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Penicillium marneffe Infection In HIV Positive Patients

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Introduction

Penicillium marneffe is a dimorphic fungus that achieved its notoriety with the coming of the HIV epidemic to South East Asia. Prior to that, it was a relatively unknown disease with less than 40 reported cases. First identified in bamboo rats in 1956, there are no other known carriers of the disease. The first human case was in a patient with Hodgkin's lymphoma in 1973 [1].

HIV in Asia and the rise of *P. marneffe* infection

The first cases of AIDS in Asia were reported in 1984 [2]. By 2006 an estimated 7.2 million people were living with HIV/AIDS in South-East Asia [3].

The first diagnosed case of *P. marneffe* infection in a HIV infected patient was in 1988 [4]. Subsequently from 1990 to 1992, over a period of just 25 months, 86 patients were diagnosed with disseminated *P. marneffe* infection, all but one of whom, were HIV positive [5]. *P. marneffe* is now the third commonest opportunistic infection in HIV patients in Northern Thailand after tuberculosis and cryptococcal meningitis [5]. In Hong Kong 7.7% to 10% of HIV patients develop *P. marneffe* infection during the course of their disease [6,7].

Mycology, immunology and epidemiology

P. marneffe is a dimorphic fungus which grows as a mycelium at 25°C and as yeast-like cells and colonies at 37°C. It is a facultative intracellular pathogen [8]. The primary route of infection is thought to be inhalation of conidia into the lungs followed by haematogenous spread especially to the reticuloendothelial system [9]. The human defense against *P. marneffe* invasion requires healthy T cells, especially CD4⁺ cells, which activate cytokines primarily by the Th1 response. An important role is played by gamma interferon, tumour necrosis factor alpha and interleukin-12. Macrophages and circulating mononuclear cells respond with an oxidative burst to kill the fungus. Neutrophils also play a role. In healthy subjects the fungus can be cleared within two to three weeks but it can be rapidly fatal in immunosuppressed patients [8].

It is still uncertain whether transmission of *P. marneffe* is a result of zoonotic or sapronotic infection. Studies in Thailand have shown a higher incidence during the rainy season [10]. The fungus may be isolated from bamboo rats and from the soil around bamboo rat burrows. A 1996 study did suggest that current occupational exposure to plants or animals was a significant risk factor [10]. However much remains to be known about the epidemiology of this infection therefore current emphasis is on early diagnosis, treatment and secondary prevention.

Clinical presentation

The clinical features of penicilliosis are non-specific. It is a diagnosis that can be easily missed in non-endemic areas. A report from the United Kingdom described a young Thai female presenting with cough, lethargy and malaise. Examination showed crusted facial skin lesions, decreased air entry in her left upper lobe and hepatosplenomegaly. The differential diagnosis included histoplasmosis, visceral leishmaniasis, tuberculosis and melioidosis. Penicilliosis was only recognized on postmortem examination [11].

Typical features of penicilliosis include fever (99%), anaemia (78%), pronounced weight loss (76%), generalized lymphadenopathy (58%) and hepatosplenomegaly (51%) [12]. Skin lesions, found in 76% of patients, included: papules with central umbilication, papular rash, maculopapular rash, subcutaneous nodules, acne like lesions and folliculitis [5]. Oral lesions included shiny papules, erosions, ulcers, and perforation of the hard palate [13]. Osteomyelitis and arthritis, of suspected haematological origin have also been described [14]. Chest radiograph abnormalities include alveolar infiltration, interstitial infiltration, mixed alveolar or interstitial infiltration, miliary infiltration, pleural effusion and cavitation [15]. Haematological abnormalities include anaemia (76%), neutropenia, thrombocytopenia, pancytopenia, hypoalbuminaemia and hyperbilirubinaemia [8,15].

