.

Of the 11 reported SLE patients infected with *T. marneffe*, fever, cough, lymph node enlargement, gastrointestinal symptoms and rashes were the most common manifestations. Among them, five patients were inaccurately diagnosed with SLE exacerbations resulting in treatment with increasing dosages of immunosuppressants. Increasing the dosage of immunosuppressant before excluding *T. marneffe* infection results in dissemination of the infection and is fatal. Hence, clinicians should be aware of this uncommon fungus and pay close attention to the results of microbiological, pathological, and laboratory investigations. Doing so will allow them to distinguish SLE activity from *T. marneffe* infection and devise appropriate treatment plans. CRP level is a good marker to distinguish between infection and active SLE; it has high sensitivity and specificity, and an increase level in CRP suggests a combined infection in patients with SLE.^{1–3} Kim et al demonstrated in a ROC analysis of CRP that the area under the curve was 0.966 (95% CI 0.925–1.007), and CRP levels higher than 1.35 mg/dL indicated infection in SLE patients with a sensitivity of 100% and a specificity of 90%.¹⁶ Seven of the reported SLE patients with *T. marneffe* infection had available CRP data, and CRP levels in all seven were elevated and higher than 1.35 mg/dL. Definitive diagnosis of *T. marneffe* infection relies on positive cultures and microscopy from a variety of clinical specimens. *T. marneffe* is a dimorphic fungus: it has a yeast form at 37°C and a mycelial form with a characteristic diffusible red pigment at 25°C.¹⁷ The yeast form is visualized using the periodic acid-Schiff stain or the Wright stain, which reveals yeast-like or sausage-like cells 2–3 mm in diameter with a central transverse septum.⁸ Acid fast staining and other specific staining procedures are helpful for differentiating *T. marneffe* from other pathogens.

A previous study showed that prolonged immunosuppression renders patients more susceptible to opportunistic

Table 1 Reported Cases of *T. marneffei* Infection in Patients with SLE

#[Ref Number]	Age (Years)/ Sex	Area	Duration of SLE	Immunosuppressant at Onset of Symptoms	Symptoms	CRP (mg/dL)	Site of Positive Culture or Histopathology	Antifungal Therapy (Duration)	SLE Therapy	Outcome
[9]	40/F	Malaysia	24 years	P + MMF	Fever, diarrhea, cough, renal failure	11.8	Blood	Vori → Itra (12 weeks)	P	Recovered
[9]	23/M	Malaysia	4 months	P + Aza + HCQ	Fever, hoarseness, sore throat, cough	3.9	Blood	AmpB → Itra (12 weeks)	ND	Recovered
[10]	25/F	Thailand	3 months	P	Fever, lymphadenopathy	–	Lymph node, lung, liver	None	P	Death
[11]	38/F	Guangzhou, China	23 years	P	Fever, skin ulcer	–	Ulcer secretion	None	NA	Death
[11]	32/M	Guangzhou, China	NA	NA	Fever, stomachache	–	Peritoneum dialysis fluid	None	NA	Death
[12]	65/F	Hong Kong, China	1 year	Aza + P	Fever	–	Blood	None	NA	Death
[13]	32/F	Hong Kong, China	3 years	NA	Fever, lymphadenopathy	28	Bone marrow, lymph node	AmpB + Fluo → Itra + Fluo → AmpB + Itra → Itra (80 weeks)	P	Recovered
[14]	32/F	Hong Kong, China	10 years	P	Fever, abdominal pain, diarrhea, lymphadenopathy	9.4	Blood, lymph node	AmpB → Itra (NA)	P	Recovered
[15]	46/F	Huizhou, China	10 years	P	Fever, subcutaneous masses, cough, abdominal pain, diarrhea, painful knee joints	10.8	Ulcer secretion, tissue biopsy	AmpB → Itra + Fluc → Itra (34 weeks)	P	Recovered
[PR]	27/F	Guangxi, China	4 years	P	Fever, skin ulcer, lymphadenopathy	4.68	Blood, ulcer secretion	Fluc (36 weeks)	P	Recovered
[PR]	49/M	Guangxi, China	2 months	P	Fever, cough, fatigue	3.899	Phlegm, bone marrow	AmpB + Vori → Itra (46 weeks)	P	Recovered

Note: ND indicates that immunosuppression therapy was received but no details were provided.

Abbreviations: SLE, systemic lupus erythematosus; Ref, reference; PR, present report; F, female; M, male; NA, not available; P, prednisolone; MMF, mycophenolate mofetil; Aza, azathioprine; HCQ, hydroxychloroquine; CRP, c-reactive proteins; Vori, voriconazole; Itra, itraconazole; AmpB, amphotericin B; Fluo, fluorocytosine; Fluc, fluconazole; MP, methylprednisolone.

infections.¹⁸ All nine reported *T. marneffeii*-infected SLE patients for whom immunosuppression data were available had undergone chronic immunosuppression before infection. Hence, long-term use of immunosuppressants may be an important risk factor for *T. marneffeii* infection in patients with SLE. However, more cases are needed to conclusively identify the relevant risk factors.

T. marneffeii infection is associated with high mortality rates, and early administration of antifungal therapy can improve prognosis.^{8,17} Agents that effectively treat *T. marneffeii* infection include voriconazole, itraconazole, amphotericin B, 5-flucytosine, and fluconazole.^{17,19} The most commonly recommended antifungal therapy is amphotericin B combined with itraconazole.^{9,15,20} Four of the 11 (36.4%) reported *T. marneffeii*-infected SLE patients died without receiving antifungal therapy. Among them, one patient refused to use antifungal drugs, one patient was not treated with antifungal agents since the diagnosis was made posthumously, and the remaining two did not have data available. The remaining seven patients were treated using a timely antifungal therapy and concomitant control of the lupus; most of them initially received amphotericin B-based antifungal drugs followed by itraconazole. All of them were cured clinically. These findings indicate timely, effective antifungal therapy, combined with control of the lupus are important for *T. marneffeii* infection in SLE patients. There is currently no standard treatment duration for *T. marneffeii* infection in HIV-negative individuals. *T. marneffeii* infection readily relapses regardless of immune system status, and there are some reports of relapse after many years.^{8,17} Hence, for SLE patients who require chronic immunosuppression, long-term antifungal therapy and follow up may be necessary. The key indicators of when to stop antifungal treatment include clinical manifestation, imaging results and laboratory examination.

Conclusion

Clinicians should be aware of *T. marneffeii* infection when SLE patients, especially those on long-term immunosuppressants, present with fever, cough, lymph node enlargement, gastrointestinal symptoms, and rash. Early diagnosis and antifungal therapy combined with control of lupus symptoms is critical for a favorable outcome.

Ethical Approval

Written informed consent was obtained from the patients for publication of this report. Copies the written consent

are available for review by the Editor of this journal. This study was approved by the ethics committee associated with the Faculty of Medicine at The First Affiliated Hospital of Guangxi Medical University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests. The abstract of this paper was presented at the American Thoracic Society International Conference as a poster presentation

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