EDITORIAL

Penicilliosis: an AIDS-defining disease in Asia

As of year 2007, there are about 33 million people worldwide living with human immunodeficiency virus (HIV) infection. In the same year, 2.4 million people became newly infected, and 2.1 million died from AIDS.[1] In contrast to the western world where the HIV epidemic shows signs of slowing down, in many parts of Asia it is growing.[2] In South and South-East Asian countries, there are 4.0 (3.3-5.1) million HIV-infected persons, of which approximately 0.34 million are new infections diagnosed in 2007. The figure in East Asian countries (including China) is less certain, but according to latest estimates, it is around 0.8 (0.62-0.96) million.[1] Faced with the growing epidemic in this part of the world, clinicians need to be familiar with the diverse presentations of HIV/AIDS, including its commonly associated opportunistic infections. In Hong Kong, *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, tuberculosis, and opportunistic fungal infections constitute the 'top three' AIDS-defining illnesses.[3,4] Among these fungal infections, 50% are penicilliosis.

Penicillium marneffei is a pathogenic dimorphic fungus, which can exist in both 'yeast' and 'mould' forms. The transition of dimorphism is temperature-dependent; in host tissues (37°C), the 'yeast' form is exhibited. It is believed that human infection occurs when fungal spores, present in soil, are inhaled. Studies in Thailand have shown an association between penicilliosis and agricultural occupations and heavy seasonal rainfalls.[5] In immunocompromised individuals with impaired T-cell response, *P marneffei* disseminates and causes life-threatening disease. Similar to other dimorphic fungal infections, penicilliosis occurs in geographically distinct areas. It is rarely reported in western countries (and then almost exclusively among travellers), but is endemic in most parts of Asia, including Thailand, India, Vietnam, Malaysia, Taiwan, and China, which includes Hong Kong.[5] Although *P marneffei* infection may occur among non-HIV immunocompromised individuals, the great majority of the reported cases are linked to HIV/AIDS. Penicilliosis is recognised as one of the commonest AIDS-related opportunistic infections in Thailand.[6] In fact, the diagnosis of penicilliosis frequently prompts clinicians to test for, and subsequently diagnose HIV infection. Thus, in endemic areas like Hong Kong, disseminated penicilliosis is included in the list of conditions known as 'AIDS indicators' or 'AIDS-defining illnesses' for the purposes of classification and surveillance.[3,4,6,7]

In this issue of the Journal, Wu et al[8] report their experience in managing disseminated penicilliosis in 44 HIV-infected patients, the largest cohort described in Hong Kong to date. Their data show that the clinical diagnosis of penicilliosis is often difficult because of non-specific symptoms (fever, malaise, mild anaemia), and it still confers high mortality (>10%), despite the availability of effective antifungal therapy. Typically, penicilliosis presents as a subacute febrile illness with pulmonary infiltration and characteristic skin lesions. In AIDS patients, the skin lesions are commonly described as umbilicated, molluscum contagiosum-like, and occur on the face, upper trunk and extremities. However, as indicated in the series described by Wu et al,[8] the characteristic skin lesions may be absent (in up to 70% of patients), and the chest radiograph can be normal (>50%). Furthermore, because of the very low CD4 count in these patients (<50 cells/mm^3), concurrent infections are often present (in up to 60% of cases), which also complicates the clinical picture. As a result, antifungal treatment may be delayed or even omitted, leading to mortality.

How should clinicians approach suspected penicilliosis? Since this is an opportunistic fungal infection, if not already known, assessment of predisposing factors, including HIV testing, is essential. In particular, the patient should be carefully examined for skin lesions and lymphadenopathy, and considered for detailed pulmonary imaging. Undertaking adequate blood cultures is important, as disseminated fungaemia is very common and affects more than 60% of *P marneffei*–infected immunocompromised patients; the fungus grows readily in most standard media, including those in routine automated blood culture systems.[5] In addition, fungal cultures should be performed on all other relevant clinical specimens, including sputum, bronchoalveolar lavage, skin lesion or lymph node biopsies, and bone marrow aspirates. The 'yeast' form can also be readily seen in histopathological sections. However, as culture results may not be available within a matter of days (and invasive procedures to obtain specimens are not always feasible), certain rapid serodiagnostic assays have been suggested so as to avoid treatment delay and fatal outcomes.[5] Two examples entail detection of: (i) serum galactomannan (an antigen common to aspergillus species),[9,10] and (ii) penicillium gene-encoded mannoprotein Mp1p antigen and antibody.[11,12] The former is more widely available and involves a so-called double-sandwich enzyme-linked immunosorbent assay, approved by the United States Food and Drug Administration to facilitate early diagnosis of invasive aspergillosis, but also cross-reacts with *P marneffei*. In contrast, the penicillium antigen and antibody assay has higher sensitivity and specificity. These tests are especially valuable in

diagnosing early disease when the fungal load is low,[11] but are not intended to replace thorough clinical evaluation and conventional fungal cultures, that constitute the gold standard for diagnosis. Finally, it is necessary to initiate systemic antifungals once clinical/laboratory evidence suggests penicillium infection in a susceptible patient. Unlike invasive aspergillosis, most *P marneffei* infections respond to treatment readily. Regrettably, there has been no randomised controlled trial to evaluate various treatment regimens; even data from observational studies are very limited. One open-label non-randomised study in AIDS-related disseminated penicilliosis reported that amphotericin B induction therapy (2 weeks) followed by itraconazole maintenance achieved a response rate of higher than 95%.[13] This has therefore become the standard of care for severe infections. The only double-blind controlled trial to date was an evaluation of itraconazole maintenance therapy, which was shown to be a highly effective form of disease suppression.[14] Non-suppressed patients almost always relapse. Newer, less toxic antifungal agents like voriconazole or posaconazole, and some echinocandins have also demonstrated excellent in-vitro activity against *P marneffei*.[5,15,16] However these treatments have not been evaluated in controlled clinical trials. With the advancement of highly active antiretroviral therapy (HAART) and immune restoration, discontinuation of life-long itraconazole therapy becomes possible. A recent study shows that patients with CD4 cell counts restored persistently to above 100 cells/mm^3 after HAART can have their itraconazole suppression safely discontinued, with a relapse rate close to 0%.[17]

Limited clinical and laboratory research has been performed on penicilliosis, largely because of its geographical distribution. There is still much to be learnt about its epidemiology, transmission, immunology and molecular diagnosis, as well as management, including issues such as immune reconstitution inflammatory syndrome after HAART.[5] Research from Hong Kong and other Asian countries has helped considerably in the understanding of this emerging AIDS-defining illness, and no doubt more contributions will also be forthcoming.

Nelson Lee, MD, FHKAM (Medicine)
E-mail: leelsn@cuhk.edu.hk
Division of Infectious Diseases
Department of Medicine and Therapeutics
The Chinese University of Hong Kong
Prince of Wales Hospital, Shatin, Hong Kong

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