A case of asymptomatic *P. marneffe* fungaemia from a patient who had an incidental finding of *P. marneffe* growth on blood culture, while being treated for *Pneumocystis jiroveci* pneumonitis has also been reported. There were no skin lesions, lymphadenopathy or hepatosplenomegaly and he remained well on itraconazole [16].

A high index of suspicion of potential infection, in at risk patients, from endemic areas is necessary for a clinical diagnosis to be made and timely treatment to be instituted.

Diagnosis

The simplest and fastest way for preliminary diagnosis is microscopic examination of Wright's stained samples of bone-marrow aspirate and touch smears of the skin biopsy and lymph node biopsy specimen. Yeast-like organisms can be seen but may sometimes be mistaken as *Histoplasma capsulatum*, *Cryptococcus neoformans*, or *Leishmania* [17].

A study of fungal cultures from bone marrow were 100% positive vs. skin cultures, 90% positive, and blood cultures, 76% positive [5]. Other potential specimens include skin scrapings, sputum, fluid from bronchoalveolar lavage, pleural fluid, liver biopsy specimens, cerebrospinal fluid, pharyngeal ulcer and palatal papule scrapings, urine, stool, kidney, pericardium and stomach or intestine samples [8]. Initial culture of samples is usually on Sabouraud dextrose agar without cycloheximide [18]. Thermal dimorphism of the fungus is demonstrated by culturing the fungus at both 25°C and 37°C [8].

Currently, the gold standard remains culture, which takes 10–14 days to demonstrate colonies with typical morphology and mould to yeast conversion [19]. A characteristic feature of the fungal culture is the production of a diffusible red pigment when grown at room temperature.

Various serological tests have been developed for the diagnosis of penicilliosis, including antigen and antibody detections. Test formats include indirect immunofluorescence, enzyme immunoassay, immunodiffusion, and so on. However, most of these tests are not readily available commercially, and they often do not have high sensitivities (immunodiffusion - 58.8%, latex agglutination -76.5%). [20]. Nested PCR is showing promising results for rapid testing with 68.8 % of culture positive samples being PCR positive and all negative samples being negative [21]. In Hong Kong the indirect immunofluorescence test is available from the Hong Kong University microbiology laboratory.

Treatment

The mortality from penicilliosis is around 20% [22], though a review of 47 patients in Hong Kong showed a lower mortality of 11%, of which 9% were not on treatment at the time of death due to late presentation or diagnosis [23].

Amphotericin B has good *in vitro* activity. The minimal inhibitory concentration (MIC) of amphotericin B ranged from 0.195–1.56 µg/mL. It is the standard first line treatment. Itraconazole also has good *in vitro* activity with MIC <0.195 µg/mL. Seventy three percent of strains are resistant to fluconazole [24]. *In vitro* studies have shown posaconazole to be equivalent to or better than itraconazole and amphotericin B [25]

The generally accepted treatment regimen is amphotericin B 0.6 mg/kg/day IV for 2 weeks followed by itraconazole 400 mg/day for 10 weeks. Subsequent life-long itraconazole 200mg daily is also recommended. Antiretroviral therapy should also be given [26]. It has been suggested that secondary prophylaxis with itraconazole may be discontinued after the initiation of HAART if the CD4+ count is sustained over 100 cells per µL. [27]

Conclusion

Reducing HIV transmission through education and harm reduction measures, and treatment of HIV infection may be the most successful means of influencing the morbidity and mortality due to *P. marneffeii* infection in South-East Asia. Prompt diagnosis and initiation of treatment remain crucial.

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Prosthetic Joint Infections

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Background

With the advances in medical science and technology, more joint replacements are seen in clinical practice. Around 600,000 joint prosthesis are inserted in the United States every year. However with an estimate of infection rate of 1-3% every year, Orthopedic device infections are becoming more common.

Bacterial pathogens and biofilm formation

Coagulase-negative staphylococci were found to be the most common pathogens implicated in prosthetic joint infections (30-40%), followed by *Staphylococcus*

aureus (15-25%), polymicrobial infections (10-12%) and Streptococci (9-10%). Of note is, in 10-11% of the infections no bacterial pathogens could be identified. One interesting observation is in prosthetic shoulder joint infection, *Propionibacterium* was found to be a common causative agent.

