Hepatic Penicilliosis in Patients Without Skin Lesions

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Penicillium marneffei is a fungal pathogen endemic to Southeast Asia [1–6]. Disseminated penicilliosis is the third most common opportunistic infection of patients with AIDS in northern Thailand and is a serious systemic illness [3]. Characteristic organisms are easily recognized in touch-smear specimens from the typical skin lesions [3], which occur in up to 80% of cases [4]. Most cases that are diagnosed early respond to treatment, but prompt diagnosis is difficult in cases without skin lesions. The mortality rate is high among undiagnosed cases [3]. We describe six patients with a characteristic clinical syndrome of hepatic penicilliosis in the hope that raised awareness will lead to earlier diagnosis of this treatable infection.

Patients and Methods

Patients. An index case of hepatic penicilliosis was seen by one of the authors (P.K.). Medical records of patients without skin lesions whose blood cultures had yielded P. marneffei were then reviewed to determine if additional cases of hepatic penicilliosis had occurred in our hospital. A prospective search for hepatic penicilliosis was conducted by screening febrile inpatients known to be infected by HIV who had neither skin lesions nor known or suspected opportunistic infections other than penicilliosis.

Penicilliosis and HIV detection. Penicilliosis was confirmed by isolation of P. marneffei from the blood and/or liver. The mycelial form of P. marneffei produces a diffuse, characteristic red pigment when cultured on Sabouraud dextrose agar at 25°C. Liver biopsy specimens stained with Grocott’s methenamine silver were examined for yeasts showing characteristic septate morphology. Sera were assayed for antibody to HIV by commercially available ELISA kits (Enzygnost Anti-HIV 1/2 [Behring, Marburg, Germany] and/or Genelavia Mixt [Sanofi Diagnostics Pasteur, Marnes-la Coquette, France] and/or Serodia-HIV [Fujirebio, Tokyo]).

Patients with positive reactions on two of these tests were considered HIV infected. Confirmatory testing by western blotting is performed at the study hospital only when the results from two commercial ELISAs are discordant or when risk factors for HIV are absent; thus, such testing was not required for the patients described herein. CD4 cells were measured in the index case by direct immunofluorescence with monoclonal antibodies of the T series (Becton Dickinson, Mountain View, CA) and flow cytometry (FACScan with SimulSet software; Becton Dickinson).

Results

Cases. The index case was a 25-year-old man who presented with high-grade fever and abdominal pain of 5 days’ duration.
The liver was tender and enlarged; no skin lesions were observed. An HIV screening test was reactive. The serum alkaline phosphatase level of 527 IU/L was accompanied by minimal elevations of transaminase and bilirubin levels. An abdominal ultrasonogram demonstrated moderate hepatic enlargement without either space-occupying lesions or bile duct dilatation.

Routine investigations failed to identify the cause of fever, and broad-spectrum antibiotic therapy was begun. However, the patient became increasingly toxic, the liver increased in size and tenderness, and the serum alkaline phosphatase level rose to 1,245 IU/L on the 10th hospital day. *P. marneffei* was eventually cultured from blood. Only 15 medical records contained sufficient information to allow retrospective analysis, and 2 cases of hepatic penicilliosis were identified from these 15 records. A further three patients were identified by prospectively screening HIV seropositive inpatients with fever of unclear etiology.

**Clinical and laboratory findings.** The six patients all presented with fever of recent onset, abdominal pain, and hepatomegaly. The median age of the four men and two women was 25 years, and the age range was 21–29 years. The median maximum serum alkaline phosphatase level was 1,245 IU, and these levels ranged from 758 IU to 1,467 IU. *P. marneffei* was isolated from the blood of all six patients and from the liver of one. Large numbers of characteristic septate yeasts were visible in the two liver biopsy specimens (figure 1).

Two patients died and one left the hospital against medical advice before blood culture results were known. Follow-up information was available on only two of the three patients who were discharged. The index case received inpatient treatment with amphotericin B, followed by maintenance therapy with itraconazole, and recovered gradually. Abdominal ultrasonography at 9 months confirmed that the liver size had returned to normal.

Two years after the beginning of treatment, serum alkaline phosphatase levels had returned to normal and there were no signs of active penicilliosis. The results of three separate CD4 cell count determinations ranged from zero to 20/mm³. Follow-up information was also available on one additional patient. This 25-year-old man responded well to treatment and was asymptomatic when last examined, 6 months after beginning treatment.

**Discussion**

The AIDS pandemic has been accompanied by a marked increase in the incidence of penicilliosis in northern Thailand. No *P. marneffei* infections had been diagnosed at Chiangrai Regional Hospital (Chiangrai, Thailand) prior to 1990, but 144 culture-proven cases of penicilliosis were seen between March 1995 and March 1996 (P. Kantipong, unpublished data). Hepatic penicilliosis is only one of the protean manifestations of *P. marneffei* infection [5], but its distinctive manifestations identify a subgroup of patients who can benefit from prompt diagnosis and curative therapy.

A rapid diagnostic test for penicilliosis is lacking, and antifungal therapy is often delayed because of the wait for microbiological or histopathologic results [3]. Two (33%) of our patients died before blood cultures had become positive. Tuberculosis is a common opportunistic infection at the study hospital, but mycobacteria have never been found in liver biopsy specimens obtained from patients with signs and symptoms of hepatic penicilliosis.

We now begin antifungal therapy while awaiting confirmatory test results for those AIDS patients suspected of having *P. marneffei* infection of the liver in whom no other cause of fever can be identified. However, other pathogens may be more important causes of hepatic disease in HIV-infected patients elsewhere, and management of such cases will vary [7, 8]. Although *P. marneffei* is predominantly an Asian pathogen, as a result of international travel the need for increased awareness of penicilliosis is worldwide [4].

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**References**

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