Fatal *Penicillium citrinum* Pneumonia with Pericarditis in a Patient with Acute Leukemia


Department of Clinical Oncology, Department of Microbiology, and Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China, and Mycology Unit, Department of Microbiology, Women’s and Children’s Hospital, Adelaide, South Australia, Australia

Received 18 March 1997/Returned for modification 10 May 1997/Accepted 1 July 1997

We report here a case of fatal *Penicillium citrinum* infection. The patient, who suffered from acute myeloid leukemia, developed signs and symptoms typical of fungal pneumonia and pericardial tamponade after undergoing standard induction chemotherapy. Despite attaining complete remission of her leukemia, the patient succumbed 8 weeks after presentation. At autopsy, multiple nodular cavitory pulmonary lesions with invasion by fungal hyphae were found. Pericardial and lung tissue obtained at autopsy grew *P. citrinum*, a fungus ubiquitous in the environment but seldom reported as a pathogen. The microbiological findings were consistent with the histopathological features and confirmed this as a case of true *P. citrinum* infection causing fatal pulmonary and pericardial complications in an immunocompromised host.

Among the 200,000 known fungal species, only 270 have been reported to be pathogenic in humans (11). With the AIDS pandemic and the increasing use of myelosuppressive cytotoxic chemotherapy, the number of patients susceptible to opportunistic fungal infections is rising. Although *Penicillium citrinum* is a fungus recognized to be ubiquitous in the environment, it has only rarely been reported as a cause of human infection. Review of the literature revealed only eight cases of mycotic keratitis (4) with single reports of urinary tract infection (3) and pneumonia (8). We report here a fatal case of *P. citrinum* pneumonia with pericarditis and massive pericardial effusion.

**Case report.** A 69-year-old Chinese woman developed fatigue, fever, anorexia, and gum bleeding during a visit to California in July 1996 and was diagnosed as having an acute leukemia. She returned to Hong Kong, where on admission to our hospital she was found to be febrile, with a temperature of 38.8°C. Blood cultures were negative. Her fever responded after 5 days to intravenous ceftazidime, teicoplanin, and amphotericin B. A diagnosis of acute myeloid leukemia (FAB subtype M5b) was confirmed, and the patient then commenced induction chemotherapy consisting of mitoxantrone and cytosine arabinoside. She tolerated chemotherapy well and remained on antimicrobials including amphotericin B until discharge on day 10 following the commencement of induction therapy. On day 14, she returned with fever and cough. Chest X-ray showed bilateral multiple patchy infiltrates. Routine sputum culture on admission grew only oral flora. She was absolutely neutropenic with a total leucocyte count of 0.3 × 10⁹/liter. Empirical antimicrobial therapy, commenced initially with netilmicin and piperacillin, was changed to ceftazidime, teicoplanin, and amphotericin B with resolution of the fever within 72 h. On day 18, she developed sudden onset of chest pain and shortness of breath, and an electrocardiogram and echocardiogram supported a clinical diagnosis of acute pericarditis associated with a small pericardial effusion. Seven days later, the patient was afibrile, the chest X-ray showed significant improvement, and the leucocyte count had increased to 3.1 × 10⁹/liter with a normal differential and no evidence of leukemic blasts. She was discharged home in good condition on oral flucanazole. In a follow-up sputum culture sent just prior to discharge on day 26, a single colony of *Conidiobolus incongruus* was identified, but the primary plate had then been overgrown by a *Penicillium* species. On day 47, she was readmitted with massive pericardial effusion, and a pericardial window was performed. Histological examination of the pericardium showed chronic inflammation and fibrosis. The cytology of the pericardial fluid showed a mixture of polymorphonuclear leucocytes, lymphocytes, and reactive mesothelial cells, but culture was negative. In light of the clinical findings and sputum culture result, a diagnosis of fungal pneumonia and pericarditis was made, and the patient was treated with amphotericin B and itraconazole in addition to broad-spectrum antibiotics. She remained stable and afibrile until day 58 postchemotherapy, when she suffered an unexpected cardiac arrest. Resuscitation was unsuccessful. An autopsy was performed.

