

## Penicilliosis in lupus patients presenting with unresolved fever: A report of 2 cases and literature review

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**Abstract.** Penicilliosis is a rare occurrence among non human immunodeficiency virus (HIV) infected patients. We report here two cases of *Penicillium marneffei* infection in patients with systemic lupus erythematosus (SLE). Both patients had a recent flare of lupus and were on immunosuppressive drugs when they presented with prolonged fever without an obvious foci of infection, unresponsive to broad-spectrum antibiotics. They were leucopaenic upon admission, with rapid deterioration during the course of the illness. Diagnosis of penicilliosis via fungal isolation from blood culture was delayed resulting in the late initiation of antifungal agents. While both patients ultimately recovered, the delay in diagnosis led to a prolonged hospital stay with increased morbidity. Clinicians should be aware of this uncommon but emerging fungal pathogen in SLE patients and maintain a high index of suspicion in diagnosing this potentially fatal but treatable disease.

### INTRODUCTION

*Penicillium marneffei*, the only thermally dimorphic fungus of *Penicillium* species is endemic in most Southeast Asian countries, including Thailand, Laos, Cambodia, Myanmar, Vietnam, Malaysia, Southern China and Taiwan (Vanittanakom *et al.*, 2006; Ustianowski *et al.*, 2008). In parallel with the human immunodeficiency virus (HIV) pandemic, the incidence of *P. marneffei* infection or penicilliosis has increased tremendously over the past two decades. In this regard, penicilliosis has been reported as the third most common opportunistic infection or AIDS-defining illness in Northern Thailand, following tuberculosis and cryptococcosis (Supparatpinyo *et al.*, 1994). Similarly in other endemic countries, it has emerged as a clinically important and relevant fungal pathogen (Wong & Lee, 1998; Vu Hai *et al.*, 2010). This opportunistic fungus usually causes progressive infection in HIV-infected individuals. There are limited case

reports in the literature documenting the presence of this infection among non-HIV but immunocompromised hosts (Jayanetra *et al.*, 1984; Xi *et al.*, 2004; Lin *et al.*, 2010). Cases of *P. marneffei* infection in patients with connective tissue disease in general and systemic lupus erythematosus (SLE) in particular are exceptionally rare (Jayanetra *et al.*, 1984; Lo *et al.*, 1995; Lam *et al.*, 1997; Xi *et al.*, 2004; Luo *et al.*, 2010). We report here two cases of penicilliosis in non-HIV SLE patients, who were treated successfully with antifungal agents.

### CASE REPORTS

#### Case 1

A 40 year-old Chinese lady with a long-standing history of SLE since 16 years old presented to an outside hospital in August 2008 with a high grade fever for two weeks, associated with diarrhoea, productive cough and renal failure (serum creatinine 715 µmol/

L). Her past medical history was significant for autoimmune haemolytic anaemia requiring splenectomy as well as biopsy proven lupus nephritis. Four months earlier, she had been diagnosed with relapse of severe lupus nephritis (LN), complicated by acute kidney injury requiring the initiation of renal replacement therapy. A renal biopsy done during that presentation revealed active WHO Class IV LN with elements of chronicity for which she received intravenous Methylprednisolone for three days and then oral prednisolone at 30 mg/d. She was also started on Mycophenolate Mofetil at 1 g bd. Her renal function subsequently improved allowing the discontinuation of haemodialysis. Upon discharge, her serum creatinine had dropped to 280 µmol/L.

During her present admission, the physical examination was unremarkable. She was anaemic (82.0 g/L) and leucopaenic (total white cell count  $2.5 \times 10^9/L$ , neutrophil 63%) with low serum complements but a normal anti-double-stranded DNA titre. Her liver function test revealed hepatitis with raised liver enzymes. Erythrocyte sedimentation rate (ESR) was 38 mm/hr and C-reactive protein (CRP) was markedly elevated (11.8 mg/dL, normal 0-0.8 mg/dL). Blood culture and sputum samples for acid fast bacilli were negative. Urine cultures returned positive for *E. coli*. Imaging studies were performed. A chest X-ray (CXR) showed right upper zone patchy opacities suggestive of consolidation while an ultrasound of the abdomen was significant only for the presence of small bilateral pleural effusions and mild ascites. She was diagnosed with *E. coli* urinary tract infection and community acquired pneumonia complicated by acute on chronic renal failure. Treatment was initiated with broad spectrum antibiotics (intravenous Piperacillin/Tazobactam and Azithromycin). At the same time, her Mycophenolate Mofetil was withheld while the oral prednisolone was maintained at 10 mg/d. Her renal failure did not improve despite aggressive attempts at hydration resulting in initiation of haemodialysis. 5 days after her admission, her condition did not show any signs of improvement and she

was transferred to our hospital for further management.

