Penicillium marneffei infection and solitary pulmonary nodule

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We report on a patient infected with human immunodeficiency virus who presented with fever, a solitary pulmonary nodule, and cervical lymphadenopathy. The diagnosis of *Penicillium marneffei* infection was made from an excisional lymph node biopsy and a sputum culture. The microbiology, pathology, diagnosis, and treatment of the case are discussed. A high level of clinical suspicion is necessary for making an early diagnosis and improving the outcome of infection.

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Key words: AIDS-related opportunistic infections; Antifungal agents; Coin lesion, pulmonary; HIV infections/ complications; Penicillium marneffei

Introduction

Penicillium marneffei infection is increasingly being recognised as a threat to patients infected with human immunodeficiency virus (HIV) who come from or have visited endemic areas of south-east Asia. Pulmonary involvement is common but the occurrence of a solitary pulmonary nodule has not been reported previously.

Case report

A 36-year-old Chinese male factory worker attended the Chest Clinic at Ruttonjee Hospital on 19 September 1996. He complained of having had a productive cough for 1 month, during which he had suffered fever and a weight loss of about 10 kg. Chest radiography showed a solitary, left mid-zone opacity (Fig 1a). He was immediately hospitalised for further investigation.

He gave a history of sexual contact with prostitutes in Macau 10 years previously and had been married to a Thai woman for 3 years. He claimed that his HIV antibody status had been checked in Hong Kong about 2 years previously, and had been found to be negative.

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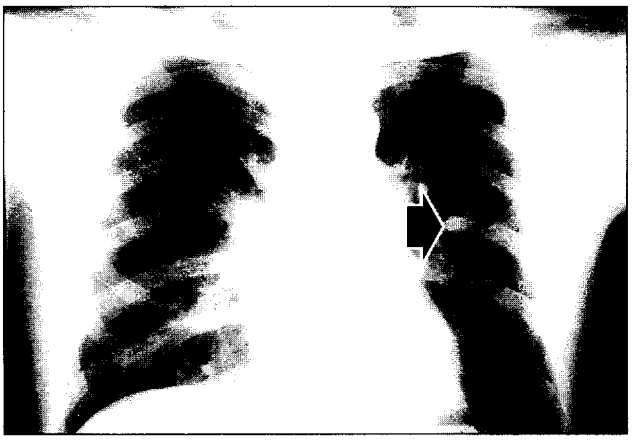
Physical examination revealed pallor, seborrhoeic dermatitis over the forehead and a 1.5-cm diameter, firm, left supraclavicular lymph node. There was no other palpable lymph node and no hepatomegaly or splenomegaly. He had a high spiking fever with a temperature of approximately 39°C. The initial blood count was as follows: haemoglobin level 88 g/L (normal range, male, 140-180 g/L); white blood cells 4.08 x 10^9/L; platelets 143 x 10^9/L; and lymphocytes 0.51 x 10^9/L. Blood, urine, and sputum were negative for bacterial culture. Empirical treatment with a third generation cephalosporin and aminoglycoside was given; there was a good clinical response.

Fibre-optic bronchoscopy with bronchial aspiration, and transbronchial biopsy of the superior segment of the lingula (without X-ray guidance) gave no diagnostic information. Computed tomography of the thorax revealed a solitary mass of 1 to 2 cm in diameter at the periphery of the lingula (Fig 1b). There was no hilar or mediastinal lymphadenopathy. Fine needle aspiration of the lymph node did not aid pathological diagnosis.

Serological tests for cytomegalovirus, toxoplasma, and *P. marneffei* were all negative. The test for HIV antibody, however, was positive; the CD4 count was 42/μL (normal range, 384-1178/μL). Excisional biopsy of the left supraclavicular lymph node was done at this point, and he was discharged in satisfactory condition and given cotrimoxazole as primary prophylaxis against *Pneumocystis carinii*.

A few days later, the patient was readmitted to hospital; he had a spiking fever, a temperature of about

1a.



