CASE REPORT

Penicillium Marneffei Infection in a Non Aids Patient: First Case Report from Malaysia

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Summary

Penicillium marneffei, a dimorphic fungus is a rare opportunistic pathogen. It is known to cause infection in immunocompromised patients and recently its occurrence in AIDS patients has been well-documented[1-3]. Disease with *Penicillium marneffei* is even rarer among previously healthy individuals. The disease is endemic in Southeast Asia and China. Recognition of this rare disease is important because it is amenable to treatment. We report a case of *P. marneffei* infection in a previously healthy individual.

Key Words: *Penicillium marneffei*, HIV, Fluconazole

Case report

A 48 year old vegetable farmer was admitted to the Hospital Kuala Lumpur (HKL) on 6th July 1995 for complaints of one month history of fever, persistent non-productive cough, lethargy and loss of 6kg of weight. One week prior to that, she had been thoroughly investigated in a private centre. Medical investigation carried out there showed that her haemoglobin was 12.2g/L, total white count 24,300/ml, with an ESR of 119mm/hr. Urine culture grew Escherichia coli. Her chest radiograph was normal but computerised axial tomography showed multiple small lymph glands at the right apex and irregular lesion in the right upper zone extending from the right hilar region. This feature was suggestive of bronchial carcinoma. She also had an enlarged lymph node in the right supraclavicular region that was biopsied but the histopathological findings was consistent with acute suppurative lymphadenitis.

On admission to HKL, she was noted to have multiple skin coloured nodular cutaneous lesions about 1cm in diameter with central ulceration and necrosis distributed on both forearms. Some lesions were pustular. There was persistent exudation of pus at her previous lymph node incision site. Clinical examination of the gastrointestinal and neurological systems were essentially normal and further investigations were done. Mantoux test was negative and repeat chest radiograph showed left pleural effusion with consolidation of the right upper zone and cardiomegaly. Echocardiogram showed pleural effusion with no evidence of vegetations on the heart valves. Her erythrocyte sedimentation rate was persistently elevated at >100mm/hr but her connective tissue disease screening tests for rheumatoid factor and antinuclear factor were negative. Bronchoscopy showed an ulcerated polypoidal masses over the proximal right main bronchus with contact bleeding and a small lesion at the anterior segment of right upper lobe. Biopsy and histological examination of the right apical segment showed scanty fibrous tissue with clumps of hyperplastic bronchial epithelial cells and infiltrates of polymorphonuclear cells. Biopsy and histological examination of the tracheal lesion showed fragments of mucosal tissue showing metaplastic squamous epithelium and dense infiltrates of plasma cells, lymphocytes and polymorphs in the subepithelial stroma. These features were consistent with a non-specific chronic inflammatory process and there was no evidence of malignancy. Skin biopsy of one on the

nodular lesions with central ulceration and necrosis on the dorsum of the right forearm showed only perivascular lymphocytic infiltrates and methenamine silver stain for fungus was negative.

The patient was started empirically on anti-tuberculous treatment consisting of rifampicin 600mg/day, isoniazid 400mg/day and pyrazinamide 2g/day. After two weeks of antituberculous treatment, she was still febrile and continued to lose weight (from 88kg to 81kg). Her hemoglobin dropped further to 9g/L. Her previous lymph node biopsy site was still not healed and its culture grew *Pseudomonas* species. Ultrasonography of the abdomen was essentially normal. Technetium bone scan showed increased uptake involving the skull, clavicle, humerus, iliac crest and femur.

She was then started on high dose intravenous ceftazidime 3g twice a day as empirical treatment for melioidosis on 24th July 1995. However the serological titer for melioidosis was less than 40 units and hence not suggestive of acute melioidosis. Three weeks later she requested discharge from the hospital, despite still having a low grade temperature and minimal clinical improvement. The previous supraclavicular biopsy site was healing at this time and she was discharged with anti-tuberculous treatment and doxycycline 100mg twice daily.

Five weeks after discharge, in September 1995, she was readmitted with an abscess in the left gluteal region and 170cc of pus was drained but no organism was identified on culture. Further bronchoscopy was done and showed similar findings as previously. She was recommenced on intravenous ceftazidime 2g thrice daily. However, based on isolation of *Candida* from the urine she was given intravenous fluconazole 200mg daily for 3 days and continued on oral fluconazole 200mg twice daily for the next 7 days. She became a febrile and well and was discharged two weeks later with further anti-tuberculous treatment and cotrimoxazole 4mg twice daily. Further follow up in the clinic showed clinical improvement, she was putting on weight (from 68 to 73kg) and her chest radiograph was clear.