Upon admission to our hospital, a full septic work up was repeated. Investigations for opportunistic infections were performed including serology for CMV which returned positive (IgG and IgM) resulting in initiation of intravenous Ganciclovir. However, her condition deteriorated rapidly on day 3 of admission. She developed septicaemic shock and respiratory failure requiring inotropic support and non invasive positive pressure ventilation. Antibiotic was upgraded to intravenous Imipenem/Cilastatin sodium and empirical intravenous Vancomycin was added. Her condition was further complicated by disseminated intravascular coagulation. Repeated CXR at this time showed diffuse alveolar shadowing which was attributed to pulmonary oedema from renal failure. Dialysis modality was changed to continuous renal replacement therapy as she was unstable haemodynamically.

With all these antimicrobial treatments and supportive care, her haemodynamics improved but she continued to be febrile. Empirical intravenous Fluconazole was added. On day 8 of her hospitalization, *P. marneffe*i was isolated from blood culture. Intravenous Amphotericin B was then started in place of Fluconazole, which was changed a day later to intravenous Voriconazole due to ongoing renal failure requiring dialysis. With these changes, the fever settled and her condition (including renal function) steadily improved resulting in cessation of ventilator and dialysis support. Her serum creatinine was stable around 270-280 µmol/L. Intravenous Ganciclovir was discontinued when CMV PCR returned negative. She was discharged well after a month of hospital stay. In total, she received two weeks of intravenous Voriconazole followed by ten weeks of oral Itraconazole.

## Case 2

A 23 year-old Chinese man had a 3-year history of autoimmune haemolysis leading up to a diagnosis of SLE in August 2008. He was started on oral prednisolone 15 mg/d, Azathioprine 50 mg/d and Hydro-

xychloroquine 200 mg/d. 4 months after the diagnosis of SLE, he presented to our hospital with a 3-week history of persistent high grade fever, associated with hoarseness of voice, sore throat and productive cough. Physical examination was significant for the presence of oral ulcers and Raynaud's phenomenon. Blood investigations obtained revealed the presence of anaemia (80.0 g/L), leukopenia ( $1.8 \times 10^9/L$ , neutrophil 66%) and low complements. His markers of lupus activity were raised with a markedly elevated anti-double-stranded DNA titre (1890 iu/ml, normal 0-200 iu/ml, ELISA method) and a 24-hour urinary protein of 2.79g. His ESR was raised at 102 mm/hr and but his CRP was only mildly elevated (3.9 mg/dL, normal 0-0.8 mg/dL). A CXR obtained on presentation was unremarkable while a direct smear of sputum for acid fast bacilli was negative. His sore throat was investigated by the use of a flexible nasopharyngolaryngeal scope which revealed the presence of a left vocal cord paralysis. An initial diagnosis of active SLE with likely LN, superimposed respiratory tract infection and vocal cord paralysis was made.

He was treated with intravenous Amoxycillin/Clavulanate and Azathioprine was withheld. On day 4 of admission, he continued to have a persistent fever which was attributed to the active lupus resulting in the administration of a 3-day course of intravenous Methylprednisolone at 500 mg/d. However, his condition failed to improve. On day ten, his antibiotic was changed to intravenous Piperacillin/Tazobactam. Blood cultures at this point remained negative. An ultrasound of the abdomen was done that was significant for early renal parenchymal disease and splenomegaly but did not reveal any cause for his persistent fever. On day 12 of admission, a repeat CXR was obtained. This now showed infiltrates at the right lower zone and the presence of minimal pleural effusion. Over the next 3 days, his respiratory status underwent a steep decline requiring the use of high flow oxygen. Repeated CXR showed a worsening of the pleural effusion and now, the presence of bilateral perihilar patchy opacities. The pleural fluid was aspirated and returned as exudative. After 15 days of hospitalization, the laboratory was able to

detect fungal growth from the blood culture. Thus, intravenous Amphotericin B was started immediately. 4 days later, (after 19 days in hospital), the fungus pathogen was finally identified as *P. marneffeii*.