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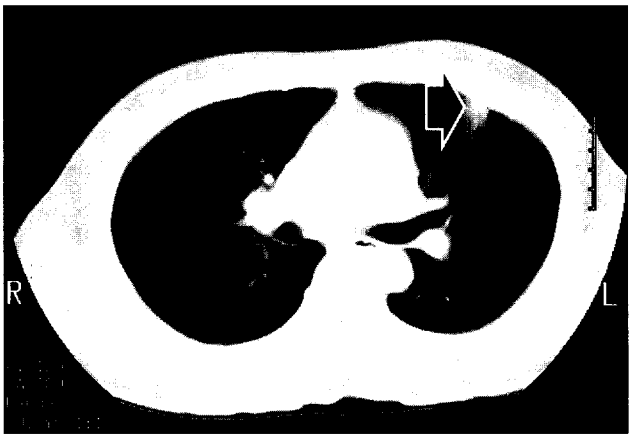


Fig 1. Solitary pulmonary nodule, as dected by chest radiography and computed tomography
(1a) chest radiograph showing a left mid-zone opacity (arrow); (1b) computed tomography of thorax showing a mass of 1 to 2 cm in diameter at the periphery of the lingula (arrow)

38.5°C, chills, and rigors. Blood investigations were as follows: haemoglobin level 84 g/L; white blood cell count 4.45 x 10^9/L; platelet count 167 x 10^9/L; lymphocyte count 0.21 x 10^9/L; serum urea 7.0 mmol/L (normal range, 3.0-6.5 mmol/L); and serum creatinine 149 μmol/L (normal range, 50-110 μmol/L). Chest radiography detected little change. A third generation cephalosporin was again given after sepsis work-up. At the same time, the histology of the excised biopsy of the left supraclavicular lymph node established a diagnosis of *P. marneffei* infection. An infusion of amphotericin B 0.5 mg/kg/day was started. Unfortunately, his condition deteriorated very rapidly, and he died just 1 day after readmission. Post-mortem examination was not done. Blood culture was negative for any organism. However, sputum culture for fungus, taken at the time of readmission grew *P. marneffei*.

Discussion

Penicillium marneffei is a thermally dimorphic fungus that is endemic in south-east Asia; it can cause deep-seated infection in both immunocompromised and apparently immunocompetent hosts. Before the HIV epidemic, *P. marneffei* infection was rare, and two thirds of cases occurred in otherwise healthy hosts. It is now, however, recognised as an additional threat to people with acquired immune deficiency syndrome in south-east Asia, particularly those in northern Thailand. After being substantiated by epidemiological evidence, *P. marneffei* infection was included on the list of diseases defining acquired immune deficiency syndrome in south-east Asia, including Hong Kong.[1]

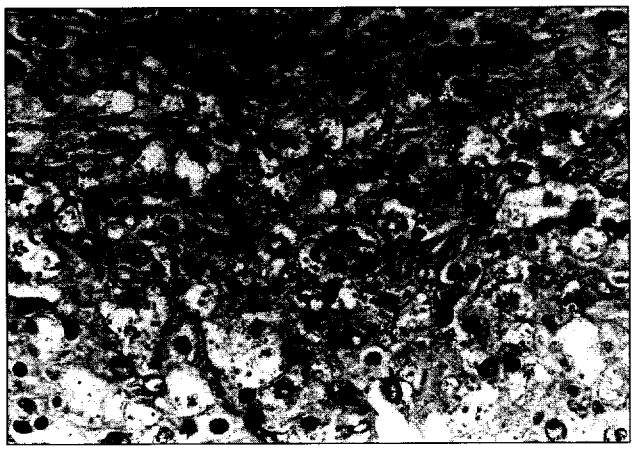
The natural source is not certain, but natural infection has been described in bamboo rats and humans[3]; infection has not been reported in other species. The portal of entry is also unknown, but both the respiratory and gastrointestinal tracts have been implicated.

Penicillium marneffei is the only species of *Penicillium* to exhibit thermal dimorphism. While it exists in the mould form at room temperature (about 25°C), it assumes the yeast form at 37°C. In the yeast form, it multiplies by fission rather than by budding; the septa can be demonstrated by staining with a methenamine-silver preparation (Fig 2b). This particular characteristic distinguishes *P. marneffei* from *Histoplasma capsulatum*, which closely mimics *P. marneffei* morphologically and histologically, and which may also cause disseminated infection.[2]

The fungus can cause three histopathological reactions in the host, namely granulomatous, suppurative, and anergic and necrotising reactions.[3] The first two responses are seen in immunocompetent hosts. In contrast, the anergic and necrotising reaction predominates in immunocompromised patients and is characterised by an association with focal necrosis, and a diffuse infiltration of histiocytes that are distended due to the proliferating fungi. Such a reaction was shown in the sections from the patient's excised lymph node (Fig 2).