Similar to the case of prosthetic valve endocarditis, bacteria form biofilm on the infected prosthetic joint material. Enclosed in a polymeric matrix, the microorganisms develop into a complex, yet organized communities. Inside bacteria are differentiated into different structural and functional heterogeneity, with resembles multicellular organisms. One of the special features of the biofilm is the reduced bacterial growth rate, which is causing a much greater resistance to antimicrobial action and killing.

Clinical presentation

Prosthetic joint infections are broadly divided into three categories, according to its time of development after prosthesis implantation. Early (0-3 months) and delayed (3 to 24 months) infections are mainly acquired in preoperative period while late infections (more than 24 months) are caused by haematogenous route, from other distant sites. Early infections, caused by more virulent organisms (e.g. *S. aureus* and Streptococci), give a more acute clinical presentation. For example, fever, warmth, joint effusion and drainage. Delayed infections give more subtle signs such as persistent joint pain and device loosening.

Diagnosis

Diagnosing prosthetic joint infection is easy at times when clinical signs are obvious, for example, pustular material drainage from sinus tract formation. However when the presentation is not that straight forward, we need to collect evidence from laboratory tests, culture results, histopathology and sophisticated imaging studies.

Serial serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) maybe helpful for monitoring of the inflammatory progress rather than for definite diagnosis. Synovial fluid yielded from image-guided joint aspiration is studied for white cell count and differential. However this method has several difficulties in the case of prosthetic joint infection. With lack of microcirculation and impaired immune response due to the presence of, the degree of inflammation is usually less than those in native joints, causing a low total white cell count. Also peri-prosthetic material for culture is not sensitive unless a large number of samples are taken.

The method of sonication has been developed in order to increase the sensitivity of culture results. The infected prosthetic joint is taken out and placed in a container with solution. Using ultrasound energy the pathogens sticking on the prosthesis are separated from the surface to the solution, which is used for further microbiological investigation. Sonication is especially helpful in patients taking antibiotics, having mixed infections and rare pathogens.

Treatment

Goal of treatment is using the least invasive treatment, in order to eradicate infection, to secure a functional, stable, and pain-free joint. While the clinical condition is, the infected tissue and implanted material should be removed by surgery. Combination of debridement with implant retention and antimicrobial therapy is another choice of treatment. In those patients with high surgical risk, chronic suppressive therapy is used if removal of infected prosthesis is not feasible.

Treatment usually combines surgery and antimicrobial agents. Antimicrobial agents should have activity against surface-adhering, stationary-phase organisms in biofilm environment. Surgical treatment includes debridement with prosthesis retention, one-stage or

two-stage exchange. Debridement with prosthetic retention requires good patient selection. Good results expected in those having duration of signs and symptoms less than 3 weeks, stable implant on presentation, and good peri-prosthetic soft tissue condition. One-stage exchange can be considered in the absence of severe co-morbidities, and difficult-to-treat organisms. If the peri-prosthetic soft tissue is compromised, a two-stage exchange surgery should be the choice. The antimicrobial therapy should consist a three-month course in those with hip replacement and six months in those with knee replacement.

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Metabolic complications of HIV infection and its treatment

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With the advent of potent combination antiretroviral therapy (cART), people living with HIV are enjoying longer life expectancy. On the other hand, they are developing non-AIDS-related morbidities, and metabolic complications leading to an increased risk of cardiovascular disease are becoming a major challenge to physicians taking care of HIV patients.