His fever settled after 4 days of Amphotericin B. He was treated for a total of 2 weeks during which time he showed marked clinical improvement. He was subsequently maintained on oral Itraconazole for another 10 weeks. He was discharged well after 33 days of hospital stay. Azathioprine was reintroduced two months later without any complications.

## DISCUSSION

While rare, reports of *P. marneffeii* infection in Malaysia emerged as early as 1995 (Rokiah *et al.*, 1995) and have been consistently reported with the most recent case being published in 2010 (Yap *et al.*, 2010). While most have been in the context of HIV infected individuals (Rokiah *et al.*, 1995; Jayaram & Chew, 2000; Othman *et al.*, 2006; Yap *et al.*, 2010), two cases affecting non AIDS patients have also been described (Saadiah *et al.*, 1999; Beh & George, 2009). Our two cases here illustrate the rare occurrence of *P. marneffeii* infection in non-HIV SLE patients. To our knowledge, there have been only 6 cases of reported penicilliosis among SLE patients (Jayanetra *et al.*, 1984; Lo *et al.*, 1995; Lam *et al.*, 1997; Xi *et al.*, 2004; Luo *et al.*, 2010). 5 of them were from Southern China and 1 from Thailand. Our 2 cases add to the limited literature available. Of the 8 total reported cases, 6 of them are females. Mean age of the patients is 37.8 years (ranges from 23 to 66 years) and half of them died. Table 1 summarises the salient features of all the reported cases of penicilliosis in SLE patients.

Penicilliosis, which was once a rare human disease has emerged as a common opportunistic infection in HIV infected individuals, and has increasingly been reported in patients with acquired cellular immune deficits e.g. transplant recipients, patients with hematologic malignancies and patients on corticosteroids or immuno-

Table 1. Summary of salient features of the reported cases of Penicilliosis in lupus patients

| No | Age | Gender | Duration of SLE | Country          | Clinical presentation                                   | Leucopaenia | Immunosuppressive agents at presentation | Outcome | Reference                      |
|----|-----|--------|-----------------|------------------|---|-------------|--|---------|--------------------------------|
| 1  | 40  | F      | 24 yr           | Malaysia         | Prolonged high fever, pneumonia, renal failure          | Yes         | Pred, MMF                                | Cured   | Present report                 |
| 2  | 23  | M      | 4 mo            | Malaysia         | Prolonged high fever, pneumonia                         | Yes         | Pred, Aza, HCQ                           | Cured   | Present report                 |
| 3  | 46  | F      | 10 yr           | Huizhou, China   | Prolonged fever, cutaneous masses, nodular lung shadows | Yes         | Pred                                     | Cured   | Luo <i>et al.</i> , 2010       |
| 4  | 38  | F      | 23 yr           | Guangzhou, China | High fever, cutaneous ulcers                            | Yes         | Pred (high dose)                         | Death   | Xi <i>et al.</i> , 2004        |
| 5  | 32  | M      | NA              | Guangzhou, China | High fever, abdominal pain                              | NA          | NA                                       | Death   | Xi <i>et al.</i> , 2004        |
| 6  | 66  | F      | 1 yr            | HK, China        | Fever, nodular lung shadows, concomitant PTB infection  | NA          | Pred, Aza                                | Death   | Lam <i>et al.</i> , 1997       |
| 7  | 32  | F      | 3 yr            | HK, China        | Prolonged high fever, lymphadenopathy, choroidal mass   | No          | Pred                                     | Cured   | Lo <i>et al.</i> , 1995        |
| 8  | 25  | F      | 3 mo            | Thailand         | High fever, lymphadenopathy, pneumonia                  | No          | Pred                                     | Death   | Jayanetra <i>et al.</i> , 1984 |

