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1375 8.7.6 Talaromyces (Penicillium) marneffei infection more commonly in individuals who have prior exposure. There is con- flicting evidence as to whether DHPS mutations are associated with poor outcomes (failure to respond to co-trimoxazole, or death) from PCP. Drug toxicity remains the biggest issue in the treatment of PCP, particularly with co-trimoxazole therapy. Novel treatment regimens with reduced toxicity would be clinically useful. Caspofungin (and the other echinocandins) have been shown in animal models to be fungistatic. In a mouse model of PCP a combination of caspofungin together with low dose co-trimoxazole (at a dose normally used for prophylaxis) was more effective than high-dose co-trimoxzole alone. Preliminary data in humans suggests a combination of caspofungin with low dose co-trimoxazole is clinically effective and is associated with a low incidence of co-trimoxazole-associated adverse events. Rtt109 is a fungus-specific histone acetyltransferase, recently charac- terized in Pneumocystis jirovecii. This protein plays a significant role in the virulence of pathogenic fungi by reducing genomic instability; Rtt109-knockout strains have significantly attenuated pathogenesis in animal models. This provides an attractive molecular target for future drug development. FURTHER READING Carmona EM, Limper AH (2011). Update on the diagnosis and treatment of Pneumocystis pneumonia. Ther Adv Respir Dis, 5, 41–59. Miller RF, Huang L, Walzer PD (2013). Pneumocystis pneumonia as- sociated with human immunodeficiency virus. Clin Chest Med, 34, 229–41. Morris A, et al. (2004). Current epidemiology of Pneumocystis pneu- monia. Emerg Infect Dis, 10, 1713–20. National Institutes of Health, AIDSinfo (2013). Guidelines for preven tion and treatment of opportunistic infections in HIV-infected adults and adolescents, 2013. http://www.aidsinfo.nih.gov Redhead SA, et al. (2006). Pneumocystis and Trypanosoma cruzi: no- menclature and typifications. J Eukaryot Microbiol, 53,

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 disease is significantly more likely to occur in the rainy season, suggesting that there may be an expansion of the environment reservoirs with favourable conditions for growth during these rainy months. In endemic areas, it is likely that a certain proportion of the population is infected, but remains asymptomatic. Patients have been reported with long periods of asymptomatic infection before presentation with clinical T. marneffei infection. In other cases, the clinical manifestation of T. marneffei infection occurred within weeks of exposure to the fungus. A study from Vietnam using a mathematical model estimated that the incubation period of this fungal infection was approximately 1 week. Clinical features Most patients with T. marneffei infection have already been in- fected with HIV and usually present late in the course of the HIV disease. The patient’s CD4+ cell count at presentation is typically 100 cells/µl or

less. Commonly, they present with symptoms and signs of infection of the reticuloendothelial system. These include fever, chills, lymphadenopathy, hepatomegaly, and splenomegaly. Cough, dyspnoea, and lung crepitations may be present. Other manifestations are secondary to dissemination of the fungus via the bloodstream. Cutaneous and subcutaneous lesions are observed in up to 80% of the patients. As in other systemic mycoses, such as histoplasmosis or paracoccidioidomycosis, skin lesions resemble molluscum contagiosum. (Fig. 8.7.6.1). They may break down and bleed (Fig. 8.7.6.2) while some larger lesions become in- durated and appear infarcted. Mucosal and palatal lesions are also seen (Fig. 8.7.6.3). Arthritis and osteomyelitis are not uncommon. Cases with mesenteric lymphangitis, colitis, genital or oropharyn- geal ulcer, retropharyngeal abscess, brain abscess, or pericarditis have been reported. HIV-negative immunocompromised patients with T. marneffei infection are less likely to have fever, splenomegaly, unbilicated skin lesions, and fungaemia, but more likely to have bone and joint infec- tions, with a longer duration of illness before the diagnosis can be made. Subcutaneous nodules, with or without subsequent abscess formation, are more commonly seen. Biochemical and haematological laboratory findings are non- specific and include elevation of liver enzymes, anaemia, and leucocytosis. The chest radiograph may show diffuse interstitial, localized alveolar, or diffuse alveolar infiltrates. Cases with chest radiographs showing cavitary lesions or lung masses have been re- ported (Fig. 8.7.6.4). Fig. 8.7.6.1 T. marneffei in an HIV-infected Thai patient: typical molluscum-like lesions. Copyright G. Watt, Bangkok, Thailand. Fig. 8.7.6.2 Bleeding into T. marneffei skin lesions. Copyright D. Walsh. Fig. 8.7.6.3 T. marneffei palatal lesions. Copyright D. Walsh.

1377 Diagnosis Diagnosis depends on familiarity with the clinical syndrome and a high index of suspicion. Presumptive diagnosis can be simply made by microscopic examination of Wright-stained samples of bone marrow aspirate, touch smears of the skin biopsy specimen, and/ or the lymph-node biopsy specimen. Many intracellular and extra- cellular basophilic, spherical, oval, and elliptical yeast cells can be seen with this technique, some of which have clear central septation, a characteristic feature of T. marneffei (Fig. 8.7.6.5). The diagnosis is confirmed by histopathological sections and/or by culturing the fungus from the blood, skin biopsy specimens, bone marrow, or lymph nodes. Cases of T. marneffei infection can clinically resemble tuberculosis, histoplasmosis, and cryptococcosis. Tests to detect the antibody or antigen of T. marneffei as well as tests based on the polymerase chain reaction have been developed. Clinical trials are needed to show their usefulness in the diagnosis of active T. marnef fei infection and in predicting relapses. They might also be used to identify HIV-infected individuals who are infected with T. marnef fei but are still asymptomatic. These individuals might then benefit from pre-emptive treatment with an antifungal agent. Treatment T. marneffei infection is a potentially fatal disease. The mortality rate is high in patients with delayed diagnoses. The fungus is sensitive to azoles, flucytosine, and amphotericin B. Among azoles, the fungus is sensitive to ketoconazole, miconazole, and itraconazole, but less sensitive to fluconazole. In HIV-infected patients, the recommended Fig. 8.7.6.4 Pulmonary lesion in an HIV-infected patient from Hong Kong. Copyright D. A. Warrell. (a) (b) Fig. 8.7.6.5 Microscopic appearance of T. marneffei yeasts in (a) skin biopsy and (b) bone marrow aspirate, showing characteristic septation. Copyright Thira Sirisanthana. 8.7.6 Talaromyces (Penicillium) marneffei infection

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