Spectrum of metabolic complications encountered in HIV-infected patients

Lipid abnormalities are common in HIV-infected patients. From the Multicentre AIDS Cohort Study, significant declines in total, LDL- and HDL-cholesterol were observed during a

mean of 8 years following seroconversion, but after initiation of cART, total and LDL-cholesterol rose by a mean of 1.30 and 0.54 mmol/l respectively [1]. The DAD (Data collection on Adverse events of anti-HIV Drugs) Study demonstrated hypercholesterolaemia in 23% and 27% of patients on non-nucleoside reverse transcriptase inhibitor- and protease inhibitor-based cART respectively, compared to 8% in those who were treatment-naïve, and hypertriglyceridemia in 32%, 40% and 15% in these three groups respectively [2].

Insulin resistance and diabetes mellitus are other commonly encountered metabolic complications in HIV-infected patients. Data from the DAD Study revealed an incidence of 5.7 cases of diabetes per 1000 person-years [3]. A recent longitudinal study from Taiwan showed a higher rate of 13 cases per 1000 person-years [4]. Higher risk of diabetes was associated with black or Asian ethnicity, family history of diabetes, obesity, hepatitis C co-infection and use of antiretrovirals, such as stavudine, indinavir and ritonavir [5].

Lipodystrophy, since its first description in 1998, becomes the most unique metabolic complication seen in HIV-infected patients. In patients with body-fat abnormalities, subcutaneous lipoatrophy is most conspicuous in the face, limbs and buttocks, while fat accumulation occurs in the viscera, breasts and over dorsocervical spine. Lipodystrophy is observed in 40-50% of HIV patients. Older age, prior AIDS diagnosis and lower nadir CD4 count are associated with higher risk of lipoatrophy and females are more prone to central fat accumulation. However, cART, particularly nucleoside analogues and protease inhibitors, is the major factor contributing to lipodystrophy. Prospective studies on patients receiving cART demonstrated a decline of limb fat at 14% per year starting from 6 months post-cART [6]. Patients with lipodystrophy also have higher risk of other metabolic

complications, including insulin resistance, diabetes and dyslipidaemia [5].

Cardiovascular risk in HIV-infected patients

Cardiovascular disease is the major non-AIDS-related cause of death in HIV-infected patients where potent cART are readily available [7]. In the DAD Study, the largest prospective study to evaluate cardiovascular risk in HIV-infected patients, 126 patients developed myocardial infarction over a period of 36,199 person-years, resulting in an incidence of 3.5 per 1000 person-years in this relatively young (median age 39) population [8].

Factors independently associated with higher cardiovascular risk included increased age, male sex, smoking, previous cardiovascular disease, presence of hypertension, diabetes, hypercholesterolaemia and hypertriglyceridaemia. In this study, the incidence of myocardial infarction increased with increased duration of exposure to cART, with an adjusted relative risk of 1.26 per additional year of exposure to cART. The risk was relatively reduced when adjusted for cholesterol and triglyceride level, reflecting that the increased cardiovascular risk associated with cART is partly accounted by the metabolic abnormalities induced by these drugs [8]. Recently, analysis of the DAD Study data also revealed increased risk of myocardial infarction with recent use of abacavir and didanosine with a relative risk of 1.90 and 1.49 respectively [9].

Contribution of HIV infection and cART on metabolic complications

As discussed above, cART plays a major role in the development of various metabolic complications and increased cardiovascular risk. The mechanisms by which various antiretroviral drugs contribute to metabolic complications have been studied extensively. For example, protease inhibitors induce insulin

resistance by binding to glucose transporter 4 on cell surface, thus inhibiting cellular glucose uptake [5]. Protease inhibitors also inhibit adipogenic transcription factors, such as sterol-regulatory enhancer-binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor gamma (PPAR- γ), thereby inhibiting lipogenesis, stimulating lipolysis, and contributing to insulin resistance, lipodystrophy and lipid abnormalities [5,6]. Nucleoside analogues, on the other hand, induce metabolic complications via mitochondrial toxicity [5, 6].