Note: *F* Female, *M* Male, *HK* Hong Kong, *NA* Not available, *Pred* Prednisolone, *MMF* Mycophenolate mofetil, *Aza* Azathioprine, *HCQ* Hydroxychloroquine

suppressive agents (Jayanetra *et al.*, 1984; Xi *et al.*, 2004; Lin *et al.*, 2010). Despite this, the pathogenesis of penicilliosis is still poorly understood. It is postulated that deficiency of CD4<sup>+</sup> T cell-mediated immunity is believed to play a key pathogenic role in AIDS patients and may also possibly be involved in immunocompromised HIV-negative patients (Vanittanakom *et al.*, 2006). Patients with active SLE disease have been shown to have reduced numbers (both absolute and relative) of T cells (La Cava, 2009). Both our patients had a recent flare of SLE (less than 6 months), were on corticosteroids and other immunosuppressive drugs and were leucopaenic on presentation. This 'perfect storm' may have predisposed them to being infected with an organism that would otherwise be uncommon outside of the HIV patient population.

The clinical features of *P. marneffei* infection in HIV infected patients are largely non-specific and can include fever, anaemia, weight loss, non-productive cough, skin lesions, hepatosplenomegaly and generalized lymphadenopathy (Supparatpinyo *et al.*, 1994). However, the presence of skin lesions may provide a clue to the underlying diagnosis. The typical skin lesions seen in HIV patients with penicilliosis are papules with central umbilication (molluscum contagiosum-like lesion) (Vanittanakom *et al.*, 2006; Ustianowski *et al.*, 2008) and can be found in up to 70-85% of the HIV patients with penicilliosis. While there are reports of nodules and cutaneous ulcers in the non-HIV cohort (Xi *et al.*, 2004; Luo *et al.*, 2010), the typical skin lesions are rarely observed, thus rendering the diagnosis of penicilliosis even more difficult. Both of our patients presented with an absence of any remarkable physical signs. The lower index of suspicion in this population group most likely led to a delay in their diagnosis.

Traditionally, laboratory diagnosis of *P. marneffei* infections depends on the microscopic identification of the fungus with subsequent confirmation by culture from clinical specimens such as blood, bone marrow aspirate, lymph node biopsies, skin biopsies, bronchoalveolar lavage samples, pleural fluid, urine and stool samples

(Vanittanakom *et al.*, 2006). However cultures from bone marrow, blood and skin biopsies despite the high yield (100%, 76% and 90%, respectively) are often time consuming and may potentially lead to diagnostic delay. Microscopic examination of Wright-stained samples of bone marrow aspirates and blood, touch smears of skin or lymph node biopsies or Giemsa stain of bronchoalveolar fluid have been reported previously, allowing a presumptive diagnosis to be made before culture results can be obtained (Supparatpinyo & Sirisanthana, 1994; Vanittanakom *et al.*, 2006). Rapid and accurate serological and molecular-based diagnostic methods are currently under development, and need to be validated in a larger number of patients before they can be widely used in clinical practice (Vanittanakom *et al.*, 2006). In our patients, the delay in fungal isolation from blood cultures resulted in late initiation of the appropriate antifungal treatment. Rapid diagnostic tools are clearly needed in future to avoid the potential delay associated with a traditional culture-based method.

Penicilliosis is associated with significant morbidity and mortality, especially in cases where the diagnosis and/or treatment is delayed. Both patients in our report had a prolonged hospital stay due to delayed diagnosis. Therefore, clinicians should employ a high index of suspicion for the presence of fungal infections especially when encountering SLE patients on immunosuppressants who do not defervesce despite administration of apparently appropriate antimicrobial therapy.

Currently, the first choice treatment regimen for penicilliosis is Amphotericin B 0.6 mg/kg/d for 2 weeks followed by Itraconazole 400 mg/d orally in two divided doses for the next 10 weeks (Sirisanthana *et al.*, 1998). For patients with renal impairment, Voriconazole is an effective and well tolerated alternative to Amphotericin B (Supparatpinyo & Schlamm, 2007).

In conclusion, the reported cases and incidence of penicilliosis among non-HIV patients have increased considerably over the recent years, resulting in significant morbidity and mortality. Clinicians should be



aware of this emerging fungal pathogen, and should consider penicilliosis as a possible aetiology in SLE patients with prolonged fever to facilitate the early detection and treatment of this potentially fatal but treatable disease, especially in countries where *P. marneffei* is endemic.

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