Penicillium marneffei is notorious for its propensity to infect the lungs and reticuloendothelial system, and to proliferate within histiocytes.[3] In immunocompromised hosts, disseminated infection usually involves the lung, lymph nodes, liver, spleen, lung, intestine, bone marrow, and skin.[2] The most common clinical manifestations of infection with this fungus in HIV-infected patients are fever, anaemia, marked weight loss, skin lesions, cough, hepatomegaly, and lymph-

2a.



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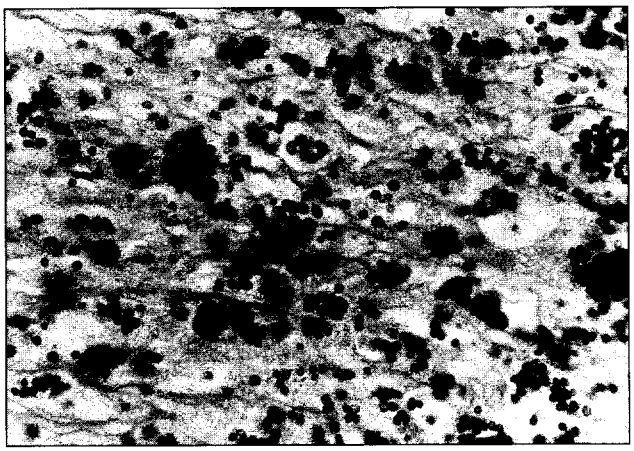

Fig 2. Sections from the excised left supraclavicular lymph node showing total effacement of architecture by sheets of histiocytes
Clusters of yeast-like organisms are present inside and outside the histiocytes. Reproduction by fission, and thick central septa can be seen focally. (2a) H&E, x400; (2b) Grocott, ie methenamine-silver preparation, x400

adenopathy.[4] The CD4 count at presentation is commonly below 100/μL[5]; such was the case presented here. Lymphadenopathy occurs in about 40% of patients[6]; positive cultures from lymph node specimens are obtained in about 8% of cases.[6] Skin lesions are usually generalised papular rashes that are mainly distributed over the face, upper trunk, and arms. Central necrotic umbilication may occur in some papules, thus mimicking *Molluscum contagiosum* infection. In the present case, the only skin lesion identified was seborrhoeic dermatitis. Skin scrapings were not tested for fungus cultures.

The following forms of lung involvement have been described from radiographic findings: diffuse reticulonodular infiltration, localised interstitial infiltration, localised alveolar infiltration,[4] discrete interstitial infiltrate in the lung base, and discrete bilateral interstitial infiltrates.[6] These parallel the histological descriptions of interstitial and alveolar involvement in some autopsy findings.[2] In the present case, the chest radiograph showed a solitary nodule in the lingula; such a finding has not been described previously. Although there was no histological confirmation from the lung nodule, the isolation of *P. marneffei* from the sputum strongly suggested the cause of death.

Penicillium marneffei can be identified in biopsies of lymph node, bone marrow, liver, respiratory tract, and skin. It can also be isolated from blood, urine, stool, sputum, and skin scrapings. Culturing of *P. marneffei* requires special culture medium and thus the identification of this fungus will be missed by conventional bacterial culture. In our case, the sputum was sent specifically for culture of *P. marneffei* in Sabouraud medium after the identification of the fungus in the section of excised lymph node; this was the only organism cultured. Diagnostic difficulty thus tends to occur because of the lack of clinical and pathological awareness and suspicion rather than a technical problem.

Although the clinical features are by no means specific, the clinical combination of HIV infection, residence in south-east Asia, fever, lung disease, and cervical lymphadenopathy should prompt the clinician to test for *P. marneffei* infection. Early diagnosis is crucial because the infection is fatal if untreated. Most cases show a favourable initial response to treatment with amphotericin B or itraconazole[6] although mortality has been high for those who present within 3 months of the diagnosis of HIV infection,[5] as in the present case. Maintenance therapy with antifungal agents such as itraconazole and fluconazole is necessary to prevent relapse in an immunocompromised patient.

Penicillium marneffei is posing an increasing threat to HIV-infected patients. A higher level of suspicion for infection by this fungus is thus necessary to ameliorate the morbidity and mortality caused by infection with this pathogen.

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