Due to the toxicities of cART, strategies of treatment interruption had been evaluated with a goal to reduce metabolic and cardiovascular risks. In a large randomized study, more than 5000 patients with CD4 count greater than 350 were randomized to continuous therapy or intermittent treatment based on CD4 count. The study was terminated prematurely because of significantly higher all-cause mortality and opportunistic diseases, as well as an unexpected increase in major cardiovascular, renal and hepatic diseases, in the treatment interruption arm [7]. These findings suggested that HIV infection per se increases cardiovascular risk independently of its treatment.

Strategies to reduce cardiovascular risk in HIV-infected patients

HIV-infected patients should be assessed regularly for cardiovascular risk factors, including obesity, smoking, hypertension, hypercholesterolemia, and diabetes. Lifestyle modification, such as smoking cessation, exercise and dietary modification is important to reduce cardiovascular risk in HIV-infected patients. Statins (e.g. pravastatin, atorvastatin, rosuvastatin) and fibrates should be used to treat hypercholesterolaemia and hypertriglyceridaemia respectively. Metformin reduces visceral fat and improves insulin sensitivity, and is recommended for patients with diabetes

and truncal obesity. Thiazolidinediones have been evaluated for treatment of lipodystrophy, but were not recommended due to inconsistent results and adverse effects on lipid profile, although it may be used to improve insulin sensitivity. Cessation of thymidine analogues, such as stavudine and zidovudine, increases limb fat. Substitution of protease inhibitors with nevirapine had been shown to improve dyslipidaemia, insulin resistance and lipodystrophy. The newer protease inhibitor, atazanavir, also has more favourable lipid profiles [6,10].

Metabolic complications are common in HIV-infected patients. Physicians should be aware of the increased cardiovascular risk and conduct appropriate interventions to screen for and treat the various metabolic conditions associated with HIV infection and its treatment.

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Journal Review

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Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA.* 2009; 301: 1231-41.

Catheter-related bloodstream infections (CRBSI), especially those associated with central venous catheters (CVCs), are a major cause of morbidity, mortality as well as cost in patients cared in intensive care units (ICUs). In order to decrease the incidence of such infections, preventive strategies, such as the use of checklists, implementation of standard practices according to guidelines and use of

antimicrobial-impregnated catheters have been employed by many centres. A recent trial looked at yet another method for prevention of CRBSI: the use of specially manufactured chlorhexidine gluconate-impregnated sponge dressings.

In this multi-center, randomized-controlled trial, a group of French investigators compared chlorhexidine dressings with standard ones, as well as routine 3-day vs. 7-day dressing changes. The trial lasted for 2 years, during which participants were recruited according to the inclusion criteria (adult ICU patients who were expected to require an arterial catheter, a central venous catheter, or both for at least 48 hours). Other forms of catheters, such as pulmonary arterial, haemodialysis, and peripherally inserted central venous catheters were not included.

A total of 1636 patients were included in the study. Use of chlorhexidine dressings was associated with a significantly lower incidence of major catheter-related infection (from 1.4 to 0.6 per 1000 catheter-days). Throughout the study period, no apparent emergence of chlorhexidine-resistant pathogens was found, and contact dermatitis occurred in 2% of participants given the chlorhexidine dressings only, compared to 1% in those given normal dressings. On the other hand, catheter colonization and infection rates were similar between the 3-day and 7-day dressing-change groups; however, the actual frequency of dressing changes differed little between groups because of the need for unplanned changes (due to soiled and leaking dressings).

Points to note: This study showed that a relatively simple intervention can significantly lower the rate of CVC-related infections even in settings where the baseline rate is already low. The observed 57% reduction in CRI incidence is very impressive and, if confirmed by larger studies, would strongly favour the use of such dressings. Although in this study the absolute risk reduction appears to be small (number needed to treat = 117), the low cost of these sponges may still allow

this intervention to be cost-effective. Further studies in this area are definitely warranted and would be awaited with much interest.

Thiel SW, Asghar MF, Micek ST, et al. Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis. Crit Care Med. 2009; 37: 819-24.