**Autopsy findings.** A total of 200 ml of lightly bloodstained pleural fluid was present in each hemithorax. Cut sections of both lungs revealed multiple nodular cavitory parenchymal lesions, measuring 0.5 to 2.0 cm. Histological sections stained with periodic acid-Schiff stain (PAS) and Grocott methenamine silver showed numerous branching hyphae surrounded by supplicative granulomatous inflammation; the hyphae were septate with acute angle branching of 30 to 45° (Fig. 1). Ziehl-Neelsen and Gram stains were negative. Foci showing extension to adjacent pulmonary vascular branches were seen, but the lesions were not angiocentric. No mycotic emboli could be identified. A few small wedge-shaped peripheral infarcts were present, which could have been secondary to small pulmonary thrombo-emboli originating from the popliteal and tibial veins, which were filled with thrombi. The pericardium was thickened, adherent to the epicardium, and covered by fibrous exudate. The myocardium and endocardium were unremarkable. Microscopic examination confirmed resolving pericarditis with fibrinous exudate and granulation tissue, and special stains (PAS, Grocott, Gram, and Ziehl-Neelsen) did not reveal...
any fungal or other infectious organisms. Other organs including the central nervous system, liver, spleen, and lymph nodes showed no signs of infiltration, inflammation, or fungal infection. Bone marrow sections showed no evidence of residual leukemia.

**Mycology.** A single colony of a rapidly growing mold was cultured on Sabouraud dextrose agar (SDA) at 30°C from the sputum specimen obtained on day 26. The colony was initially white and waxy and then became powdery and radially folded. Pyriform conidia, measuring 20 by 30 μm, with single, pointed basal papillae were present. These were subcultured onto SDA but did not develop villi with prolonged incubation, and the species was identified as *C. incongruus*. The primary sputum culture plates had become overgrown by a *Penicillium* species, and the colony was identified as *P. citrinum* and sent to a reference laboratory (Mycology Unit, Women’s and Children’s Hospital, Adelaide, Australia), where this identification was confirmed according to the protocol of Pitt (10).

Antifungal sensitivity testing by E test (AB Biodisk, Solna, Sweden) on Casitone extract agar revealed that the postmortem *P. citrinum* isolate demonstrated marked in vitro resistance to amphotericin B, itraconazole, fluconazole, and 5-flucytosine with MICs of >32 μg/ml (no zones of inhibition present) and a ketoconazole MIC of 1 μg/ml.

**Discussion.** Members of the genus *Penicillium* are abundant in the environment, rarely cause disease in humans, and are encountered most commonly in the clinical laboratory as culture contaminants. A true infection can be established only by histological demonstration of tissue invasion (7). Apart from the reports of *P. citrinum* infections referred to in the introduction (3, 4, 8), other *Penicillium* species associated with infections in humans include *P. chrysogenum*, causing necro-
mised patients are now relatively common. It is not surprising, therefore, that fungi of low pathogenicity are increasingly being identified as a cause of opportunistic infections. Perfect and Schell (9) have summarized this problem with a lengthy list of fungal opportunists and emphasized that immunocompromised patients may be infected with more than one type of fungus. Von-Eiff et al. (13) reported 42 pulmonary fungal infections in 143 febrile immunocompromised patients, of whom approximately 7% had more than one fungal pathogen, as suspected but not proved in our patient.

Fungal pneumonia continues to be a fatal illness despite early diagnosis. Xu et al. (15) reported 115 cases of fungal pneumonia in immunocompromised hosts. Although over 80% of cases received antifungal therapy with intravenous amphotericin B, the mortality was 80.9%.

In summary, we report an unusual case of P. citrinum pneumonia with pericarditis in a patient with acute leukemia. Realization that this common “contaminant” can behave as a pathogen in the immunocompromised host should alert both clinicians and microbiologists to the fact that isolation of P. citrinum may indicate the presence of a serious and potentially fatal fungal infection.

**Isolate accession number.** The P. citrinum isolate has been deposited in the culture collection of the Centraalbureau voor Schimmelcultures, Baarn, The Netherlands (accession number, CBS 865.97).

**REFERENCES**