However, in January 1996 she was readmitted with fever and weight loss (from 73 to 65kg) and developed even more abscesses in the submental region, right supraclavicular fossa and left scalp. This time repeat biopsy of the lymph node in the right supraclavicular region done on 16th February 1996 grew filamentous fungi of *P.marneffei* and similar organisms was also isolated from the scalp abscess. She was then commenced on intravenous amphotericin B and itraconazole 200mg twice daily. While in the ward she had repeated episodes of *Klebsiella* septicaemia through an infected Hickman catheter used for administration of amphotericin. The catheter was later removed. Since then she remained afebrile and her abscesses cleared. Repeat bone scan showed improvement. She was discharged from the ward two months later after receiving a total dose of 1.3g of amphotericin and itraconazole was continued at 200mg twice daily for a complete six months. Enumeration of T and B cells for her blood showed normal T and B cells and normal CD4 and CD8 count. Blood test for HIV was repeatedly done and was negative. Since then, for the past two years she has been on regular clinic follow up and has been well.

Mycological Examination

The lymph node biopsy was inoculated onto Sabourauds dextrose agar (SDA) with 0.5% chloramphenicol and incubated at room temperature. Mold like colonies appeared which after 2 weeks produced red pigment that diffuses into the medium. Microscopically the colonies consist of septate branched hyphae with lateral and terminal conidiophores. The conidiophores have basal stipes and terminal verticils of three to five metulae. The metulae bear four to seven phialides each of which produces long basipetal unbranched chains of conidia. These are features characteristic of *P.marneffei*.

Discussion

P.marneffei is a rare pathogen that infects even healthy subjects[1]. It was first isolated from the bamboo rat in 1959. The first reported human case was produced by accidental inoculation of the finger[1]. Disease with this

organism has been rare until a recent report of *P.marneffei* infection in 86 HIV infected patients between June 1990 and June 1992 by Supparatpinyo[2] and during that period he identified only one case in a non-HIV infected patient. This disease is indeed very rare in a healthy individual. The common clinical manifestations are fever, weight loss, cough, diarrhea, anemia, lymphadenopathy and cutaneous abscesses. Specific cutaneous lesions are papules or nodules with central necrotic umbilication not unlike that of *Molluscum contagiosum*. A simple rapid diagnosis can be made from smears made from cutaneous lesions or bone marrow aspirate stained with methenamine-silver that shows yeast-like organism characteristic of *P.marneffei* engulfed in macrophages. The organism is confirmed by culture and microscopic characteristics.

P.marneffei cause two clinical types of disease: focal infection and fatal progressive, disseminated infection. There are however, three distinctive tissue reactions to *P.marneffei* infection: granulomatous, suppurative and anergic with necrosis. The granulomatous pattern consists of epithelioid granulomas with multinucleated giant cells where the organism is usually sparse and difficult to demonstrate. The second pattern, as demonstrated by our patient, is suppuration which is a reaction by neutrophils and fibrin to the yeast cells. This is common in the lung, skin and subcutaneous tissue. Both these patterns of infection are seen in healthy individuals. The anergic and necrotising reaction is characterized by a diffuse infiltrate of histiocytes distended by proliferating intracellular fungi and focal necrosis. This progressive and disseminated infection is typically seen in immunocompromised patients. It seems likely that a defect in cell-mediated immunity with a decrease of effective peripheral T-helper lymphocytes is responsible for this.

Up to now there is no data available about the transmission to man, but it seems likely that cough and diarrhea is due to direct inhalation and ingestion respectively. The innoculative route is also a possibility since this organism is found in the soil as maybe the case in our patient who was a farmer. Amphotericin and itraconazole have been shown to be effective in the treatment of *P.marneffei* infection[3]. Our patient showed an initial response when given fluconazole for 10 days for candidaemia; however, relapse occurred because of inadequate treatment for *P.marneffei.*

Conclusion

P.marneffei infection is endemic in Southeast Asia and is perhaps underdiagnosed. Without a high clinical index of suspicion, it maybe missed. Not only are immunocompromised patients at risk but healthy individual with occupational exposure may else be infected. Cure can be expected with early appropriate treatment especially in a previously healthy individual.

References

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