Severe sepsis and septic shock are associated with a high mortality rate worldwide. Early, goal-directed resuscitation and rapid initiation of appropriate antimicrobial therapy have proved beneficial for septic patients in trial settings, and have become the cornerstones of most sepsis treatment guidelines. However, clinician compliance to such guidelines may be suboptimal and hence could be a factor leading to poor outcomes among septic patients.

In order to improve outcomes in septic patients, investigators from a US hospital used a standardized order set for treating patients admitted with severe sepsis and septic shock, based on recommendations from the Surviving Sepsis Campaign. The order set was implemented in the whole hospital since June 2005. In a subsequent retrospective study, the researchers have compared patient care and outcomes 18 months before and 18 months after the implementation of the order-set, using a data set of 400 patients.

As compared with patients in the "before" group, those in the "after" group received significantly more intravenous fluids during the first 12 hours (mean, 1627 vs. 2054 mL), more appropriate initial antibiotic therapy (53.0% vs. 65.5%), as well as earlier antibiotic treatment (mean, 995 vs. 737 minutes). Patients in the "after" group also had significantly less need for vasopressors, lower incidences of organ failure, shorter hospital stays, and reduced in-hospital mortality rates (39.5% vs. 55.0%). Treatment before order-set implementation and higher APACHE II scores were independently associated with in-hospital mortality.

Points to note: Strict adherence to treatment protocols by clinicians appeared to be beneficial for septic patients. Due to the limitation of the study design, we cannot determine how much of this success is attributable to the implementation of the standardized order set alone. Nevertheless, this program could serve as a useful model for other hospitals and should inspire similar changes in practice in units looking after critically ill, septic patients.

Olson RP, Harrell LJ, Kaye KS. Antibiotic resistance in urinary isolates of Escherichia coli from college women with urinary tract infections. Antimicrob Agents Chemother. 2009; 53: 1285-6.

Most major treatment guidelines for uncomplicated urinary tract infections (UTIs) in women recommend use of trimethoprim-sulfamethoxazole (TMP-SMX) as the first-line treatment, unless the local *E. coli* resistance rates rise to 20% or above for this agent. Recently, due to the emergence of drug resistance among urinary bacterial isolates, this threshold has been reached (or even surpassed) in some areas of the world. In addition, increasing use of quinolones has led to escalating resistance to these agents among urinary isolates as well. Investigators from Duke University have recently conducted a study to find out the latest prevalence of drug resistance among urinary *E. coli* isolates in young women in US.

Records of over 150 college women with symptomatic UTI presenting to a student health clinic, with urine cultures positive for *E. coli*, were retrospectively reviewed for the 2 year period spanning 2005 to 2007. Antibiotic susceptibilities of the women's isolates were compared with those of all urinary *E. coli* isolates from the Duke Medical System during the same period (n=10,289). Ampicillin and TMP-SMX resistance rates in the female students' isolates — 37% and 30%, respectively — were similar to those seen in the health-system isolates.

Ciprofloxacin-resistant strains were found in 7% of the female students' isolates (20% in the health-system isolates), and was more frequently encountered in those with previous UTIs. On the other hand, nitrofurantoin resistance was found in none of the students' isolates and in only 3% of the health-system isolates.

Points to note: Limited by its retrospective design, this study included only patients who had urine cultures and sensitivity tests performed (i.e. more likely to be from those cases failing empirical therapy), and hence it was possible that the resistance rates were probably somewhat overestimated. The results seemed to suggest that TMP-SMX is no longer suitable for use as first-line empirical therapy for uncomplicated UTIs in young women, due to the high resistance rate observed to this agent. The authors suggested that nitrofurantoin should be considered as a first-line empirical treatment, whereas ciprofloxacin might be appropriate for use in women with no previous history of UTIs. It remains to be seen whether these recommendations are equally applicable to the local community setting; further studies would definitely be required in this area before such conclusions could be drawn.